Volume 41 Number 7

PHARM

PLUS: Spray-Dried Dispersions : Deviation Investigations : Iron Analysis

JULY 2017 Volume 41 Number 7

Advancing Development & Manufacturing

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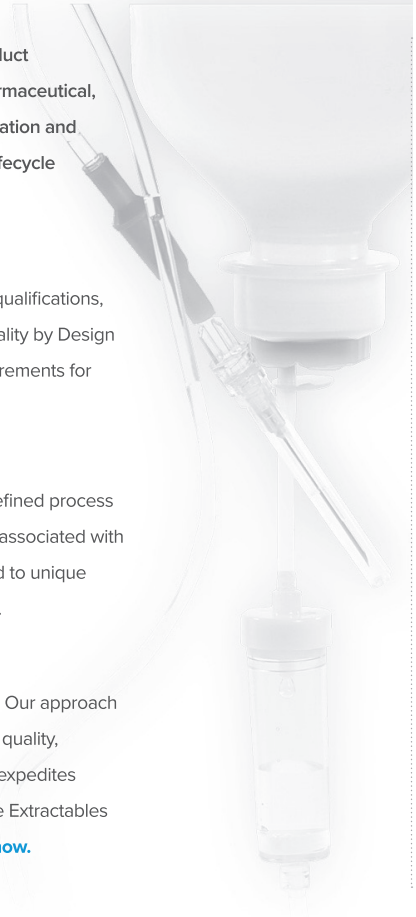

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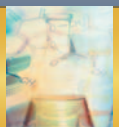

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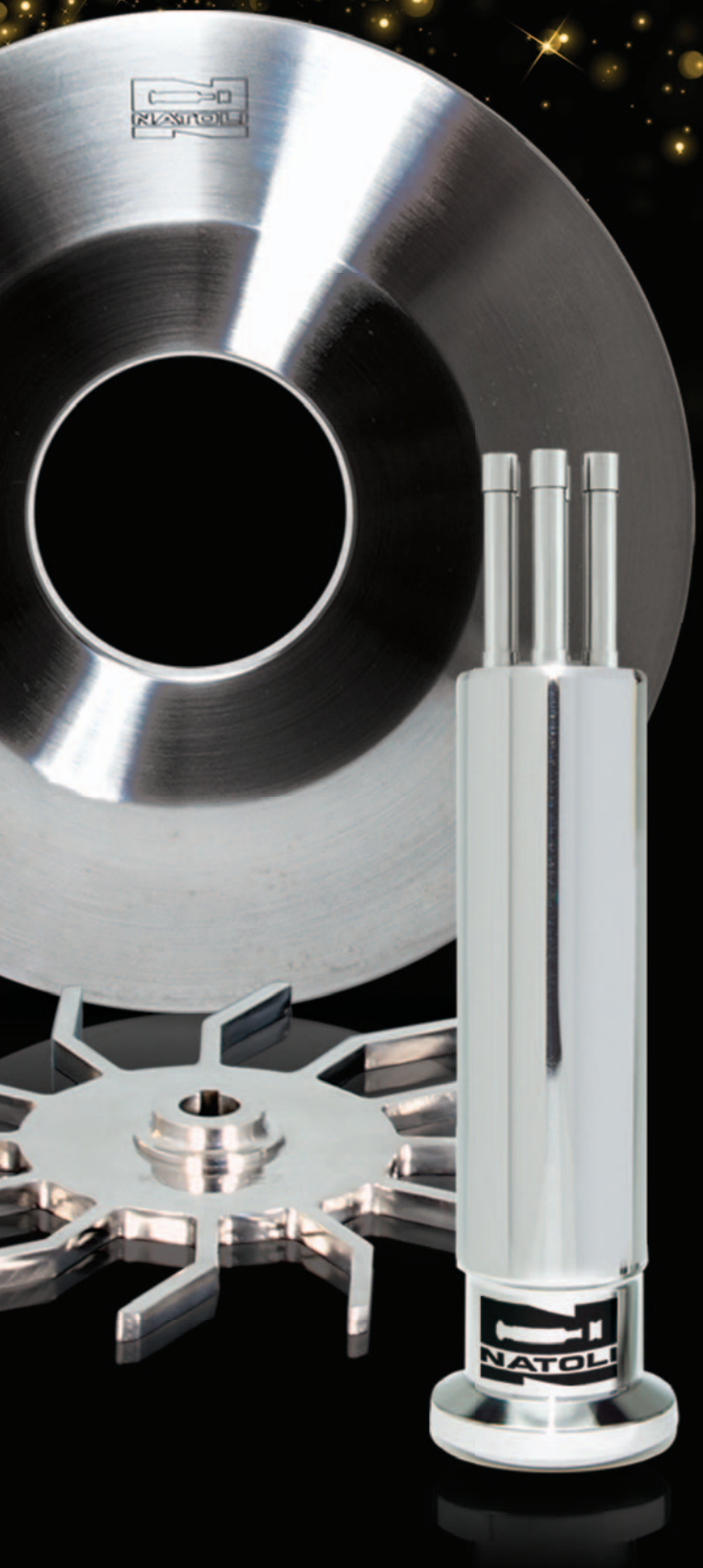

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Pharmaceutical Technology is the authoritative source of peer-reviewed research and expert analyses for scientists, engineers, and managers engaged in process development, manufacturing, formulation and drug delivery, API synthesis, analytical technology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

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On the cover

COVER STORY

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SPECIAL SECTION: 40TH ANNIVERSARY

Continued on page 8

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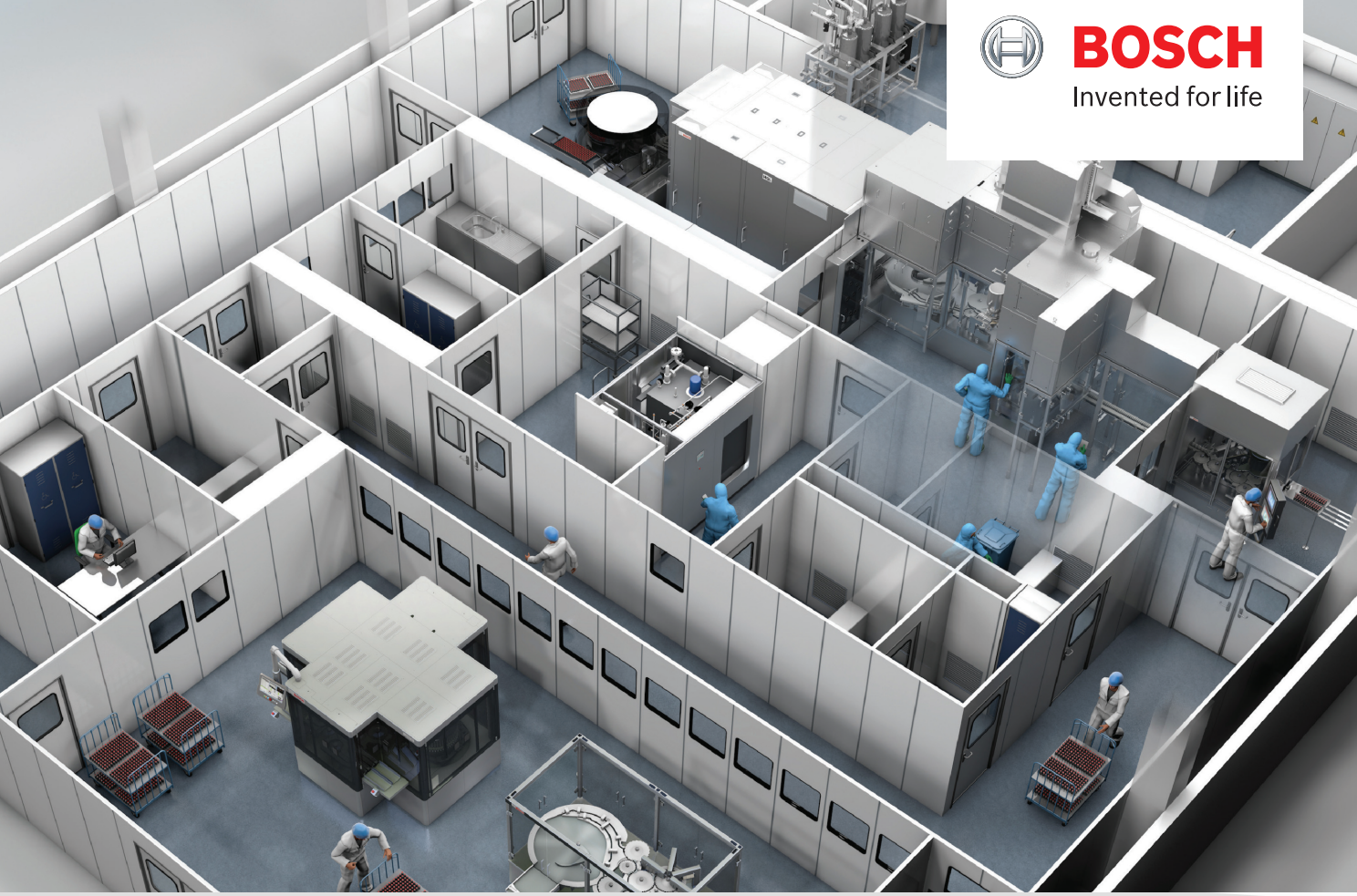

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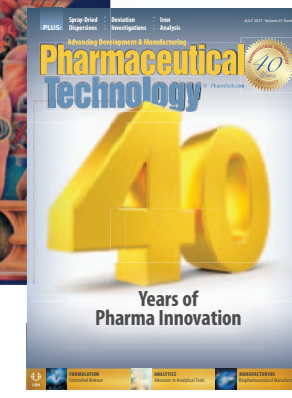

JULY 2017

The Commitment Continues

Rita Peters and Mike Tracey

Pharmaceutical Technology marks 40 years covering the bio/pharma industry.

In the premiere issue of *Pharmaceutical Technology* magazine, which was published in June 1977, Publisher Edward D. Aster described the new publication as "committed to serving the needs and interests of quality-assurance, quality-control, and production-management personnel engaged in the manufacture of drug and pharmaceutical preparations, clinical diagnostics, and cosmetics" (1).

Four decades later, we are pleased to publish this special issue commemorating 40 years of technical articles, peer-review papers, news, new technology reports, and analysis for bio/pharmaceutical formulation, development, and manufacturing.

In the years since the initial publication, *PharmTech* has expanded its coverage to meet market dynamics, added a European edition, developed a comprehensive Internet presence through *PharmTech.com*, and provided the insight needed to successfully bring drugs to market.

The magazine's success is the result of contributions from pharma industry leaders, scientists, formulators, and technical experts. We extend our thanks to the authors, advisory board members, and contributors who have shaped the editorial focus of the publication.

In business-to-business publishing, where the publication is supported financially through advertising, the editors strive to maintain objective coverage of developing technologies and services. We appreciate the patronage of advertisers that provided financial support for the publication while recognizing the importance of an independent source of pharmaceutical development and manufacturing information.

Above all, we would like to thank the loyal readers who turn to the print magazine, website, newsletters, and other *PharmTech* media properties for information about bio/pharma development and manufacturing.

In this issue, the editors interview industry experts involved drug development and manufacturing processes, to reflect on industry progress and suggest areas that need improvement.

Regulatory oversight: Washington columnist Jill Wechsler reviews significant legislation enacted in the past 40 years that changed the way drugs are developed and manufactured (page 20).

Formulation: The history of poly(lactide-glycolide) for parenteral drug formulations with extended-release properties and the need for a safe supply of the product are reviewed (page 26).

Excipients: Tablet and capsule coatings have progressed from sugar coatings to copolymers, thanks to advances in formulations and equipment (page 34).

Drug product manufacturing: Advances in automation, containment, robotics, and drug delivery devices have improved the quality and cost-effectiveness of drug manufacturing (page 38).

Continuous manufacturing: The regulatory approval of the first continuous manufacturing lines for oral solid-dosage drugs is sparking interest among other drug companies and contract manufacturers (page 48).

Biologics drug manufacturing: Single-use technology, more productive bioreactors, and improved upstream and downstream processes set the stage for flexible manufacturing (page 60).

Analytics: Representatives from instrument manufacturing companies identified advances in analytical technology that have improved accuracy, performance, characterization, and in-process monitoring (page 66).

Packaging: Drug companies continue to develop innovative packaging to promote patient adherence to prescribed drug regimens, including smartphone options (page 72).

Contract services: The history of outsourcing, as well as future prospects for the market segment, are discussed in two features (page 76).

Rita Peters,
Editorial Director

Mike Tracey,
Publisher

Reference

1. E.D. Aster, "Welcome", *Pharm. Tech.*, 1(1) 5 (1977). **PT/40**

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The Ross Model 42N-36S Sanitary Ribbon Blender (pictured) has a 36-cu.-ft. maximum working capacity. Driven by a 25HP inverter-duty gearmotor, the fabricated double ribbon agitator turns to up to 40 rpm within the U-shaped trough, producing a balanced lateral and radial movement of batch materials. Wetted parts are stainless steel 316 polished to 150-grit for ease of cleaning. The blender cover includes safety grating and a custom bag dump station. A 150-psig ASME code stamped dimpled stainless steel jacket is supplied around the trough for heating/cooling. Multiple spray bars and nozzles deliver liquid raw materials and clean-in-place solution.

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The Model 2500 Select–Bathless Dissolution Tester from Distek eliminates the water bath and all associated maintenance while heater jackets raise media temperature from ambient to 37 °C in less than 15 minutes. Wireless in-shaft temperature sensors continuously monitor and display the in-vessel temperature for each vessel. The dissolution tester includes a touch screen, electronic tracking of serialized stirring elements, qualification status and due dates, and reporting and method storage capabilities.

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The system is designed for efficient oxygen transfer, mixing, and CO_2 stripping. These combined features ensure cell culture performance with reproducible high-density growth of even sensitive cell lines. As a result, BIOSTAT STR bioreactors are suitable for achieving very high cell densities in continuous processes and for safe manufacture of vaccines and recombinant proteins in cGMP environments. Pictured is the BIOSTAT STR bioreactor in 500 L.

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Pharma's Past Serves as Prologue to Its Future

Rita Peters

The more pharma science and technology change, the more business and policy concerns stay the same.

In the 40 years since *Pharmaceutical Technology* magazine was first published, the pharmaceutical industry has weathered shifts in medical, scientific, regulatory, and business practices to discover, develop, and manufacture medicines for patients globally. Genomic studies have provided insight into disease conditions. Materials research in particle sciences and nanotechnology have fostered advances in formulation and drug delivery. Biologic-based drugs have addressed previously untreated diseases. And advances in analytical technologies have enabled more comprehensive and accurate studies of cellular and chemical behavior.

The drug development and manufacturing process in 2017 is more technologically advanced, and has benefited from the application of scientific, risk-based approaches. Still, the industry faces challenges including shrinking internal pipelines, market-share incursions from generic drugs, regulatory inconsistencies from region to region, supply chain threats, aging equipment and facilities, drug pricing pressures, and investor demands for financial performance.

While the bio/pharmaceutical industry has witnessed many changes during the past 40 years, some sentiments expressed in 1977 still ring true. In a guest editorial the first issue of *Pharmaceutical Technology* (1), George H. Hopkins, president of the Parenteral Drug Association at the time, commented that pharmaceutical scientists and companies enjoyed the respect of society at large; however, he wrote, "the times, they are a-changing. Society is beginning to challenge many institutions and agencies that were once held in awe."

People have lost faith in the integrity of elected officials, he continued, "due, in a large part, to demonstrated venality on the federal, state, and local levels." And, he noted, "the pharmaceutical industry has been accused of setting prices that yield exorbitant profits on some drug products."

Payer and policymaker concerns about the high cost of drug products continue today fueled by high-profile examples of price inflation by Turing Pharmaceuticals, under the leadership of Martin Shkreli, and Mylan Pharmaceuticals. The contentious debate over healthcare in the United States also centers on drug costs.

The rise and fall of the blockbuster

Patent expirations of blockbuster drugs have had a significant impact on the pharmaceutical companies and their approaches to research and development. As drug innovator companies lost exclusivity to high-revenue generating drugs in the early 2010s, Big Pharma adopted business alternatives such as developing drugs for unmet medical needs, adding generic-drug businesses, partnering with other companies, acquiring or licensing therapies from startup companies, or marketing their drug products in new geographic areas.

From 1977–2016, FDA approved, on average, 26 new molecular entities (NMEs) per year. The number of NMEs per year has trended slightly upward since 1977, with banner years

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for approvals in 1996 (53 approvals), 2014 (41 approvals), and 2015 (45 approvals) (2, 3).

In recent years, FDA's expedited approval pathways—fast track, breakthrough, priority review, and accelerated approval—have played a major role in bringing new drugs, particularly for orphan or rare diseases, to market. Nearly three-quarters of the NMEs approved in 2016 were reviewed under one or more expedited approval pathway. Biologic-based drugs represent a growing share of the approved NMEs; small molecule drugs, however, remained the primary type of drug approved.

Managing regulatory oversight

In 1977, Hopkins lamented the "sometimes conflicting regulatory constraints" from a range of health and environmental agencies as "each new scientific discovery creates for society a fresh set of problems, and each new set of problems creates in turn new controls and a new bureaucracy to administer these controls."

On the regulatory front, legislation, supporting regulations, and guidance documents shaped manufacturing practices and business approaches. Drug license holders looking to extend their product distribution to new geographic regions faced varying regulatory requirements and approval processes from region to region.

In 1978, 21 *Code of Federal Regulations* Parts 210 and 211 were issued, establishing good manufacturing practices for drug products. The Orphan Drug Act of 1983 provided incentives for drug companies to develop therapies for patients with rare diseases. Generic drugs gained an abbreviated approval pathway in 1984 via the Hatch-Waxman Act. The Prescription Drug User Fee Act of 1992 funded FDA resources to reduce the time needed for drug approvals.

More recently, the Patient Protection and Affordable Care Act of 2009 created an abbreviated licensure pathway for biological products that are "biosimilar" or "interchangeable" with an FDA-licensed biological product; a June 2017 Supreme Court decision eased the path for biosimilar approvals.

The Food and Drug Administration Safety and Innovation Act of 2012 established regulations for tracking drug products through the supply chain, measures needed to prevent global prescription drug theft and diversion. Implementation dates in the US, however, were extended as the industry struggled to meet deadlines.

The 21st Century Cures Act of 2016 provided alternatives to expedite clinical trials, encouraged patient involvement in drug development, and provided for FDA staffing to reduce a backlog of generic-drug applications.

Quality at the forefront

Pressures to lower manufacturing costs and improve the financial bottom line enticed drug license holders to seek less costly materials and manufacturing services offshore, often with limited US regulatory oversight. In addition, some companies were deterred from investing in new equipment or facilities due to low return on investment, or concerns about a costly post-approval change process. Resulting quality issues led to ongoing drug shortages, particularly for low-cost parenteral drugs.

In a 2017 *Pharmaceutical Technology* survey (4) of US bio/pharma quality and manufacturing professionals, respondents said that FDA could improve drug quality by inspecting more offshore facilities, and favored the use of self-reporting and inspection waivers to facilities that meet predefined quality metrics.

In recent years, FDA has stepped up inspections of API and drug product manufacturers and issued more warning letters to facilities in India and China. The agency also proposed proactive measures to address quality through a quality metrics program. After several years of industry study and debate, the program remained at the draft guidance stage as of June 2017.

Nearly half of the survey respondents who reported quality-related problems attributed the issues to human error and documentation practices; nearly one-third cited manufacturing-related issues.

During facility inspections in fiscal years 2012–2106 (5), however, FDA identified shortfalls in quality procedures and processes—a lack of written quality control procedures, lack of investigation to batch discrepancies, lack of scientifically sound laboratory controls, and a lack of written procedures for production and process controls—as the leading sources of quality issues.

Despite these agency findings, more than 40% of the respondents could not identify a formal quality management system used at their facility and many noted that their facilities lacked formal maintenance programs.

Technology of the times

Advertisements in the first issue of *Pharmaceutical Technology* promoted equipment, supplies, and materials—the predecessors of today's technologies—including tablet coating and manufacturing systems, sterilizers, packaging components, tubing, filters and filter cartridges, freeze dryers, powder media, dissolution testing instruments, biohazard process isolation equipment, water purification systems, and particle counters.

Product descriptions reflected the technology of the era, which may seem dangerous or antiquated, by today's standards. Several filter manufacturers noted that their products were "asbestos-free." A data acquisition system was touted for its ability to gather information from a "computer-directed analyzer", store it on a tape cartridge, and automatically collate and print results.

In 1977, high-performance liquid chromatography (HPLC) was gaining acceptance in pharmaceutical development. Since that time, HPLC, mass spectrometry, differential scanning calorimetry, and other instruments have become more sophisticated and accurate, providing more information about small molecules and biologics. These instruments have helped drug

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developers meet the requirements of orthogonal testing techniques encouraged by FDA.

The early application of computer-controlled pharmaceutical manufacturing was profiled in a February 1978 article (6) about Merck Sharp & Dohme's $23 million ($89 million in 2017 dollars) "fully computer-controlled tableting plant" in Elkton, VA. The facility was opened to "launch America into a new era of pharmaceutical manufacturing that is as far removed from apothecarial compounding as the space shuttle is from the Pilgrims' Mayflower."

The facility featured the "awesome absence of human beings." Two employees monitored computer operations; four people, with two-way radios, monitored a continuous production operation that had 420 regulating and sensing devices. The process included an aqueous coating process, continuous granulating and blending, continuous fluidizing of coating film, and a computer system to print data for batch records.

While this facility represented cutting edge technology in 1978, return on investment was an overriding concern. In the article, Merck Chairman and CEO John J. Horan noted that the innovation demonstrated in the plant would be threatened if public policy led to "government reimbursement at levels that do not support this kind of activity."

Despite this early attempt at continuous manufacturing, batch processes remained the primary manufacturing approach in the ensuing decades. To address quality issues and reduce the potential of drug shortages, FDA encouraged drug makers to embrace modern manufacturing methods. The agency's approval of two continuous manufacturing processes in 2016—a new manufacturing process and the transition of a legacy batch manufacturing process to continuous mode—has encouraged other drug manufacturers and contract manufacturers to explore continuous processing.

Other technology advances are discussed in the 40th anniversary section of this issue.

Lessons still to be learned

In the 1977 guest editorial, Hopkins warned about legislators and scientists operating in silos and not communicating, or intentionally ignoring advice. "If we accept the fact that many of today's problems stem from technological advances evolving at a pace faster than our present ability to assimilate them, we must also recognize that these same technological capabilities are our major resource in developing solutions to our problems," he wrote. "The scientist cannot continue to innovate in his ivory tower, leaving the potential applications of his new discoveries to outside agencies of uncertain technical competence."

As technology and information channels advance at a rapid pace, and patient, payer, investor, and politically connected groups maneuver for a voice in the bio/pharma industry, the need for bio/pharmaceutical companies, industry suppliers, and regulators to innovate and communicate in concert once again rings true.

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PERSPECTIVE: FROM ART TO SCIENCE

Russell Madsen, president of The Williamsburg Group, LLC and member of *Pharmaceutical Technology*'s Editorial Advisory Board, discusses how technology has advanced the industry, especially regarding data management.

PharmTech: During your more than 50 years in the pharmaceutical industry, how has the industry evolved? What advances have been made? What were some factors that hindered advances?

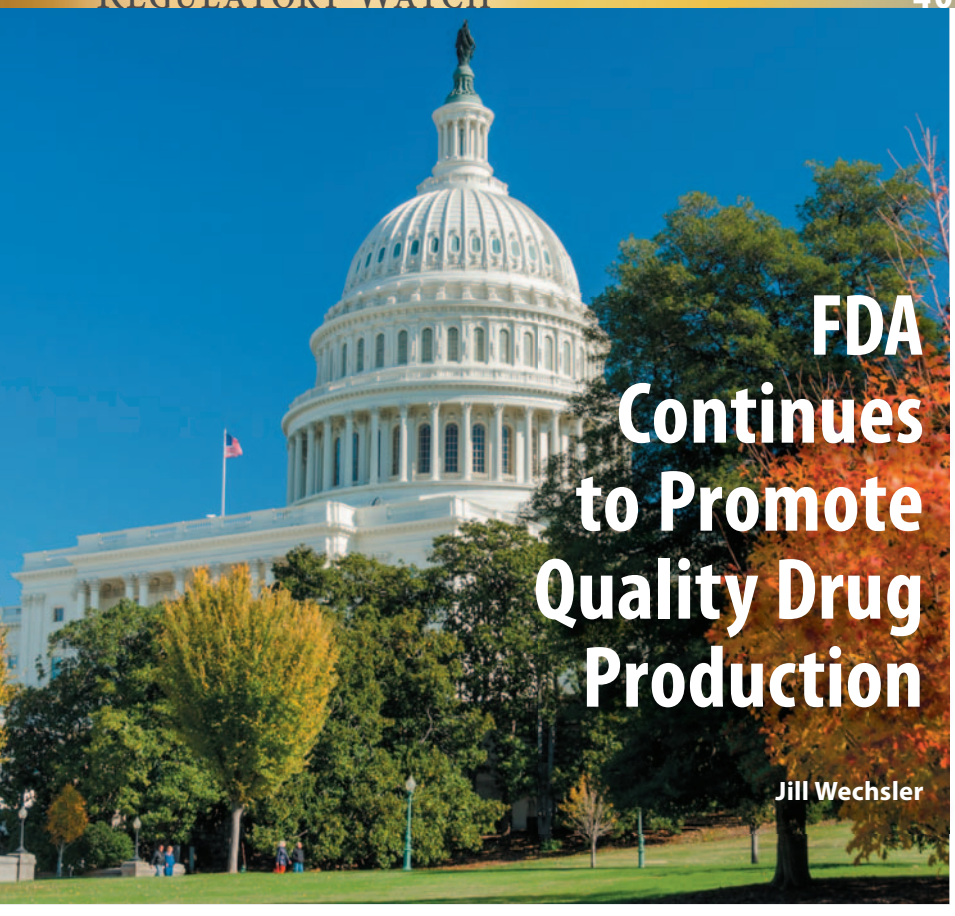
Madsen: Computers and information technology have transformed the industry. In 1965, computers and data processing were used primarily for financial purposes and top-level management information systems. There were no PCs, and the Internet had not been invented. Records and forms were produced using typewriters and were photocopied to be filled in by hand. Transmission of records was by mail, or fax if more rapid movement was necessary.

The use of paper records hampered drug development because it was not easy to evaluate the masses of data resulting from formulation, stability, safety, and clinical studies to optimize manufacturing processes and to ensure the final commercial formulation was the same as the one(s) used for clinical trials. Multivariate analysis was a dream.

The company I worked for in 1965 was much more integrated than those of today. On a single campus, we conducted R&D, synthesized many of our APIs, manufactured oral and sterile finished products, produced rubber stoppers, printed labels, and manufactured unit cartons.

Manufacturing has moved from art to science. The dryness of granulations used to be literally determined by operator 'feel', and sugar-coated tablets were coated and polished by skilled operators who knew when the finished tablets were 'good' by sight. Now, these operations are automated and scientifically controlled.

Chemical analysis was done using titration and spectrophotometry. Gas chromatography was just coming into general use in 1965 and high-performance liquid chromatography, now a mainstay of pharmaceutical analysis, didn't take hold until the mid-1970s. Laboratory information management systems (LIMS) were in their infancy until the mid-1990s.



FDA Continues to Promote Quality Drug Production

Jill Wechsler

CDER's Janet Woodcock endorses modern drug manufacturing to ensure access to safe and reliable medicines.

As pharmaceutical manufacturing became more scientific and complex during the second half of the 20th Century, the government's role in setting standards and regulating the testing and development of medicines and vaccines expanded and evolved. As with many government programs, public health crises involving contaminated vaccines and deadly elixirs spurred demands for more effective oversight. The thalidomide tragedy of the 1960s led to legislation to better ensure the safety and effectiveness of drugs and biologics, establishing new rules for drug marketing and current good manufacturing practices (cGMPs) and expanding FDA in the process.

Through the following decades, Congress further strengthened oversight of over-the-counter drugs and medical devices. The Orphan Drug Act of 1983 created incentives for developing treatments for rare diseases. The landmark Hatch-Waxman Act of 1984 established a pathway for abbreviated testing and efficient approval of less costly generic drugs. Meanwhile, the AIDS epidemic pressured FDA officials in 1988 to facilitate access to, and accelerate the development and approval of, experimental therapies for patients with serious, life-threatening diseases without available treatment.

FDA had some 7300 staffers in 1977, approximately 1000 involved in drug regulation, when *Pharmaceutical Technology* magazine began to report on the technical, scientific, and regulatory issues shaping modern drug development and production. Today, FDA's staff nears 17,000, about 5000 in the Center for Drug Evaluation and Research (CDER) and 1400 in the Center for Biologics Evaluation and Research (CBER). Much of this expansion has been supported by industry-paid user fees, which were first authorized by the Prescription Drug User Fee Act (PDUFA) of 1992 to enhance FDA's ability to process drug applications more efficiently—and to reduce the lag between when new drugs came to market in the United States compared to Europe.

FDA has grown from 7300 staffers in 1977 to nearly 17,000 today.

FDA drug regulatory policies continued to evolve under CDER Director Janet Woodcock, who took the helm in 1994 and has led the center since then, except during a 2005–2008 stint in the FDA Commissioner's office. She followed CDER's first director, clinical pharmacologist Carl Peck, who came to the new center in 1987 in time to deal with the generic-drug scandal that rocked the agency and with the challenges in overseeing development of new therapies for AIDS and other critical diseases.

During the 1990s, Congress and FDA set new policies for dietary supplements, incentives for developing medicines for children, expanded safeguards and information for participants in clinical trials, more leeway for drug advertising and communications, streamlined oversight of combi-

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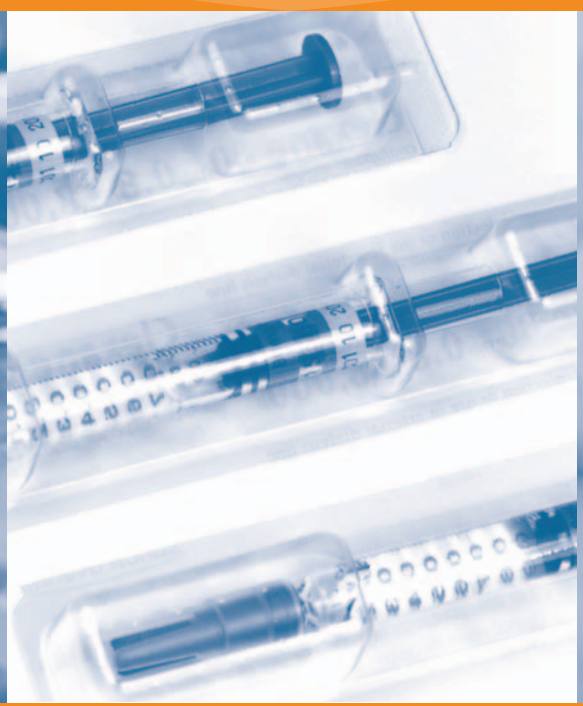

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nation products, and the development of countermeasures to biological and chemical attacks, among other key initiatives. Serious side effects from widely used pain therapies in 2004 led to expanded oversight of drug safety and adverse events.

Emphasizing quality

A main initiative for Woodcock has been to encourage industry adoption of modern manufacturing systems that can reliably produce high quality medicines. Through the 1900s, Woodcock recalled in a recent interview with *Pharmaceutical Technology*, not much changed in pharmaceutical manufacturing, as companies continued to use basic pharmaceutical compounding processes, scaled up. She was concerned that FDA policies discouraged change, where existing operations met established requirements.

But a more efficient drug-approval process demanded by the drug user fee program, along with surging applications for generic drugs, prompted further CDER reorganization. The Office of Pharmaceutical Science (OPS) was established in 1995 to better oversee the quality aspects of prescription drugs, providing a home for the chemists, pharmacologists, and other staffers involved with evaluating the chemistry, manufacturing, and controls sections of applications for new drugs and generics.

This new structure was helpful when CDER assumed responsibility in 2003 for regulating the growing volume of monoclonal antibodies and therapeutic proteins overseen by CBER. The shift aimed to reduce differences in review processes for drugs and biotech therapies, while also enhancing CBER's ability to address important public health issues related to vaccines, blood supply, and gene therapies and cellular products, which now are emerging as vital cutting-edge therapies. OPS created a new Office of Biotechnology Products to assess manufacturing and quality issues, now including biosimilars.

Meanwhile, Woodcock continued to press for manufacturing-related changes in FDA regulations, launching the Pharmaceutical Quality for the 21st Century initiative in 2002 to update cGMP guidance documents and to apply risk-based approaches to regulation and inspections. The program encouraged manufacturers to adopt integrated quality systems and online technologies that support continuous manufacturing under a science-based process analytical technology (PAT) initiative. CDER sought closer collaboration with standards setting organizations and the International Council for Harmonization (ICH) to establish global standards for drug testing and production, leading to important ICH guidelines on quality risk management.

Woodcock sees more biopharma companies adopting newer technologies in the commercial production space, moves that she considers particularly suited to generic-drug makers.

Despite these efforts, serious problems in manufacturing processes and in drug quality continued to plague the pharmaceutical industry, often leading to plant closures, product recalls, and drug shortages that compromised patient care. Patient deaths linked to contaminated heparin from China in 2008 and the fungal meningitis outbreak of 2012 caused by faulty large-scale compounding of common injectables, led to legislation expanding FDA oversight of pharmacy compounding and establishing a framework for a global identification and track-and-trace system for pharmaceutical ingredients and finished products by 2023.

A more streamlined and efficient field inspection program for drug manufacturing facilities has been a related goal, particularly as the international pharmaceutical pipeline has taxed field inspection operations. After years of effort, FDA now is implementing a more risk-based inspection model that equates the frequency and scope of facility inspections with a range of factors related to plant operations and produce characteristics. The agency's Program Alignment initiative similarly aims to better target inspections by FDA's field force to high-risk situations, working with a specialized pharmaceutical inspectorate to gain added expertise in evaluating targeted sites. FDA officials also are advancing mutual reliance agreements with competent regulatory authorities in Europe and other regions to establish common standards for pharmaceutical inspections and reduce the need for every agency to conduct its own, often redundant, site visits.

Worth the investment

These initiatives now are being implemented by CDER's Office of Pharmaceutical Quality (OPQ), established in January 2015 to further improve the management of ever-increasing generic-drug applications and thousands of manufacturing supplements, to better coordinate center and field inspection activities, and to promote industry investment in robust quality systems and modern manufacturing technology. Woodcock sees more biopharma companies adopting newer technologies in the commercial production space, moves that she considers particularly suited to

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generic-drug makers, where "more automated continuous methods have a high probability of getting it right the first time."

The value of modern manufacturing methods is particularly apparent with breakthrough drugs and other highly innovative products designed for very small patient populations, Woodcock points out. The fairly new breakthrough designation program has been highly successful, but in multiple situations, she has found that "manufacturing is a rate limiting step" in bringing vital new therapies to patients quickly. Similarly, efficient development of much-anticipated biosimilars requires cutting-edge production systems. In the past, efficient manufacturing scale-up was not that important because clinical development took so long, Woodcock observes. But today, she adds, "breakthrough has shown that time is money."

Woodcock hopes that such developments will encourage more pharma companies to adopt production systems that may be smaller and more agile as well as more reliable. Such approaches may be helpful in implementing changes over a product's lifecycle and reducing the volume of manufacturing supplements filed with FDA every year.

Even though changes in drug production systems require considerable upfront capital investment, the significant advantages in being able to make high-quality products more reliably and at lower cost should be worth the outlay, Woodcock observes. By avoiding recalls and line shutdowns, more efficient manufacturing should be seen as a competitive advantage, and those who make the investment first, she says, "will be far out in front of the curve." **PT/40**

PERSPECTIVE: BIG PHARMA NO LONGER THE CENTER OF INNOVATION

Chris Moreton, PhD, partner at FinnBrit Consulting and a member of *PharmTech's* Editorial Advisory Board, discusses how the role of Big Pharma has changed over the years and the positive effects of regulations.

Pharma industry advancements

PharmTech: During your 40 years in the pharmaceutical industry, how has it evolved? What advances have been made? What were some factors that hindered advances?

Moreton: Industry has evolved in several ways. For example, in the early 1970s, Big Pharma was the center for drug discovery and innovation. That is no longer the case, and it can be argued that Big Pharma companies today are more centers of marketing and sales than drug discovery. The centers of drug discovery are increasingly in universities and smaller start-ups.

There have been many advances, including:

- Better understanding of drug interaction with receptors
- Better analytical methods (e.g., the introduction of high-performance liquid chromatography, better spectroscopic methods, hyphenated methods, etc.)
- Combinatorial chemistry
- High-throughput screening
- Recombinant DNA technology and other biotechnology tools
- Better understanding of drug absorption and efflux
- Better understanding of drug safety
- Methods to allow the formulation of poorly water soluble drugs
- Drugs commercially available today can save lives, improve patients' quality of life, and allow them to lead more productive lives.
- Regulatory sciences.

I am not sure there have been many factors that have hindered medical advances, apart from arrogance on the part of certain individuals. For example, company executives who have ignored requests from FDA to undertake clinical studies in a certain way, and then complain because their new drug applications were not accepted.

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Moreton: My top three would be:

- The advent of biotechnology-derived drugs
- Better understanding of drug delivery for all types of drug molecules and routes of administration
- The introduction of better analytical methods because these methods have allowed us to investigate and monitor materials and processes in ways that have allowed us to see deeper into mechanisms and organism.

PharmTech: How have regulations and standards advanced or hindered advances?

Moreton: I do not believe that regulations have hindered advances. They may have hindered less scrupulous promotion of certain drug products, and they may have prevented dangerous or inadequately effective medicines from getting to market, but I regard those as pluses.

I think the regulations have actually saved lives, and promoted better research and testing.

The future of Pharma

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Moreton: I think we will see oral delivery of peptide drugs, and this will open new areas of opportunity for the development of new treatments for diseases. We will likely see even more consolidation in all branches of the pharmaceutical sector. There will also be an accompanying further shift of drug discovery to smaller organizations with a concomitant growth in the contract sectors.

I think we may also see skills shortages in some areas as older people retire and there is no succession planning. Younger people are not able to get the training today that was available to me 45 years ago. Training is being increasingly cut back in all organizations.

—Chris Moreton has been a member of Pharmaceutical Technology's *Editorial Advisory Board since 2003.*

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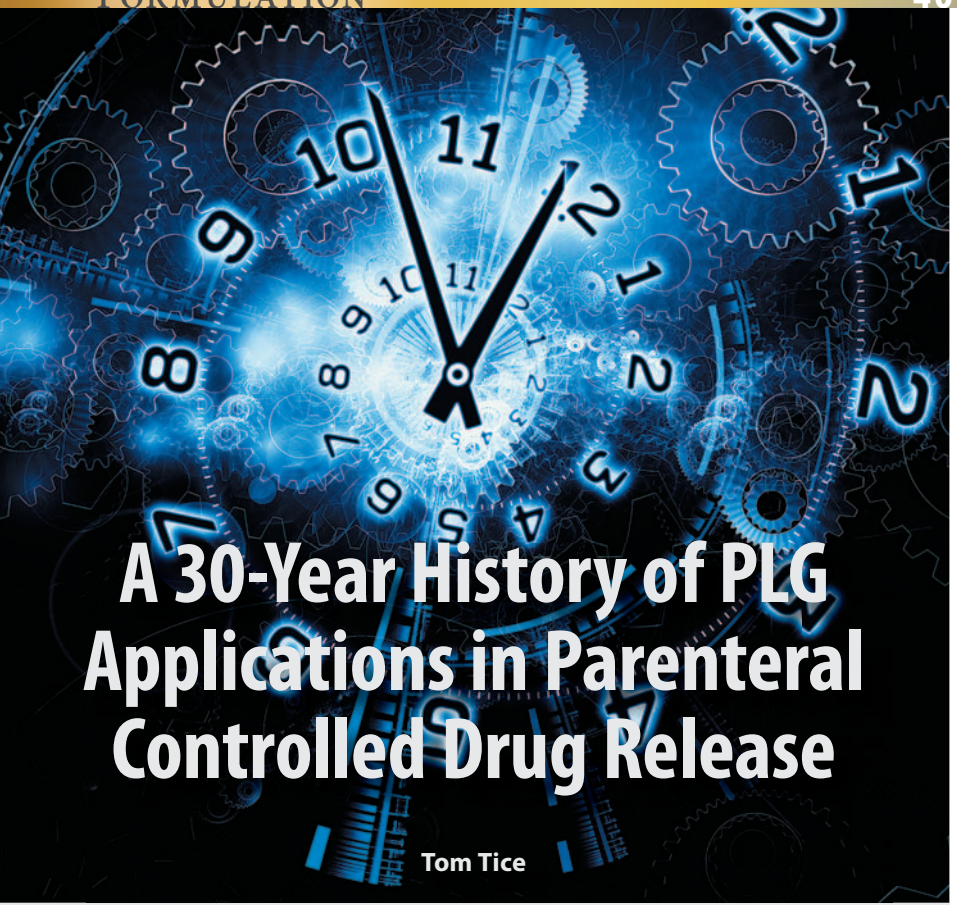

A 30-Year History of PLG Applications in Parenteral Controlled Drug Release

Tom Tice

Poly(lactide-glycolide) has been used for drug-delivery applications in numerous commercial drug products because of its beneficial physicochemical properties, long safety record, and reliable commercial supply.

The history of poly(lactide-glycolide) (PLG) for drug-delivery applications can be told through the number of products that has steadily emerged on the market since the first product was launched in 1986. More than 35 commercial drug products have relied on the beneficial physical and chemical properties of PLG, its long safety record, and the reliable commercial supply of this polymer.

Tom Tice, PhD, is senior director, Global Technical Marketing, Evonik Industries.

The first PLG drug delivery patent

US Patent 3,773,919 (1) was the first issued drug-delivery patent describing PLG/drug compositions. This patent, assigned to E.I. du Pont de Nemours and Company, was issued on Nov. 20, 1973. George Boswell and Richard Scribner were the groundbreaking inventors. They were experimenting with PLG-based drug delivery in the late 1960s, as indicated by the 1969 filing date. The patent describes the use of polylactide in drug formulations as a means of providing slow and sustained release of the drug over a controlled period. Pharmaceutical depot compositions described in the patent include injectable particles with sizes ranging from 0.1 to 1000 micron. The patent specification defines polylactides as polyesters generally derived from α-hydroxycarboxylic acids and specifically derived from lactic acid (α-hydroxypropionic acid). Polylactide, polyglycolide, and poly(lactide-co-glycolide) copolymers, therefore, are described. The patent specification lists many classes of drugs, including small molecules and peptides, but not proteins. The inventors interestingly foresaw the potential of this drug-delivery technology for antipsychotic agents, natural and synthetic hormones, narcotic antagonists, vitamin B12, and peptides such as bacitracin, polymyxin B sulfate, and sodium colistimethate. Emphasis was placed on the delivery of endocrine agents such as natural steroids and non-steroidal agents for fertility control, progestogens, estrogens, androgens, antiandrogens, corticoids, anabolic agents, and anti-inflammatory actives. Today, there are a number of PLG-based pharmaceutical products on the market that deliver many of the drug substances listed in the patent.

Long-acting contraceptives

In the 1970s, there was a lot of interest in controlled-release research for pharmaceutical applications. Much of this activity focused on the development of long-acting contraceptives. The goal was to develop formulations that released contraceptive steroids at a programmed rate for one month or longer following a single parenteral administration. Initially, researchers in the contraception field used non-biodegradable silicone materials as controlled-release excipients (2). PLG polymers were later found to have good biocompatibility and desirable bioabsorption properties; as a result, many investigators began to formulate contraceptive steroids with PLG as functional polymers. Various dosage forms, including injectable microparticles, implants, and fibers, were investigated for both systemic and local delivery (3).

Who sees opportunity at a molecular level?

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With a global mission, the Program for Applied Research for Fertility Regulation (PARFR) funded several contraceptive programs. One of these programs involved injectable PLG microparticles for the release of norethisterone for one month and three months. The Southern Research Institute and the University of Alabama at Birmingham performed this program. Successful preclinical work led to the preparation of norethisterone microparticles for clinical trials, which represented the first use of PLG microparticles in human clinical trials in 1981 (4).

Animal contraception work funded by Syntex in 1979 led to significant discoveries. This work involved the peptide drug nafarelin, an analog of luteinizing hormone-releasing hormone (LHRH). Naferelin was difficult to microencapsulate because of its good water solubility. Also at the time, little was known about the release profile of large, water-soluble molecules such as peptides from PLG polymers. A milestone occurred when a Southern Research Institute/Syntex team developed a phase-separation microencapsulation process for LHRH peptides that was much different from emulsion-based, solvent evaporation processes used to encapsulate steroids. This achievement opened the door to producing one-month formulations that showed sustained release of LHRH in animals (5, 6).

Debiopharm, a Swiss-based biopharmaceutical company, recognized that controlled-release LHRH for the suppression of testosterone had greater potential for the treatment of prostate cancer than contraception. Having licensed triptorelin, another LHRH analog, Debiopharm contracted Southern Research Institute in 1981 to develop triptorelin microparticles with PLG. This effort led to the market launch of Decapeptyl SR (sustained-release triptorelin) in Europe in 1986, which was the first PLG injectable microparticle product on the market as well as the first injectable peptide-releasing product to be commercialized (7). It is still on the market today distributed by Ferring and Ipsen-Beaufour.

TAP, a joint venture of Takeda and Abbott, also used PLG microparticle technology for the one-month delivery of another LHRH analog, leuprolide. Again, the indication was prostate cancer. The product was launched as Lupron Depot (leuprolide acetate depot suspension) in 1989 (8), and it became a blockbuster drug with sales exceeding that of a liquid leuprolide product, which demonstrated the value of complex, extended-release parenteral products based on PLG excipients. Furthermore, because of the ability to tune the resorption rate of PLG polymers, TAP was able to extend the lifecycle of Lupron Depot with the launch of three-, four-, and six-month leuprolide microparticle products. Other LHRH/PLG microparticles emerged on the market as well, including Sanofi's Sprecur MP for the one-month delivery of buserelin and Watson's Trelstar Depot and Trelstar LA for the one- and three-month delivery of triptorelin pamoate, respectively.

Other extended-release microparticles

In the 1970s, the Sandoz drug-delivery group in Basel was actively developing extended-release, drug-delivery formulations with PLG polymers. First, Sandoz developed and launched Parlodel LAR (long acting repeatable bromocriptine). Parlodel LAR microparticles delivered bromocriptine for one month (9). With the goal to provide a more continuous drug-delivery pattern for their next extended release products, Sandoz developed a branched PLG polymer made with glucose as the initiator. This branched PLG or star PLG polymer was the basis of Sandostatin LAR, a successful product that releases octreotide, a somatostatin peptide, for four weeks. The product was launched in 1997 and is indicated for the treatment of acromegaly and carcinoid cancers (10). In 2014, Novartis launched another somatostatin microparticle product with PLG—Signifor LAR, which delivers the peptide pasireotide for the same indication as Sandostatin LAR. Interestingly, these microparticles comprise a blend of PLG polymers. Ipsen-Beaufor has a somatostatin PLG microparticle product on the market as well, called Somatuline LA (lanreotide).

To date, Genentech is the only company that launched an extended-release PLG microparticle product for the delivery of a protein. This product, Nutropin Depot, releases recombinant human growth hormone for the treatment for growth hormone deficiency in pediatric patients. This product went on the market in 1999 (11).

Examples of other PLG microparticles on the market include Risperdal Consta (risperidone for antipsychotic indications), Vivitrol (naltrexone for alcohol addiction), and Bydureon (GLP1 peptide to treat type 2 diabetes).

Extended-release implants

In addition to PLG microparticles, PLG implants also played a role in controlled-release drug delivery of pharmaceutical products. A melt extrusion process, similar to fiber-spinning, is commonly used to make PLG implants. PLG drug-delivery implants are typically cylindrical rods about 1 cm long and 2 mm in diameter, with the drug dispersed within the PLG matrix core. Once an implant is injected, it can release the drug for weeks and months. After the drug is spent, the implant bioabsorbs.

While naferelin microparticles were being developed, ICI Pharma was working on a PLG implant for the one-month extended release of goserelin, another LHRH analog. This work led to the launch of Zoladex (goserelin) in 1990 by ICI Pharma. Sanofi's Profact Depot for the two- to three-month delivery of buserelin is another PLG/LHRH implant on the market.

Ozurdex (dexamethasone intravitreal implant) is the first PLG extended-release implant administered to the eye using a specifically designed applicator. The PLG implant releases 700 µg of dexamethasone for

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one month to treat macular edema and uveitis.

The most recent PLG implant introduced on the market is Scenesse developed by Evonik for the Australian company Clinuvel Pharmaceuticals. It releases the peptide afamelanotide, a photoprotective drug that protects against sunlight damage by increasing melanin in the skin. Scenesse is indicated for the treatment of erythropoietic protoporphyria, a severe skin disorder caused by the body's inability to protect itself from sunlight.

Local drug delivery

In the early 1980s, localized drug delivery was another novel concept pursued with PLG polymers. One program, funded by the US Army Institute of Dental Research, focused on the local delivery of antibiotics to treat battle wounds (12). The concept was for a soldier to apply a powder of controlled-release PLG/antibiotic microparticles directly into a wound. The microparticles would then slowly release the antibiotic and maintain a high level of drug at the wound site for 14 or 21 days to achieve efficacy without requiring daily, oral dosing.

OraPharm successfully brought the concept of local delivery to the market to treat bacterial infections using PLG excipient. Its Arestin (minocycline) PLG microparticles treat periodontal diseases. The dry microparticle powder is administered to the periodontal pocket using a cartridge system that is provided in the product's kit. Once administered, the microparticles stay in the pocket and release minocycline for two weeks. In addition to drug release, the PLG excipient plays a role in keeping the microparticles in the pocket.

In-situ forming drug delivery

In-situ forming PLG drug delivery was an approach invented by Southern Research Institute scientists. The concept involves administering a PLG polymer solution containing the drug substance such as the antibiotic doxycycline. The resulting liquid formulation is placed into a diseased periodontal pocket. Once in the pocket, the formulation solidifies due to solvent extraction, taking on the shape of the pocket and releasing antibiotic into the pocket for seven days (13). The key with this approach is that the formulation stays in the pocket during antibiotic treatment, especially as the pocket heals and decreases in size. The technology was licensed to Vipont Research Laboratories, which later became Atrix Laboratories. In 1999, Atrix successfully launched a periodontitis product branded as Atridox. Atrix also applied this *in-situ* forming technology to systemic delivery, for example in its Eligard product (leuprolide acetate injectable suspension) for the extended release of LHRH to treat prostate cancer (14).

Nanoparticles

PLG-based drug-delivery technology can be formed into nanoparticles (i.e., particles less than 1 µm in diameter). These nanoparticles can contain encapsulated drug, typically hydrophobic ones. Proteins, such as antibodies, and other moieties can be conjugated on the surface of the nanoparticles as a way of targeting them to specific cells.

Polymeric micelles represent a specific class of PLG-based drug-delivery nanoparticles, whereby a diblock of polylactide and polyethylene glycol (PEG) with hydrophobic and hydrophilic regions respectively allows for self-assembly of the polymer chains into 50-nm nanoparticles. The resulting core-shell constructs have PEG oriented on the surface. Moieties conjugated to the surface are used to target the nanoparticles to biological sites and to minimize toxicity. Genexol (paclitaxel) by Samyang is an example of a PLG polymeric micelle product on the market. Paclitaxol is encapsulated within the hydrophobic core of the polymeric micelle, and the product is indicated for the treatment of breast, lung, and ovarian cancers. The PLG polymeric micelle technology enhances the solubility of paclitaxel and allows significantly higher dosing of paclitaxel to patients without additional toxicity (15).

Vaccines

Researchers have investigated the use of PLG microparticles to encapsulate vaccine antigens. Microparticles of less than 10 µm in diameter are taken up by macrophages, dendritic cells, and Peyer's patches. The engulfed microparticles then release the vaccine antigen within these cells, triggering the cells to produce immunoglobulin antibody titers, which provide mucosal and T-cell responses.

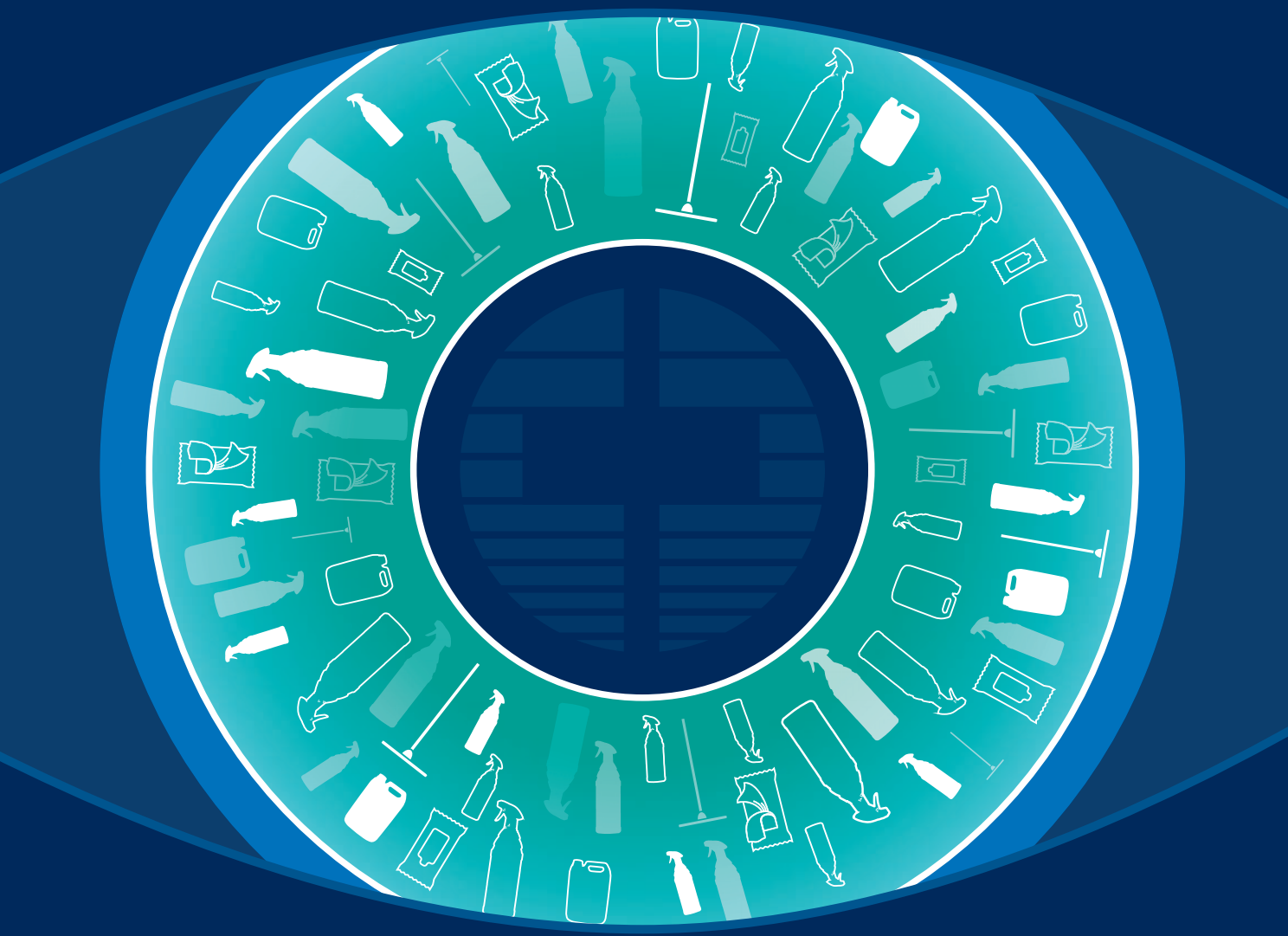
The crucial role of commercial polymer supply

The supply of lactide/glycolide polymers plays a crucial role in the success of PLG-based drug-delivery products. Commercially manufactured PLG has been important in supplying the quantities needed for drug-delivery products, as well as ensuring that the PLG polymers have consistent and desired properties.

During early times, laboratories had to make their own PLG polymers and monomers. These polymers, especially polymers with high glycolide content (e.g., 50:50 lactide:glycolide polymers) had solubility challenges due to their long glycolide blocks. Also, polymer solubility varied from batch to batch, making it difficult to perform robust formulation processing and achieve reproducible drug-delivery performance from microparticles and implants. Resomer polymers offer more consistent properties with better and reproducible solubility.

The future for PLG drug delivery

The majority of biopharmaceutical drugs being developed today will require parenteral administration, and many of these compounds will require extended-release performance. Complex, parenteral drug-delivery technologies will meet these requirements. Safe and proven excipients, such as PLG polymers with consistent properties, will play a key role in formulation development.



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PERSPECTIVE: DRUG COSTS AND PHARMA'S FUTURE

Binodh Desilva, PhD, president of the American Association of Pharmaceutical Scientists (AAPS), discusses how drug costs, biosimilars, and cloud-based technologies will shape the pharmaceutical industry in the years to come.

The evolution of pharma

PharmTech: How has the pharmaceutical industry evolved since AAPS was founded in 1986? What advances have been made? How have regulations and standards changed?

Desilva (AAPS): The pharmaceutical and biotechnology industry has seen the following advances that have expedited the drug development process:

- Availability of big data in the form of rich databases
- Availability of the mobile technology, which enables worldwide access
- Technological advances (e.g., robotics, highly sensitive instrumentation, CRISPR technology, decreased cost of genome sequencing)
- 3D printing of organs and drugs
- Savvy consumer/patient advocacy groups engaging with industry and regulators
- Patient-focused healthcare
- Global travel and the rapid spread of diseases across continents necessitates that first-world countries pay close attention to third-world issues.

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Desilva (AAPS): The biosimilar market and availability of low-cost biologic therapeutics will occupy both the regulators and industry to think innovative ways to conduct research and drug development. The use of biomarkers as diagnostics, as well as prognosis, will enable industry academic collaborations in translational research. [The] supply chain will be affected by the power of the cloud-based technologies. [And there will be] more regulations on the cost of drugs. Political and social influence on this will be more revolutionary than before. Payers will become more sophisticated by using trends and big data to their advantage.

The evolution of AAPS

PharmTech: How has your organization changed over the past 30 years?

Desilva (AAPS): We have changed to adapt to the trends in the industry. We provide cutting-edge, applied educational opportunities for the pharmaceutical science community [and] a forum to connect with scientists from many disciplines and discuss and debate regulations with pharma and regulators from all over the world. We provide expert opinions on regulatory guidance and scientific topics. [And] we develop award-winning journals that focus on the science and news that affect our members.

PharmTech: How has your organization influenced the pharma industry?

Desilva (AAPS): By providing a forum for scientific and technical education and professional development; networking opportunities with academics, regulators, and pharma scientists from around the world; expert opinions on regulatory guidance; and student activities that enable pharma industry to populate their pipeline of the next generation of scientists.

PharmTech: How is your organization planning to grow and affect the industry in the next 10 years?

Desilva (AAPS): It is AAPS' mission to advance the capacity of pharmaceutical scientists to develop products and therapies that improve product health. To that end, the organization is focusing on four organizational pillars as part of our strategic vision:

- Advancing scientific discovery, exchange, and learning
- Working to increase awareness and understanding of the role and positive societal impact of pharmaceutical scientists
- Expanding professional development offerings to meet members' needs throughout their careers
- Fostering AAPS' global community.

In this way, AAPS will steadily move toward our vision of advancing the pharmaceutical sciences to drive prevention and cures.

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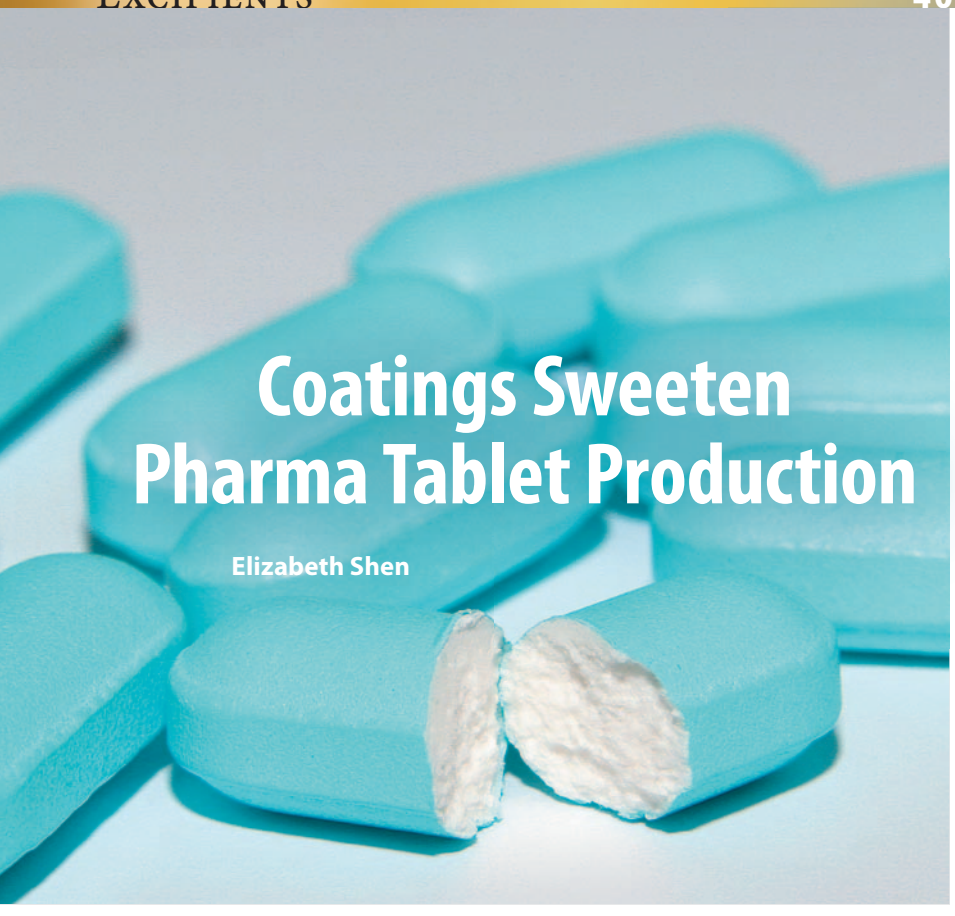

Coatings Sweeten Pharma Tablet Production

Elizabeth Shen

Materials and equipment innovations have advanced tablet coating from sugar to copolymers and simplified pharma production.

Advances in film coatings for pharmaceutical products have picked up the pace within the past 10 years with introduction of new technologies to support product stability improvements and increase process efficiency. The benefits are many; chief among them enabling manufacturers to simplify the progression from lab scale to full-scale production utilizing existing equipment, even when operating in challenging heat and humidity environments around the world.

Coating pills and tablets has been going on since the 1600s in the form of sugar coating to improve their robustness, stability, taste masking, and swallowability (1). Surprisingly, the original process continues today. While sugar-coating ingredients and processes are simple, skilled operators are required to judge when a batch needs additional sugar. Specialized handling of organic solvent materials is needed to apply the initial sub-coat. The process takes days and sometimes weeks to complete, with sealing, bulking, coloring, and final polishing of sugar-coated tablets (2).

With the introduction of polymer-based film coating in the 1950s, coating cycle times were cut from days to hours. With the new film coating process, a polymer solution is continuously sprayed onto the tablets resulting in a thin, uniform film coat (approximately 30 µm), providing numerous benefits including added tablet strength, improved bulk flow, easier swallowing, and improved aesthetics for product differentiation. The industry, however, was not quick to adopt this new process as organic solvents were still required and capital investment in perforated coating pan equipment was necessary (3).

Early film coatings were prepared in-house by the pharmaceutical manufacturers that sourced, tested, and combined the multiple components most often into hydroalcoholic systems. The coating ingredients were generally comprised of polymer, plasticizer, and pigment. Each ingredient could vary from batch to batch and required special preparation steps including high shear mixing and/or de-aerating. Maintaining color consistency from batch to batch—neither a specialty nor priority of pharmaceutical industry—presented another challenge. Combining these factors, it is easy to understand why early adoption of film coatings was a challenge.

The move to aqueous-based coatings

As coating equipment improved, so did the film coating formulations and processes, moving from hydroalcoholic systems to fully aqueous processes. These coating systems were designed ready for use, with all ingredients selected and the color matched to meet individual specifications, removing the complexity of in-house development, material sourcing, and quality control. The prepared formulations were developed for ease of use: a single blended dry powder is added to water and the dispersion is ready for coating a short time later. Colorcon introduced the first fully formulated film coating system, an opaque dry dispersion, under the tradename Opadry in 1985 (4).

Hypromellose (HPMC) and other cellulosic polymers were included as the film forming agent for the early coating applications, and HPMC is prevalent today, mostly through precedence for use, rather than technical superiority. This polymer offers excellent film strength, but can result in finished product defects like peeling and logo bridging due to poor adhesion and elasticity. HPMC viscosity increases exponentially, limiting solids content of dispersions to 10–15% (w/w).

Later in the 1980s, coating innovations were introduced to improve productivity by inclusion of polysaccharides

Elizabeth Shen, PhD, is technical marketing manager at Colorcon, Inc.

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to the film coating formulation, resulting in a decrease of overall viscosity for the coating dispersion, resulting in faster application (5). These formulations also have limitations, with weaker films and a tendency for chipping on friable tablet cores.

Polymers advance productivity

The tempo started to pick up in the 1990s, with the exploration of non-cellulosic polymers such as polyvinyl alcohol (PVA) for film coating application. PVA provides a significant barrier to moisture and can also be coated at cooler and warmer temperatures than HPMC. Other advantages for PVA in film coatings include superior adhesion and lower viscosity compared to HPMC systems. Solids content could be increased to 20% for PVA systems, allowing for quicker process cycle times. The high adhesion, however, comes with a challenging tackiness that caused substantial sticking between tablets at higher spray rates. With clever formulation of the coating system, tackiness can be minimized to prevent defects and maximize coating productivity with PVA systems.

From a regulatory standpoint, PVA ran into some hurdles as it was not broadly acceptable. However, seeing the obvious technical advantages over existing HPMC-based coatings, Colorcon obtained several patents for PVA-based film coatings (6), and the path cleared for introduction to the market when generally-recognized-as-safe status was granted for PVA in 2003.

Most recently, polyvinyl alcohol–polyethylene glycol (PVA-PEG) graft copolymer has been recognized as a material with exceptional film coating properties. This polymer provides extremely low viscosity at high solids content (upwards of 30% solids), which allows for unparalleled productivity and maintains a smooth coating surface.

The productivity of PVA–PEG coatings allows manufacturers to break previous bottlenecks in the coating processes. Coating was often seen as the rate-limiting step in solid dose manufacturing; unmatched productivity allows for higher coating throughputs in batch and continuous processing (7,8).

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PERSPECTIVE: FOCUS ON EXCIPIENTS

Priscilla Zawislak, Chair, IPEC-Americas, tells *Pharmaceutical Technology* how the role of excipients has evolved over the years and how the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) has assisted in developing advancements in the industry.

The evolution of pharma

PharmTech: Since IPEC-Americas was founded in 1991, how has the pharmaceutical industry evolved and what advances have been made?

Zawislak (IPEC): Twenty-six years ago, excipients were not the focus of the pharmaceutical industry. Not much thought was given to these 'inactives' being functional and impacting the performance of the finished drug product. Today, there are more dosage forms, combination products, and emerging technologies in drug development and manufacturer, all of which excipients have a key role in.

PharmTech: How have regulations and standards changed?

Zawislak (IPEC): In the past, excipients were rarely distinguished from APIs or finished drugs in regulations. Today, excipients are a top priority among regulatory agencies. GMPs and risk assessment for excipients are now the subject of global regulations. Third-party excipient GMP certification is growing as a means to facilitate supplier qualification. Excipient composition and harmonization of monographs are getting increased attention. There are still opportunities, in many countries to continue to bring focus on excipients and distinguishing them from APIs.

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Zawislak (IPEC): Emerging technologies for drug development, combination products, biopharma, and novel excipients [will be developed]. Regulations will need to keep pace with these.

The evolution of IPEC

PharmTech: How has your organization changed since it was first founded?

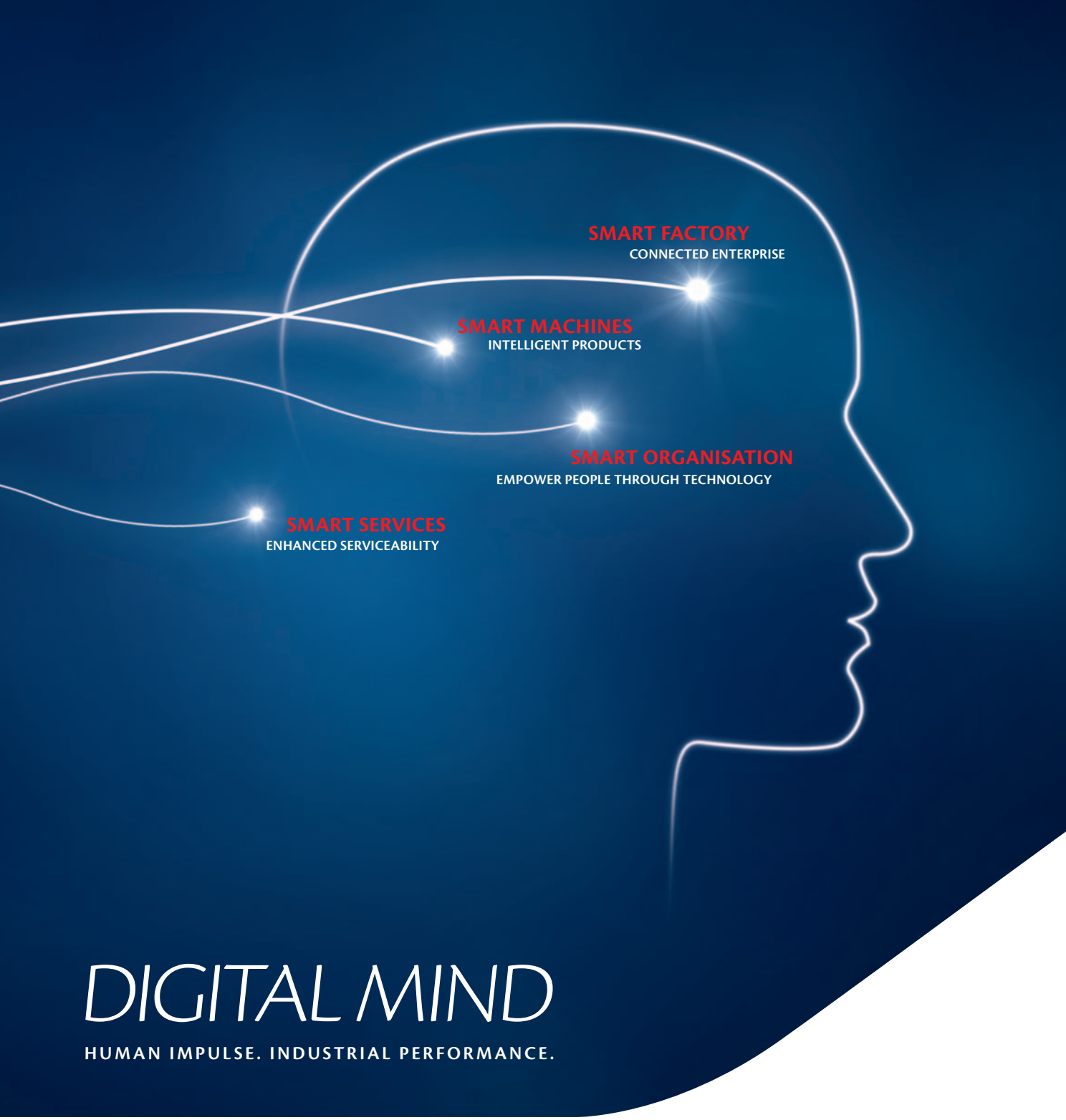
Zawislak (IPEC): IPEC grew from one US-based trade association to a global federation representing five regions (the United States, Europe, Japan, China, and India). IPEC-Americas went from 12 companies to almost 100 members today. We continue to reach out globally via partnerships with other associations (e.g., Latin America and Canada). We've issued 16 guidelines as well as several position papers for the makers and users community. We are now the 'go-to' organization for anything related to excipients.

PharmTech: How has your organization influenced the pharma industry?

Zawislak (IPEC): Our guidelines have become the standards in the industry. We have been instrumental in assisting pharmacopeias globally with the standards-setting process and monograph harmonization. We've worked closely with FDA and other countries' agencies on topics related to excipients.

PharmTech: How is your organization planning to grow and affect the industry in the next 10 years?

Zawislak (IPEC): We are exploring additional global expansion and expansion into markets such as biopharma, medical devices, veterinary drugs, etc.



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Forty Years of Drug Product Manufacturing Advances

Jennifer Markarian

Oral solid-dosage and parenteral drug manufacturing equipment and systems have made great strides in safety and efficiency.

Although the pharmaceutical industry is criticized for its slowness to accept change, it has made manufacturing improvements in the past decades in response to changes in drug delivery (e.g., multi-layer tablets and prefilled syringes); market demands for cost-efficiency and the flexibility to make smaller batches; and regulatory demands for higher product quality, process robustness, and worker safety. Advances in automation, process control, and connected systems have been adopted. Continuous manufacturing has not replaced traditional batch manufacturing, but its concepts are better understood and accepted, and the first commercial, continuous solid-dosage processes are up and running (see pg. 48 in this issue for more on continuous manufacturing).

Parenteral manufacturing and fill/finish

The pharmaceutical industry's aging manufacturing facilities, particularly for parenteral drugs, have been pointed to as a cause of drug shortages, and organizations such as the Parenteral Drug Association have taskforces dedicated to overcoming the challenges to modernization, including post-approval changes (1). In many facilities, however, modern technologies have been implemented and shown to improve efficiency, quality, and flexibility.

One of the keys has been removing human intervention with automation and cleanroom systems, such as restricted access barrier systems (RABS) and isolators. "RABS achieves the sterility assurance level required by regulatory authorities and allows for rapid product changeover along with high safety," explains Bernd Stauss, senior vice-president of Pharmaceutical Production/Engineering at Vetter Pharma-Fertigung. An improved RABS concept called Vetter CleanRoom Technology (V-CRT) combines the advantages of both isolator and RABS technology with fully-automated decontamination of the cleanroom using hydrogen peroxide, says Stauss.

Blow-fill-seal (BFS) technology is another aseptic technology that reduces human intervention. In the automated process, containers are formed, filled, and sealed continuously; BFS is particularly useful for single-dose containers and terminally sterilized drug products (2).

Other new drug-delivery systems, such as prefilled syringes and autoinjectors, and the development of ready-to-fill syringes, vials, and cartridges resulted in more flexible machine platforms for filling different formats. Automated inspection improves quality. In addition, 100% in-process checkweighing prevents product loss, adds Christian Treitel, director, Business Development Pharma, Bosch Packaging Technology.

The use of robots, particularly in fill/finish, continues to expand (3). Robotics were being used at Vetter by the 1990s, notes Stauss. Fully automated lines with robotics are the way of the future, says Treitel, who adds, "Connected industry solutions will bring more intelligence into production. These technologies will help achieve higher productivity, safety, and efficiency."

Containment for highly potent drug manufacturing

Improvements in containment for working with highly potent drug substances have been driven by the growing use of highly potent APIs in solid-dosage drugs and antibody drug conjugates, as well as a push for better protection of workers and prevention of cross-contamination. Concepts such as occupational exposure bands (OEBs) and occupational exposure limits (OELs) allowed better definition

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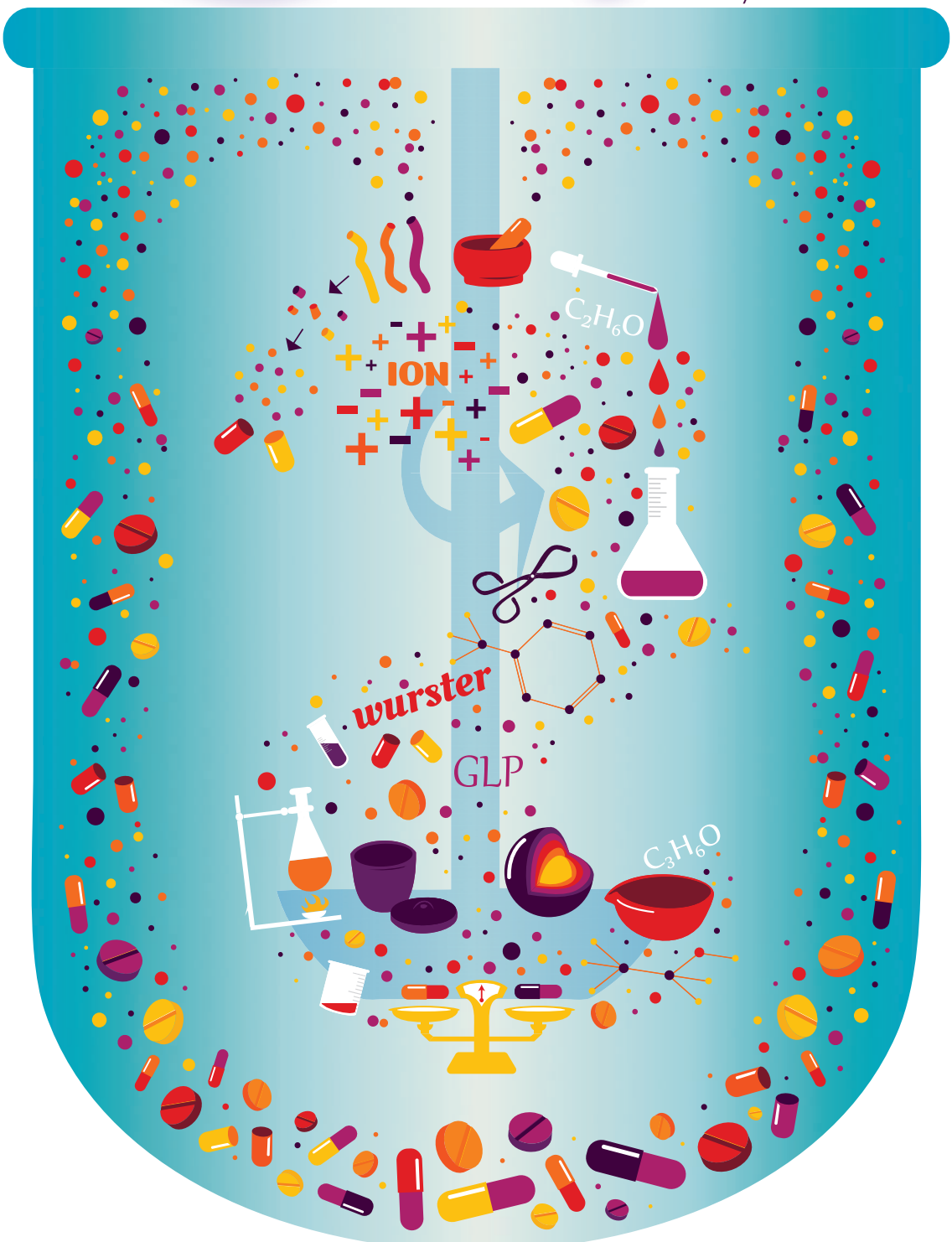

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of drug hazards and the containment strategies needed to handle them safely. "OEBs/OELs were used in the United States first, and Europe started to use them around 15 years ago, followed more recently by Asia," notes Richard Denk, head of the Containment Group at SKAN. European guidelines published in 2014 (4) that require setting permitted daily exposures (PDEs) for each product have led to better data availability as well as an increasing need for containment equipment.

Equipment innovations, such as new technologies for isolators and product transfer systems, have made it easier for manufacturers to operate under low OEL conditions, but there is still room for improvement. Robotics, for one, are poised for implementation in this area and would remove human intervention. In the future, equipment such as fluid-bed dryer or a high-shear mixer would benefit from being designed for integrated containment rather than being adapted for containment after the fact, suggests Denk.

Capsule filling

Capsule filling equipment has progressively obtained increased speeds, higher efficiency, and greater flexibility, along with quality measures such as automated weight control and inspection. "Dosing accuracy has become an essential feature of capsule filling machines," says Treitel at Bosch Packaging Technology.

A significant change in capsule filling has been the type of products filled. "Over the past 10 years, the production of capsules containing multiple products has increased," says Stan Matthews, sales manager of the Processing division at MG America, the US subsidiary of MG2 of Italy, which celebrated its 30th anniversary in its New Jersey headquarters in 2017. "Combinations could include, for example, two different types of pellets, tablet and pellet, or powder and pellet. Machines that are capable of filling powder, pellets, tablets, micro-tablets, and other forms on one capsule filler give manufacturers flexibility. On-board weight-control systems are capable of measuring and controlling the net fill weight of multiple components in each capsule. These changes are driven by continued changes in market demands

EVOLUTION OF DOSAGE-FORM DEVELOPMENT AND MANUFACTURING STRATEGIES

Anil Kane, executive director, Global Head of Technical & Scientific Affairs at Patheon, shared his perspective of changes to solid-dosage pharmaceutical manufacturing.

PharmTech: What have been the most significant changes in solid-dosage manufacturing in the past 40 years and in the past five or 10 years?

Kane (Patheon): A shrinking new drug-discovery pipeline has led to significant changes in dosage form development and manufacturing strategies, infrastructure requirements, and methodologies. Examples include evaluating existing molecules for newer indications in the same or different therapeutic categories and combining new drug entities with off-patent drug candidates for synergistic effects or other clinical benefits of fixed-dose combinations. Applying a much higher level of process understanding and robustness justification, as required by regulatory authorities, using principles of quality by design (QbD) and a systematic approach, have led to the evolution of fully-instrumented equipment with data capture, sensor feedback loops, and possible real-time release opportunities. Other changes have been increasing automation, documentation control, and training to bring in a culture of quality.

Safe handling of many of the new drugs that are high potent requires fully contained equipment, processes, and systems to safeguard the health of operators. Facilities and environmental controls are now required to be designed around plant personnel safety. Automated, closed-loop product transfers between processes, isolators, and equipment with clean-in-place (CIP) or wash-in-place (WIP) capabilities enable production.

With an aging population, there is a need to have products suitable for geriatric patients. Combination therapies, reducing pill burden, and minimizing the challenge of polypharmacy enhances patient compliance. The need for better and palatable drug products for the pediatric population also requires changes in strategy to manufacture patient-friendly dosage forms for better compliance. Pediatric formats (e.g., sprinkles, mini-tablets, and dispersible tablets), controlled-release dosage forms, and fixed-dose combinations (e.g., multi-layer tablets or multi-particulates in capsules) have driven the need for equipment to support manufacture of these novel dosage forms.

We have also seen early-stage investment and adoption of continuous manufacturing. Drivers include reduced API requirements for clinical and commercial launch, better process understanding and control, and a significant lower cost of commercial goods.

Quality, compliance, and data integrity requirements in the pharmaceutical industry have led to increased automation and documentation control with minimum operator interface. Regulatory submissions now require a much deeper understanding of the process and development of pharmaceutics that justify a robust quality product. Evolution of systems and procedures in drug substance and drug product manufacturing, using a systematic approach of understanding the molecule, utilizing risk assessment, and scaling up the process by first principles and having a mechanistic understanding helps to meet this requirement.

PharmTech: What trends or developments do you foresee for the near future?

Kane (Patheon): The industry will slowly embrace the long-term benefits of continuous manufacturing and will invest in this model to develop clinical and commercial products. Multiple-drug combinations will continue; we have seen two to four drug candidates being combined into a single dosage form, which is convenient to patients and will hopefully improve compliance.

Combining diagnostic devices and drugs (from a technology standpoint and having a clear regulatory approval pathway) will bring several benefits to patients. In addition, drugs have been targeted to specific sites of activity or absorption to enhance the therapeutic effect. Use of biodegradable sensors, imaging techniques, and application of medical/pharmaceutical electronics will help deliver drugs accurately and at a predetermined rate for enhanced efficacy. Ingestible sensors could potentially monitor the compliance of drug administration and also monitor drug misuse. Technological advances such as these can help personalize therapy and delivery of the right drug(s) for improving therapy.

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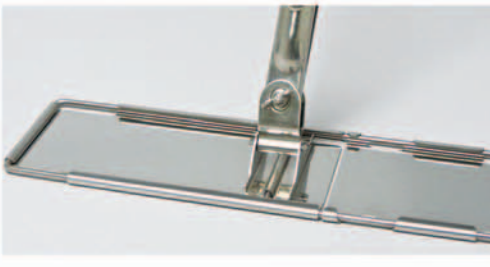

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from consumers and new advances in pharmaceutical development. A new trend in capsule filling technology is the continued push toward continuous manufacturing."

In addition to these new dosage forms, Treitel points to increased yield, using the tamping pin principle as another significant introduction. "Today, powders are dosed on high-performance tamping pin stations with minimal product loss," says Treitel. "Further requirements for capsule filling machines are combination filling, inline weighing systems that offer secure and documented processes, and containment applications in several versions for highly potent active substances. In the past 5–10 years, the focus has been more on small batches and flexible machines, as well as process analytical technology. The pharmaceutical industry is also requesting quicker product change over and shorter cleaning cycles."

Tableting

Tablets were a widely used dosage form 40 years ago and still are today, but the equipment used to make them has been transformed in efficiency, quality, and even safety of operation. Increasing automation and connected, "smart" machines are leading the way into the future, which is likely to see greater integration of tableting into continuous solid-dosage processes. *Pharmaceutical Technology* spoke with Matt Bundenthal, direct sales and communications manager at Fette; Alex Bunting, marketing manager at I Holland; Fred Murray, president of KORSCH; Michael Fazio, sales manager, Batch & Continuous Processing Systems at L.B. Bohle; and Dale Natoli, owner and president at Natoli, about how tableting has changed and what they expect for the future.

PharmTech: What have been the most significant changes in tableting in the past 40 years and in the past five or 10 years? What have been the drivers for these changes?

Murray (KORSCH): The most significant changes in the world of pharmaceutical tableting is related to advancement in drug-delivery methodologies. The focus on simple, single-layer, immediate release therapies has been replaced by a wide range of innovative delivery platforms including bi-layer, tri-layer, and tablet-in-tablet technologies. Most recently, microchip in tablet technology has been developed to improve compliance with critical therapies. Extended-release products, combination products, and the ability to deliver drug substances exactly where and when they are needed have driven these changes. The equipment manufacturers have responded with specialty machines that facilitate these new tablet formats, both for product development and on a commercial scale.

A second significant change is related to the clear focus on operational efficiencies and flexible equipment. Many years ago, it was not unusual to tour a manufacturing facility and see only a small percentage of the equipment in operation. Today, under significant pricing and competitive pressures, there is a major emphasis on overall operating efficiency, uptime, and product yields. The development of new and innovative drug delivery platforms requires flexible equipment that can produce a wide range of product formats, with fast changeover, for maximum utility. Today, a single tablet compression machine can produce single-layer, bi-layer, tri-layer, and tablet-in-tablet products, in combination with an exchangeable turret capability, to facilitate the production of literally any tablet size and format, with high efficiency.

In the past five years, continuous manufacturing has also been established as a viable alternative to batch processing. For some products, continuous manufacturing technology offers significant advantages for new product

INNOVATIONS IN COATING

Harlan Hall, who founded The Coating Place 41 years ago, worked indirectly with Dale Wurster, the inventor of the Wurster fluid-bed coating process, and the protoype equipment he created. Hall shared his perspective with *Pharmaceutical Technology*.

PharmTech: How has the Wurster coating process for pharmaceutical tablets changed over the past decades?

Hall: Prior to the mid-1970s, use of the process was limited to a few companies, mostly coating fairly large particles. In the 1970s, the Wisconsin Alumni Research Foundation (WARF) did extensive work in extending the practical use of the Wurster process to smaller particles (as low as 10 micron) and helped develop a number of new products using this technology. This work continued when Coating Place was founded in 1976 and began providing contract services using this technology. In the mid to late 1970s, equipment manufacturers adopted many of the innovations pioneered by WARF, and coating of smaller particles became more common. Innovations including continuous clean filters and larger expansion chambers became industry standard, and improved Wurster plate design and linear scale-up pushed the state of the art.

The development in the 1970s of taste-masked dosage forms, and particularly chewable and liquid-dosage forms, arose from the ability to manufacture small, coated particles at commercial scale. As equipment to prepare experimental quantities of such particles became more common, more pharmaceutical companies became familiar with Wurster technology, leading to new products. The development of water-based coatings allowed more companies to pursue this work without need to be concerned with control of solvent emissions.

PharmTech: What trends or new developments do you foresee for the near future?

Hall: A number of companies are developing more sophisticated small-particle products that combine small particle technology, multiple functional coatings, and targeted drug delivery. These new developments permit products with sophisticated release profiles and better control of higher potency APIs.

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development and scale-up, increased product quality, and reduced operator intervention.

Natoli (Natoli): The reintroduction of the multi-tip tool has created significant changes in tablet manufacturing. Recent developments in multi-tip tooling include assembly-type punches, which reduce costs by allowing the reuse of punch bodies and repair or replacement of individual punch tips. Vented caps allow the cleaning of punches as an assembled unit and the use of compressed air to remove residual moisture. The development of multi-tip reject verification tools provides the assurance needed by the pharmaceutical industry to validate tablet sizes and weights, making multi-tip tooling a viable option. These technological advances in multi-tip tooling, made within the past 10–15 years, have greatly increased tablet production, which reduces operational costs by saving energy, minimizing labor, and decreasing manufacturing footprints. These benefits are driven by continued pressures from both regulatory bodies and the pharmaceutical industry.

Bunting (I Holland): The requirement for higher productivity and efficiency, while maintaining top quality tablets, has become more prevalent during the past 40 years, and innovations have advanced to keep pace with the ever-growing demand driven by developing markets to produce tablets for the masses. Perhaps one of the major advancements has been multi-tip tooling, which has helped to cater to this demand. Multi-tip tooling has transformed the quantity of tablets produced and it is now considered the most productive form of tablet manufacture where it can be applied. A difference in the past decade is the request for reduced lead times; multi-tip tooling has helped to keep these lead times and allow manufacturers to meet the time-to-market demand.

The influence of developing countries is also a huge driver for change. Due to increasingly strict controls and standards, these countries are aligning with good manufacturing practices (GMP) and regulatory demands, with production volumes increasing at an astounding rate. The developing world must comply to GMP and regulatory requirements to distribute their products globally, which requires major investment in upgrading manufacturing facilities. I Holland is working in these countries to help them develop their processes and products.

Bundenthal (Fette): Changes in tablet press technology can be correlated with the need for a higher degree of control over finished tablet quality, at higher machine speeds; the requirement for presses that can efficaciously compress more challenging formulations; a request from end users for maximum versatility in machine design; and cost-cutting targets, relating to issues such as final yield percentages.

The introduction of pre-compression represents one of the most significant—and useful—changes. It greatly increases overall compression efficacy by helping eliminate entrapped air and reducing the incidence of phenomena such as capping and 'picking.' Real-time compression force monitoring and control, and the subsequent ability to automatically reject out-of-spec tablets, has led directly to increased machine speeds, better quality control, and improved yields. Computer-controlled, recipe-driven machines ultimately improved repeatability across batches, with reduced set-up time. The appearance of motorized feeders (and the elimination of 'open' or gravity feeders)

PERSPECTIVE: CONSOLIDATION SHAPES PHARMA

Jim Agalloco, president of Agalloco & Associates, says technology and outsourcing have both significantly impacted the pharmaceutical industry.

Pharma industry advancements

PharmTech: During the past 40 years, how has the pharmaceutical industry evolved? What advances have been made?

Agalloco: It's gotten smaller; consolidation of firms as well as outsourcing of many of what used to be internally supported activities has dramatically changed the way it operates. Automation and computerization of systems have reduced both manual labor requirements and the potential for mistakes. Data assembly and review has been made considerably easier. An excessive and sometimes increasing fear of regulators has slowed the implementation of new technologies. A general de-emphasis of manufacturing as an important aspect has reduced investment in new technologies and facilities.

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Agalloco: The introduction of the personal computer—led to changes in the means by which data and documents could be assembled, analyzed, and used in ways not previously possible. Isolators—leading toward safer, more reliable, and less expensive production of both sterile and highly potent components. Validation, as a universal expectation, has fostered the introduction of quality-by-design principles in the development, introduction, and continued production of pharmaceutical products.

PharmTech: How have regulations and standards advanced or hindered advances?

Agalloco: [The European Medicines Agency's] over-emphasis on specific numbers in many of its standards has prevented technical advances. Regulations should focus more on 'what to do' rather than on 'how to do' to allow for increased innovation.

The future of Pharma

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Agalloco: Increased used of closed systems for sterile product; single-use disposable for liquids; introduction of continuous manufacturing for larger volume products; and increased use of automated inspection systems.

—Jim Agalloco has been working in the pharmaceutical industry for more than 45 years and has been a member of Pharmaceutical Technology's *Editorial Advisory Board since 2005.*

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improved die-filling characteristics. Enhancements to multi-layer functionality, especially for bi-layer tablets, include dynamic first-layer sampling, prevention of cross-contamination, and weight control for individual layers. Inventions such as removable turret assemblies revolutionized fast changeover. The growth of potent compounds led to high-containment technologies, such as wash-in-place features, glove ports, door interlocks, and rapid transfer ports. And the need for greater operator safety led to additions such as guards and shrouds surrounding turrets, switch-controlled interlocks on access doors, protected discharge chutes, and electro-magnetic brakes.

Fazio (L.B. Bohle): Pharma manufacturing has come a long way in terms of mechanical engineering controls. Over the past 15–20 years, we have experienced a trending demand for highly contained capital equipment; more often, our clients' formulations include a potent API. Contained oral solid-dosage equipment projects can be sophisticated and challenging because process air handling and mechanical interfaces must be more tightly managed. Contained process equipment serves as protection of both personnel and pharmaceuticals products alike.

Automation, process control, and process analytical technology (PAT) has also changed, and has become crucial to ensure high-quality production of pharmaceutical products.

PharmTech: What trends or new developments do you foresee for the near future?

Bundenthal (Fette): Tablet press manufacturers continue to design machines that offer ever-increasing versatility. Another trend is integrating tablet presses into continuous manufacturing lines, using control systems with up- and downstream control 'handshakes.' In addition, features allow presses to 'talk' to and send data to a client's in-house network.

PERSPECTIVE: BIOTECHNOLOGY MOVES INDUSTRY TOWARD PERSONALIZED MEDICINE

Mike Arnold, board chair of the International Society for Pharmaceutical Engineering (ISPE), discusses how the introduction of biotechnology has pushed the industry in the direction of personalized medicine.

The evolution of Pharma

PharmTech: How has the pharmaceutical industry evolved since ISPE was founded in 1980?

Arnold (ISPE): In the 1980s, the advent of biotechnology marked the beginning of the industry's transformation. Biotechnology has contributed to the discovery and manufacture of large-molecule pharmaceutical drugs, and the development of biosimilars. Today, biotech commands significant market share and is driving the development of modern pharmaceutical manufacturing technologies and practices.

Equally significant has been the impact of globalization on the industry, including the ability to reach greater numbers of patients. The resulting market and supply-chain complexities have accentuated the need for development of global standards in regulation and quality, as well as the need for greater transparency and quality oversight.

PharmTech: What do you foresee for the next 10 years in pharma innovations?

Arnold (ISPE): Medicine will become more personalized as biotechnology evolves; patients will reap the benefits of technological innovation. Enter the world of 'Patient Centricity'. The world will become more 'flat' and regulatory operations will become more harmonized.

Biotechnology will have hit its stride and with it modern pharmaceutical manufacturing technologies and practices. It is easy to imagine that pharmaceutical manufacturing professionals will move away from treatments and progress more toward cures.

The evolution of ISPE

PharmTech: How has your organization changed over the years?

Arnold (ISPE): In 1980, a few North American engineers who believed the industry needed an organization that would deal with practical applications of science and technology for technical professionals founded ISPE. Almost four decades later, membership is global, and has expanded beyond engineering to include broad representation from pharmaceutical professionals and regulatory agencies. ISPE's mandate has evolved. Our solutions help members manufacture quality medicines for patients, by providing rapid access to information, driving efficient manufacturing operations, and shaping issues of local and regional relevance. On the regulatory front, we focus on facility licensing, manufacturing processes, quality operations, and supply chain sustainability.

PharmTech: How has your organization influenced the pharma industry?

Arnold (ISPE): ISPE is a collaborative organization that pursues knowledge on behalf of its members. Knowledge sharing and collaboration are its goals. ISPE's conference program and Training Institute offer participants access to the best and most innovative thinkers, teachers, and trainers. ISPE executives work with regulatory agencies and industry organizations to research, and understand drug shortages, quality metrics, quality culture, data integrity, and assist in the drive toward harmonized global regulatory expectations.

Through our relationships with members, regulatory agencies, and life-science professionals around the world, we hope to influence progress in all facets of modern pharmaceutical manufacturing practice.

PharmTech: How is your organization planning to grow and affect the industry in the next 10 years?

Arnold (ISPE): ISPE recognizes that helping the industry involves more than training and tooling its people in the basics of facilities and equipment, production systems, and quality systems. We intend to strengthen our position as the go-to organization for knowledge regarding designing, building, and operating pharmaceutical plants across all technology platforms. We will continue to respond head-on to evolving industry challenges by fostering knowledge exchange and related professional development that is focused on achieving results. Through our efforts, we will improve the quality of life for patients worldwide.

Fazio (L.B. Bohle): Continuous processing is a developing manufacturing platform for the future. We have experienced an increasing number of end-user pharmaceutical companies evaluating their drug candidates on our fully continuous manufacturing line in our Pharmaceutical Technology Center, which was built in 2014. Pharmaceutical manufacturers and FDA see merit in and support the evolution of pharma manufacturing from batch to continuous because of inherent features, such as smaller footprint, faster and less costly scale up, flexible batch sizes, and improved quality.

Natoli (Natoli): As the industry works toward continuous manufacturing, tool-to-die clearances will become even more critical in the near future. These tolerances will necessitate tooling to be engineered to meet the needs of specific powder characteristics and particle sizes. Furthermore, current estimates indicate that only 15–20% of the pharmaceutical industry use multi-tip tooling, and we predict that this usage will increase due to its advantages.

Bunting (I Holland): The pressure for shorter lead times and cost efficiency is leading companies to investment in new technologies and processes. On top of this, stringent quality requirements drive the need to improve production from end to end, through durable tablet tooling and the associated maintenance equipment.

The adoption of continuous manufacturing, I think, will be an important trend in the future and one which will help in reducing reaction time and time to market. The challenge, then, is for the upstream and downstream processes to keep up with each other. In the case of a quality tooling manufacturer, we continue to develop even more ways to maximize uptime by producing solutions to problems that compromise the maximum output and yield. I Holland is working toward this goal with the introduction of XDF (eXtended Dwell Flat), a novel, patented, elliptical head form which has been designed to increase dwell time on existing presses without the need for expensive modifications. As the importance of increased productivity continues to grow, XDF can give users higher press speeds for challenging products and formulations, enhancing tablet compaction and cohesion.

Murray (KORSCH): These trends of more complex drug delivery platforms, and an increased emphasis on operating efficiencies will continue. The use of continuous process technology will also be more widely used and accepted. From an equipment perspective, tablet compression machines are going to become smarter and more connected. They will self-diagnose, include on-board help systems to guide the user through every aspect of the operation and maintenance, and be fully integrated to central SCADA [supervisory control and data acquisition] and manufacturing execution systems. They will monitor and report on operating efficiency, and leverage new technologies to permit remote support by service experts.

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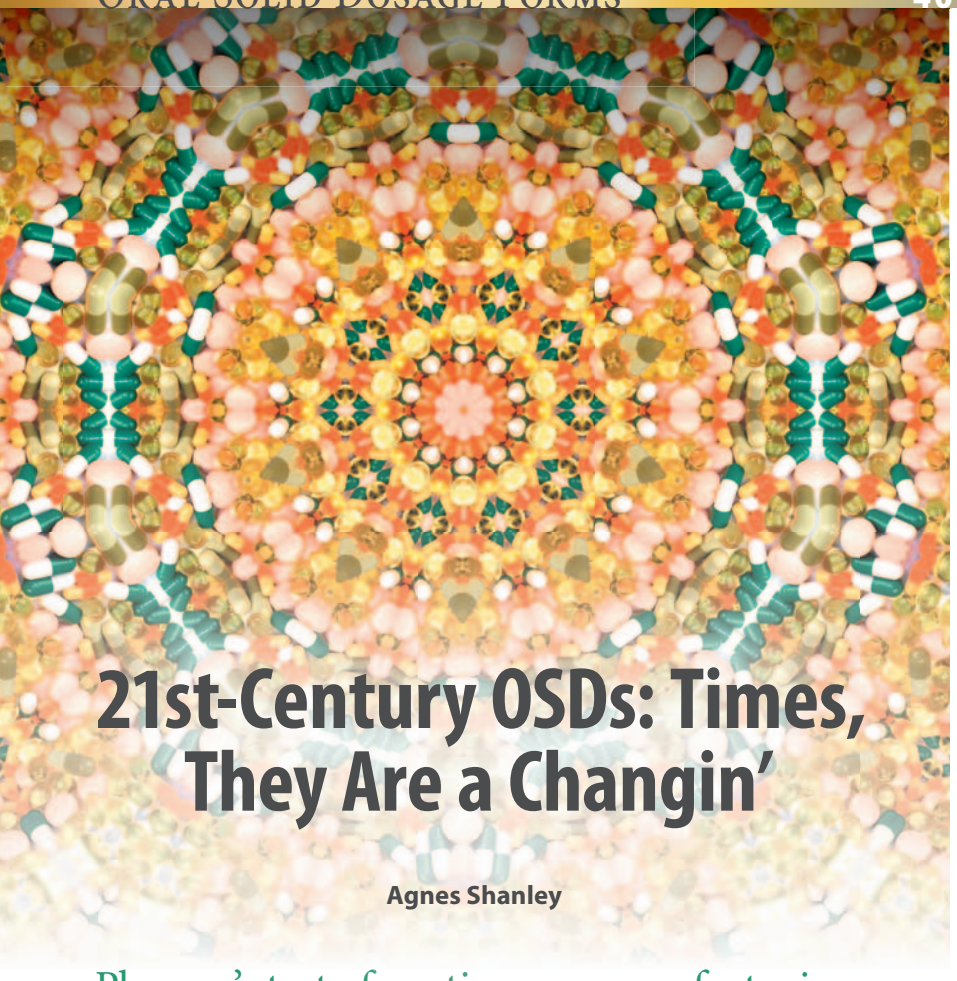


21st-Century OSDs: Times, They Are a Changin'

Agnes Shanley

Pharma's test of continuous manufacturing is starting with oral solid-dosage forms.

FDA's current good manufacturing practices for finished drugs were first published in 1963 (1), a year before Bob Dylan's song captured the spirit of change that was to define the decade. GMPs would become law in 1978. At most pharmaceutical facilities, however, little had changed since the 1950s, with the same manufacturing processes and equipment, and the same test-centered approaches to quality assurance.

Decades later, pharma has remained in that same time warp, as Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), said at the American Association of Pharmaceutical Scientists' annual meeting in 2011 (2). She shared predictions that pharmaceutical manufacturers would spend the next 25 years moving to cleaner, flexible, and more efficient continuous manufacturing. Years earlier, FDA had established a framework based on statistics, multivariate analysis, and more advanced process control, to help them reach this goal (3).

Nobody wants to be first

Six years into that transformation, change may be more of a trickle than a flood, but it is starting in oral solid-dosage-form (OSD) facilities, as more companies explore alternatives to batch manufacturing. "In manufacturing, nobody in pharma wants to be the first to introduce anything new," says Dave Di Prospero, director of pharmaceutical process technology at CRB USA and cofounder of the International Society of Pharmaceutical Engineers (ISPE)'s OSD Community of Practice. "But, with FDA approvals of new continuously manufactured drugs by Vertex, and the transition of a legacy therapy from batch to continuous by Johnson & Johnson's (J&J) Janssen Pharmaceuticals, more companies are getting on board with continuous processing," he says, "so the 'first' is now behind us." The European Medicines Agency approved Janssen's continuous line for Prezista (Darunavir) in June 2017, a year after FDA.

Continuous processing is being used at Novartis, which first brought the technology into mainstream conversation with its 10-year, $65-million research program with the Massachusetts Institute of Technology, as well as Pfizer, Merck, and GlaxoSmithKline.

Contract manufacturers are also investing in continuous. Patheon, for instance, completed a continuous manufacturing facility in Greenville, NC earlier this year, appointing former Rutgers post doc and Janssen process engineer Eric Jaycock (4) as director of continuous manufacturing. "I thought they would be the last ones to grab hold, but CMOs want to offer continuous processing as a service, and view it as a competitive advantage," says Russ Somma, principal of Sommatech Consulting. "Having CMOs in the game allows more manufacturers to dip their toes into continuous processing without risky investment," he adds.

Reducing cost of goods

Generic-drug manufacturers are attracted to continuous, based on its potential to reduce the cost of goods, as well as plant footprint, staffing, raw materials, and solvent requirements, says Bayan Takizawa, an MD and chemical engineer, cofounder, and chief business officer of CONTINUUS Pharma, a spinoff of the MIT-Novartis partnership whose goal is to help more companies understand and harness the benefits of continuous processes. The company offers its Integrated Continuous Manufacturing (ICM) platform (**Fig. 1**), which encompasses continuous production, from raw materials and APIs through finished dosage forms, and was developed through the MIT-Novartis partnership. "Generics margins are signifi-

cantly lower than those of big pharma, so even if we can reduce cost of goods by 30–50%, that's a huge impact," he says.

Both high and low-end benefits

Pfizer is using continuous on both extremes of the value spectrum, reducing throughput and costs for some of its high-volume generic APIs, but also for high-end products including personalized therapies. "Inherently, you have to understand the process better in order to manufacture continuously than you do in batch, so you have to work harder upfront and invest more during the R&D period with continuous," says Kevin Nepveux, vice-president of global technology services at Pfizer, "but it pays off in a more reliable process."

"Agility also becomes more important with personalized therapies," he says. "And with semicontinuous you can reduce lead time by 50% or more, so you can respond to accelerated approvals or changes in market demand."

Second approvals spike expected

Over the past few years, adoption of continuous processes had increased at a lower than expected rate, says Pamela Docherty, life-sciences industry manager at Siemens. However, she notes that more pharmaceutical companies are now working on continuous processes for legacy products, while more equipment vendors are offering solutions designed for continuous operations. Within the next two years, she says, these changes, plus a growing number of continuously manufactured products in R&D, should result in a second spike in approvals of continuously manufactured drugs that could lead to exponential growth.

By working with academic consortia and pharmaceutical companies, equipment manufacturers have become important partners in the move to continuous processing. "We've gotten to where we are now through collaboration involving pharmaceutical companies, equipment vendors, and academia," says Di Prospero.

GEA Pharma Systems, which entered the continuous area in 2003, established a joint venture with Siemens in 2016, leveraging the SiPAT analytic software and Siemens' advanced process control platforms, together with its continuous OSD platform, ConsiGma, which is already being used by a number of big pharma companies. The system integrates raw material dosing and blending, wet or melt granulation, drying or cooling, tableting, and coating on one line, with online quality control built in. Other equipment vendors that are active in continuous include L B Bohle, Glatt Process Systems, and IMA, a tablet press manufacturer based in Italy, which is an investor in and strategic partner with CONTINUUS Pharmaceuticals.

Issues and challenges

Obstacles remain to industry's adoption of continuous, however. There are some lingering doubts about regulatory support, as well as technical challenges, particularly around real-time release testing (RTRT) (see **Sidebar**).

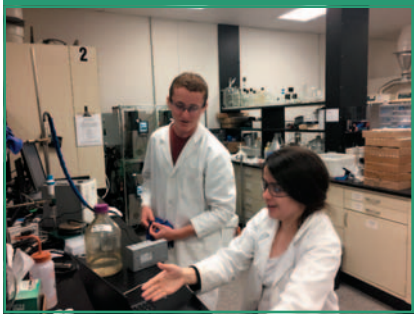
On the practical side, there is also a need for equipment designs that would speed cleaning and product changeovers at continuous lines. In some facilities, it can take several weeks to tear down, clean, and set up a continuous line, says Di Prospero.

Case by case, or end to end?

Novartis and MIT envisioned homogeneous, end-to-end continuous manufacturing in their research, and Novartis is working on an end-to-end continuous facility in Basel, Switzerland. Upstream, continuous processes are being developed for APIs (see **Sidebar**), and for biopharmaceutical manufacturing.

"Implementing the end-to-end approach is really challenging, from the technical but also from the corporate side, and it's unlikely that we'll see more than a handful of companies taking this approach in the next decade or two. It's simply too front-loaded from a cost perspective, and there's too much product-specific complexity to be addressed to allow the business case to work out," says Doug Hausner, associate director of the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) based at Rutgers University in New Jersey.

Figure 1: Engineers at CONTINUUS discuss requirements for a continuous pharma installation.



C-SOPS (**Fig 2**) has been around for 10 years now, collaborating with industry and regulatory agencies, and has transferred continuous process knowhow to industrial partners including Janssen, which collaborated with C-SOPs on the continuous direct compression process that it uses at its facility in Puerto Rico (5). Hausner expects continuous to be developed, first, for OSD and then for APIs, but sees limited instances where there will be a clear business case for integrating the two.

Each company's decision whether or not to adopt continuous processes, and where to use them, will be based largely on its tolerance for risk, says Takizawa. Most companies today are taking a case-by-case strategy.

Adoption will also depend on how opportunities arise, says Jamie Clayton, operations director at Freeman Technology, a UK vendor of powder flow characterization technologies. Many different configurations are possible, involving combinations of continuous, semicontinuous, and semibatch systems, which can all be considered some form of continuous processing. "In some cases, companies may use continuous process equipment for unit operations as discrete elements within a larger overall batch process," he says.

Processing advances

On the process side, continuous processing has intensified interest in di-

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FIGURE 1 COURTESY OF CONTINUUS PHARMACEUTICALS

Single-Vendor CDMOs Bring Speed and Cost Savings to the Table

Anil Kane
Executive Director and Global Head of Formulation Sciences
Patheon

Robert Fry
Chief Economist
Robert Fry Economics, LLC

Paul Nelson
Vice President of Supply Chain and R&D
Amring Pharmaceuticals

Doug Johnson
President
OCAM Solutions, Inc.

As drug developers face the ever-pressing need to get molecules to market as efficiently as possible, firms large and small are increasingly turning to CDMOs for help. The CDMO industry is evolving to meet this need, spurring some larger providers to offer forward-thinking services in the form of end-to-end supply chain models for pharmaceutical and biopharmaceutical clients.

At a panel discussion held at CPhI North America 2017 in Philadelphia, four industry experts discussed how working with a single-source CDMO partner can accelerate time to market, add cost savings, and improve a formulation's chances of achieving regulatory success.

Speed and the Single-Source Model

According to Anil Kane, executive director and global head of formulation sciences at Patheon, speed is essential in drug development. Patients need their medications, and competitors are vying to get their products to market first. Working with even more compressed timelines are firms racing toward commercialization with life-saving therapies that have fast-track status. Likewise, small biopharmas deal with incredible time pressure as they function in a market-driven environment.

Unfortunately, a multi-vendor approach often adds more time and effort than many firms would like. Drug developers need to negotiate numerous vendor contracts, complete technology transfers, conduct revalidation, and complete other time-consuming tasks.

Compare this approach to a single-source vendor option, which has the unique ability for both drug substance and drug product teams to collaborate from development through commercialization, representing a major shift in the drug development world. Aligned services in end-to-end supply chains include the development and optimization of drug substances and products; the manufacture of supplies in batch through commercial sizes; clinical and commercial packaging; supply chain management; and more.

Because cross-team collaboration allows for real-time feedback about both the drug substance and drug product, one can move efficiently from an API to a drug product with fewer errors. Potential problem areas (like poor solubility, bioavailability, or process-ability) can be worked out before the process is scaled up. If formulation problems are caught in early development phases and work is completed to understand the molecule and its characteristics, developers will benefit from more robust process development that avoids costly and time-consuming "re-dos" during scale-up.

Other time-savings that surface when all aspects of a project lie with the same vendor are those associated with external technology transfers, vendor qualification, negotiations, and follow-up. All these activities are eliminated on the client end. According to one CDMO, its trademarked single-vendor network "eliminates 8–12 weeks of development time for small molecules and 14–20 weeks for large."[1]

While the single-source CDMO option may well be a forward-thinking approach in the world of pharmaceuticals and biopharmaceuticals, there is a strong precedent for it in other manufacturing sectors. For instance, Robert Fry, chief economist at Robert Fry Economics, LLC, explained that Toyota's lean manufacturing model limited the number of suppliers it worked with so that the car maker could produce new models much faster than its competitors.

Breaking Down Barriers: Communication in a Single-Source Model

A single vendor offers access to a network of experts across several disciplines who can share knowledge about a project as a molecule moves from phase to phase, thus helping to ensure it stays on a path toward commercial success.

Paul Nelson, vice president of supply chain and R&D at Amring Pharmaceuticals, offered an example of how having such knowledge through a single vendor could have benefited a recent R&D project he worked on. Several molecules in his pipeline had development work completed in India while the manufacturing activities were conducted in France. The project came to a halt after the first pilot batches were made poorly. An investigation was launched to determine the source of the problem, probing the possibility of a development issue, tech transfer problem, manufacturing issue, or something else. The time-consuming process caused a significant delay.

If the development and initial manufacturing work had both been done by a single vendor, the problem may not have occurred. But if it had, the open channels of communications that a single provider offers would have made identifying the root cause of the issue much easier.

Doug Johnson, president of OCAM Solutions, Inc., adds that communication in a single-vendor network helped fix a major problem his client had with an API. Had the client used multiple vendors, resolving the issue would have required breaking a commitment with one manufacturer and starting a new contract with another vendor. Rather, the single-source vendor was responsible for figuring out how to remedy the problem with the API because it was their work to begin with.

A single vendor with involvement in a project from soup to nuts has a unique opportunity to help their client by integrating information that is generated from all points along the project continuum. "A single vendor can leverage expertise typically stashed in silos across different stages of the process, from API development to formulation and the supply chain," noted Kane.

For example, in the Patheon OneSource™ model, a single program manager oversees all activities, and bridges various teams and sites performing the work. Having a program manager so close to the client and the operations brings efficiency and speed to the process.

Nelson agreed that this type of program management strategy can be key to a project's success. Decisions on sourcing of API development and subsequent manufacturing are usually made before an application for regulatory approval is filed. Many companies do not have the coordination needed to determine where final commercialization will be done at the time they are getting ready to file. A program manager can facilitate good coordination and look at the value stream that cuts across all business units and functions.

Due Diligence: Selecting the Right Partner

When helping pharma clients evaluate single-source vendors, Johnson said he looks for four must-have characteristics: capability, flexibility, stability, and caring.

- A variety of capabilities are essential for helping to improve a process and elevate a compound from early-stage work through commercialization. When trying to make a good match between what a client is looking for in an outsourcing partner and the CDMO's capabilities, Nelson added that the process is as much an art as it is a science. Several CDMOs may all have similar equipment, but what really differentiates them are the dedication and knowledge of the individuals working on the projects. Is that know-how and capability embedded in the organization? In some cases, clients have been burned by the claim that an outsourcing partner had competencies in areas it did not.
- Without fail, unexpected twists and turns will surface during drug development. A CDMO's flexibility is critical, especially in early phases. Firms should have the dexterity to address unanticipated problems quickly and adjust.
- The vendor cannot simply provide a service; they must have a track record of providing services well. CDMOs ted to acquire other companies with expertise in a specific area. A single-source vendor must also be reliable and stable—fiscally and in terms of longevity, all while putting out high-quality work.
- Larger CDMOs may be working on hundreds of projects simultaneously, but a good partner also ensures every client receives the attention it deserves.

If a client pays more to have these four elements in a single provider, Johnson said it is money well spent in exchange for time saved and a better end-product.

Streamlining from the Start: One Vendor, One Contract

A key advantage of the single-vendor network is that clients will only have one contract. Having to negotiate contracts and legal agreements with multiple vendors requires a lot of time and energy—even if just two suppliers are involved. Nelson said he has seen contract negotiations between two vendors working on the same project take as long as 18 months to finalize. This, of course, takes time away from doing more valuable tasks, thus the single-source provider is far more efficient in this respect.

When negotiating a contract with a single supplier, it is critical to get the language right. From the stance of an economist, Fry said incentives must be balanced such that both parties benefit from doing the right thing. It is crucial to consider all contingencies and to cover all the bases. For example, is the client protected if the price of raw material sharply increased?

Nelson noted that risk management is also important when looking at an end-to-end supply chain. There is economic risk, the change of a supply interruption, and even location risk, for instance, if the vendor is in a hurricane zone. All types of risk must be examined to build the best risk-management strategy.

Summary

Like any new technology, some pharmaceutical companies are still hesitant to adopt the single-vendor sourcing model, especially small, emerging firms. While some companies are taking a watch-and-wait approach to see how the single-vendor concept pans out, those that are already embracing it are reaping the benefits of efficiency and expertise.

i Patheon OneSource™, www.patheon.com/onesource/index.html, accessed June 1, 2017.

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Figure 2: Post-doc engineers at Rutgers' C-SOPS work on process development.

rect compression, a simpler and less energy-intensive OSD process than dry or wet granulation, which involves the addition of liquid, high-shear granulation, and drying, says Hausner.

Continuous eliminates the need for scaleup, one of the biggest bottlenecks in drug development, allowing manufacturers to move more nimbly into clinical and commercial production. "With continuous, you don't scale up; you scale out, by extending your processing time, which can save a lot of money," says Takizawa.

Eli Lilly, which has also collaborated with C-SOPS, is using direct compression at two identical GMP facilities, one in Puerto Rico and another in Indianapolis, where a third development facility is based. As Hausner explains, the three facilities are identical down to the software, except for a refill system on the commercial production line.

The company's strategy is designed to leverage information at earlier development stages, and streamline process development. "As soon as they get a new molecule and have enough material available for experimentation and process development, they can do development and have the commercial process figured out by the time Phase II clinical trials begin. This way, they've minimized variability within clinical trials, and, if and when the drug is approved, they'll be ready to go," says Hausner. The twin GMP plants won two category awards at the 2016 International Society for Pharmaceutical Engineers (ISPE) Facility of the Year Award program (6).

Understanding wet granulation

Advances are also being made in continuous wet granulation, aided by research collaboration with equipment manufacturers. GEA has been working with academic consortia and pharmaceutical manufacturers in this area.

Vertex uses continuous wet granulation, while Pfizer uses both continuous direct compression and continuous granulation. The company worked with GEA and other equipment vendors on a

CONTINUOUS API MANUFACTURING

A growing number of companies around the world are using continuous processes to make small-molecule APIs. "There's more potential for continuous with APIs, just from a cost standpoint, than for drug product," says Kevin Nepveux, vice-president of global technology services at Pfizer, which is taking a hybrid, or case-by-case approach to continuous API and oral solid dosage (OSD) form manufacturing.

"There is a lot of value to using continuous to telescope API steps and replace traditional steps that are bottlenecks or safety risks," he says. "And you can do a lot of chemistry in flow cells that you wouldn't want to do in a batch environment, just for safety and process control reasons." One application would be flow hydrogenation for catalytic hydrogenations, while opportunities also exist in continuous crystallization and drying, he says.

The need for safer API production is driving demand for industrial-scale continuous chemical reactors, says Yi Jiang, global business director, Corning Reactor Technologies, which has developed continuous Advanced Flow Reactor (AFR) products for use in API and fine-chemical manufacturing.

Corning began developing the technology in 2002 and has improved it, Jiang says, to the point where, compared with traditional batch reactors, AFR reactors can enable at least 100 times enhancement in mixing and 1000 times improvement in heat transfer performance, allowing operating cost reductions of 30–40%. "Continuous flow technology has redefined reactor productivity," says Jiang, "so that it is no longer based on volume of output, but on how effectively the chemical is processed." Continuous also speeds up and simplifies API scale up, just as it does for OSD.

Corning's AFR has been recognized as an inherently safer technology (IST), says Jiang, and Corning has been seeing increased demand for the technology, particularly in China. The Chinese government has mandated increased chemical reactor safety since 2016, when a major explosion at one facility in Tianjin killed more than 160 people.

Recent years have seen growing worldwide demand for industrial-scale APR equipment, says Jiang. In October 2016, the API manufacturer Angelini Pharma, installed an industrial-scale AFR reactor at its facility in Aprilia, Italy (1). Demand is particularly strong in India and China, which are producing more of the world's APIs. AFR is installed at the top 10 API manufacturers' facilities in India, says Jiang. "There is a clear need for inherently safer technology which will continue to drive growth, but in a greener way that reduces environmental impact," Jiang says.

Could end-to-end take off in developing markets?

Where integrated facilities might not always make economic sense in the United States and Western Europe, there are questions about whether end-to-end continuous processing facilities might take off in developing markets. A number of countries are requiring that more drug substance be developed onshore and integrated with drug product manufacturing.

Dave Di Prospero, director of pharmaceutical process technology at CRB USA and cofounder of the International Society of Pharmaceutical Engineers (ISPE)'s OSD Community of Practice, recalls Kalbio Medika, an Indonesian company that won honorable mention at ISPE's 2017 Facility of the Year awards program for its new biopharma API facility (1). Even though the facility manufactures biopharmaceuticals and is not completely continuous, the reasons for its design reflect Indonesia's goals to have more of its pharmaceutical supply chain located on shore. Indonesia manufactures 70% of its fiinished drugs, but still imports 90% of raw materials, and the government wants its drug manufacturers to make more ingredients onshore, says Di Prospero.

— Agnes Shanley

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MOVING TOWARD REAL-TIME RELEASE TESTING

One challenge that continuous processing faces is the difficulties of developing real-time alternatives to dissolution that would allow real-time release testing (RTRT), promised years ago by FDA's process analytical technology (PAT) initiative, to be used with continuous manufacturing.

Progress has been made for more straightforward products, and Janssen Pharma is expected to file a post-approval change including RTRT for its continuous facility in Puerto Rico, according to Doug Hausner, associate director of the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), which helped Janssen develop the approach.

"The industry has made progress in developing process models, establishing a foundation for inputs and outputs to the system, understanding what needs to be controlled and modeling that," says Hausner. "Manufacturers have also gained an understanding of how PAT fits into that picture, how much time you have to make a certain measurement and where that information needs to go." Without a model for dissolution, however, you may be doing quality assurance (QA) online, but you aren't truly releasing product in the regulatory sense, he says.

Offline methods

Currently, the only method widely applied in dissolution testing is the offline laboratory-based method of dissolving samples in heated, agitated liquid baths and drawing samples for spectral transmission analysis, says Chris O'Callaghan, senior product manager at Innopharma Technology, which develops near infra-red (NIR) PAT and visualization systems.

"As a method, dissolution is right up there with reading the entrails of goats," says NIR spectroscopist Emil Ciurczak, principal of Doramax Consulting. "We want to know whether a tablet or capsule will break if moisture changes and whether it will extract and be available to the body. There's a very tenuous dotted line between releasing in a 900-mL flask and blood levels. The testing is clinically done once, but they don't really know, if after six months or a year if it changes, short of doing clinical studies on older batches," he says.

While a clear need exists for an in-line real-time alternative to this method, development in the field has been limited, says O'Callaghan. The physical and chemical interactions governing the *in-vitro* dissolution process are highly complex and cannot be easily modeled from first principles based on the product data that are available inline, or accelerated in a way to make the testing applicable in-line, he says.

This leaves model-based prediction of dissolution performance based on measurable process parameters and critical quality attributes (CQAs) as the only possible real-time method available. Approaches using spectrometry or particle size have been discussed, but haven't yet been widely adopted, due in part to the difficulty of modeling.

Innopharma has been collaborating Glatt and other technology vendors who work in the continuous processing space, to develop models that would enable real-time prediction of the release profile of a coated multiparticulate material in controlled-release formulas (1). The company is now working to improve and expand its predictive model, says O'Callaghan (Figure).

"The effects of multiple key processing parameters on the relationship between coating thickness and release profile are being studied in order to develop a more comprehensive dissolution prediction mechanism," he says, noting that this would be a key control element for a new self-guided coating control system that the company is now developing. "The coating's aim is to reduce waste and improve the speed in manufacturing of modified release products by aiding to maintain an optimal coating trajectory and rapid determination of the process end-point, with the ultimate goal of enabling true real-time release," says O' Callahan.

Figure: An Innopharma Labs researcher at work. The company is developing models to predict dissolution testing results in real time for controlled release formulations.

Advanced manufacturing: the next stage

The next stage of evolution will see pharma adopting advanced manufacturing techniques, for both batch and continuous, says Ian Jones, Innopharma's CEO. "When we talk about advanced manufacturing, we think of the Industrial Internet of Things (IoT), Industry 4.0, machine-to-machine connectivity, and the adoption of artificial intelligence philosophies. All of these components can be used to develop and manufacture formulations in a more rapid, lean, and safe manner," he says.

"In order for there to be a real opportunity for real-time release to be realized, these PAT techniques need to be combined with control models thereby enabling predictive control of these dynamic batch and continuous processes," Jones says.

The company is now working to develop self-guided granulation and coating, and demonstrating their potential use in 'hands off' manufacturing at the company's pilot plant in Dublin. "We can track CQAs of the process using our PAT tools, track and control the process in accordance with a model and activate the phase changes and endpoint based on our tools and models, monitoring progress from a mobile phone in real time," says Jones.

Process signature is key

On a more basic level, for RTRT to take shape throughout pharma, the industry will have to change the way it views control. "Manufacturers have to understand that the process signature is key, and not the measurements and numbers you got out of the operation. Process signature shows that process is where it belongs, and that's where RTRT comes in," says Russ Somma, principal of Sommatech Consulting, noting that some companies are already at this point. "When they aren't, it's often because quality organizations are not comfortable with that approach," he says.

Where dissolution testing is concerned, Somma worries about whether it will be used for process control, or for the patient. "In the end, the therapeutic window on a particular compound could be a lot wider, based on pharmacokinetics, than dissolution allows, and dissolution may have no direct relevance on effect, if, for example, the drug is very soluble," Somma says.

With a poorly absorbed compound, however, the problem becomes more complex. "Until we get *in-vitro in-vivo* correlation really working well, we still have a lot of work to do," he says.

— *Agnes Shanley*

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FIGURE COURTESY OF INNOPHARMA LABS.

proprietary mixing platform that blends multiple ingredients and sizes particles continuously. It includes an automated weigh dispense system, continuous mixing, and continuous granulation allowing users to go from weigh dispense to mixing/granulation to a tablet press. Nepveux and his colleagues plan to add a few more unit operations to Pfizer's continuous portfolio. "We can select all or parts of the platform to use, depending on the product," he says, "and it will be the main way that we develop innovative OSD, and transfer legacy products from batch to continuous when it makes sense."

In one project (6), GEA and Freeman Technology used QbD principles to see how raw material properties influence granule properties in a wet granulation, and how granule properties then determine critical quality attributes in tablets, says Clayton. Using Freeman's FT 4 powder rheometer and GEA's ConsiGma 1 high-shear wet granulator, studies showed a direct relationship between bulk flow properties of granules and tablet hardness.

"We've done quite a lot of work with dry and wet granulation, to learn how granulate properties can be targeted by adjusting critical process parameters, and how granule properties can then be linked to the critical quality attributes of tablets," Clayton says. The company is currently marketing Lenterra flow measurement tools, which are process analytical technology (PAT) devices that can measure drag force and wall shear stress to monitor processes inline or define optimal process parameters or granulation endpoints.

Improving material feed systems

Some of the most important advances in continuous OSD have come on the feed side, says Di Prospero, because it is important, but challenging, to achieve a good feed of ingredients, including API, in a controlled and accurate configuration. Lilly spent a considerable amount of time perfecting this technology, he says. Accuracy is improving as more is understood about how the physical properties of raw materials effect the process (7), and vendors are offering solutions designed for continuous processes, such as Coperion K-tron's smart refill technology, which uses an algorithm to store and trend weight to speed measurements (8).

GEA, meanwhile, has incorporated better feeding mechanisms in its integrated continuous equipment designs, such as ConsiGma. Miniaturization and close integration have enabled major improvements in equipment design, across the board, says Richard Steiner, business development manager for pharma applications at GEA.

Facility advantages

One of the biggest attractions of continuous processing is the reductions in facility size and layout that it permits,

PROCESS VALIDATION EVOLUTION—THE LIFECYCLE APPROACH

FDA issued the guidance document *Process Validation: General Principles and Practices*, which formalized the lifecycle approach to process validation in January 2011 (1). This document represented a significant evolution of thinking on validation, updated FDA expectations for process validation, and integrated other contemporary pharmaceutical manufacturing principles. The lifecycle approach to validation described activities categorized in three integrated stages that encompass the entire product continuum from development through commercial product discontinuation. The following discussion briefly describes events leading to development of the lifecycle approach, and proposes some future applications of this approach.

Validation evolution: Origin to future

The origins of validation may be traced to the Elixir Sulfanilamide tragedy in 1937, when an improperly prepared medicine caused more than 100 deaths. This tragedy caused passage of the 1938 Food, Drug, and Cosmetic Act (FD&C Act), which granted FDA more jurisdiction over drug products. The FD&C Act authorized facility inspections; later an amendment allowed inspectors to examine records connected with manufactured drugs.

cGMPs. The next major timeline event specifically involving validation occurred in the 1960s and 1970s leading to publishing of the Current Good Manufacturing Practices in 1978 (2). While the term "validation" was freely mentioned in FDA discussions during this timeframe, definition, expectations, or applications were not explained. Preliminary discussions introduced concepts such as product design, protocols, acceptance criteria, qualification, documentation, and statistics—fundamentals of validation. A GMP for large volume parenterals was proposed that focused on sterilization, water systems, HVAC, and other systems to be prospectively demonstrated to operate as intended. Efforts then shifted to non-aseptic products and processes. Industry discussions and workshops helped to further develop validation thinking. Retrospective and concurrent validation approaches evolved, and the "three-lot" concept was born. A definition of validation was finally proposed that focused on the essence of validation: Documented evidence that the system does what it is supposed to do. The validation concept was definitely evolving.

The first FDA validation guidance. FDA issued *Guideline on General Principles of Process Validation* in 1987 (3). While this guidance and subsequent related documents mentioned the importance of product development and ongoing commercial post-validation manufacturing, the emphasis of validation was on the three documented validation conformance lots. The 1987 guidance briefly mentions "... adequate product and process design ...", "... quality, safety, and effectiveness must be designed and built into the product...", and "During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, electrical, and performance characteristics." In addition to discussing actual validation protocols, the guidance mentions several post-validation considerations as follows: "...quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact product effectiveness or product characteristics, and whenever there are changes in product characteristics." Also, "The quality assurance procedures should establish the circumstances under which revalidation is required."

FDA validation guidance 2011. Significant changes to the 1987 validation approach and introduction of a formalized lifecycle approach evolved during the 2000s. It had been long realized that manufacture of three validation lots was not sufficient to ensure successful product manufacturing throughout a product's commercial lifetime. A new approach addressing the totality of manufacturing was needed. Process validation was newly defined with focus on data from the process design stage throughout commercial production. Process validation stages were clearly identified; in brief, Stage 1–Process understanding; Stage 2–Process demonstration; and Stage 3–Process monitoring to ensure continued successful performance. The lifecycle approach to process validation is a significant paradigm change compared to the 1987 approach. The 1987 approach emphasized documentation of the demonstrated (three lots) process; the 2011 approach emphasized Stage 1 understanding and Stage 3 monitoring. Stage 2 was realized to be a "snapshot in time" providing little assurance of the repeatability of the manufacturing process. The new Stages 1 and 3 emphases necessitated ongoing organizational integration of development and support staff with the quality function to ensure manufacturing control for the entire product lifecycle.

Future. Validation practitioners have already proposed use of the lifecycle approach in other pharmaceutical applications. Other processes such as cleaning, packaging, and analytical should follow the understanding-demonstration-monitoring validation stage approach. Equipment, facilities, utilities, computers, and similar systems should also be addressed by a lifecycle approach. Equipment systems that comprise processes such as HVAC systems and water systems should be addressed as validated processes. Finally, quality systems should be designed as business processes and addressed in process design, demonstration, and ongoing monitoring of performance. Applying a lifecycle approach to the aforementioned applications with corresponding stages has a further benefit of unifying divergent approaches to validation within the organization.

Final thoughts

This brief discussion has summarized the evolution of validation origins to potential future applications. The latest stage, the lifecycle approach as described in the 2011 FDA guidance, is truly a seminal document that has already profoundly influenced validation practice and will continue to do so in new applications in the future.

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says Di Prospero. In a typical batch processing facility, dispensing, granulation, milling, blending, compression, coating, and sub operations are running, each requiring a room and additional support spaces, he says. In a continuous facility, they are linked together and can fit in a single room. "We've seen square footages go from 30,000 to 40,000 down to 3000 or 4000 with continuous," he says. "And with reduced footprint comes reduced utility requirements and less heating, ventilation, and air conditioning (HVAC)."

Continuous processes also lend themselves well to containment, which has become a prerequisite since formulations have been using highly active pharmaceutical ingredients, says Somma. "With traditional batch, containment is needed at the dispenser, granulator, and every other transfer point within the process. With continuous, you've reduced your need for containment from 15–20 points down to two, says Di Prospero.

Both containment and miniaturization trends come together in the Portable Continuous Miniature and Modular (PCMM), portable, GMP OSD facilities that combine G-Con's modular production pods and GEA's continuous processing technology. Pfizer has developed a prototype of the concept, which would allow units to be rapidly deployed where and when needed (9).

PAT and process control

Users say that quality by design and process analytical technologies are essential for continuous processes. "You cannot control continuous processes with traditional in-process control sampling and off-line, laboratory-based testing," says Nepveux.

PAT has improved significantly in the past 5–10 years, he says, to a point where it has become an enabler for continuous, Nepveux says. "We're getting away from big instruments that you try to plug in through a port." In the past, he notes, it was a challenge to get a window into a process and be sure that it was truly representative of what was going on in that process. Today, Nepveux says, creative sensing technology avoids this problem.

"There are technically effective and cost-effective PAT sensors that can look at potency, particle size, moisture, blend uniformity, and all the different types of measurements that you might want to take across a process," he says, "so that part is there now."

An area where industry remains challenged is in overall continuous process control, notes Di Prospero. "As continuous OSD plants run, there may be situations where, for example, mixer speeds have to change without affecting the endpoints," he says, so there is a need to control all the processes and have them talk to each other. "The hardware pieces are all there, but the software and the control integration with PAT is still evolving," he says.

Different companies may take different approaches to control, says Nepveux, with some basing it on resi-

dence time, and others on a feedback loop in which real-time results are used to modify key parameters to maintain the same output. "The question then becomes: Are you going to assume that your inputs are fixed, or do you expect them to have reasonable amount of variability, and have processes adapt to that?" he says, noting that Pfizer takes the latter approach.

The other big challenge has been the control systems themselves, not just single loop but multivariate, high-level process control. "You can make a unit operation continuous, but if you cannot control it effectively, then, when you have to connect to other steps, it won't go very far," says Nepveux.

However, pharmaceutical manufacturers are showing interest in using advanced process control, or model predictive control, for different interacting components within the line. "They want to go beyond traditional proportional-integral-derivative (PID) control and ensure that the process stays within specifications and remains stable," says Docherty. "Pharma wasn't using this type of control all that much in the past, but now some applications require it," she says.

New appreciation for soft sensors

Pharmaceutical manufacturers are also beginning to recognize the benefit and importance of soft sensors, computer programs that process different measurements and calculate new data points based on the interactions of those measurements, without requiring that data to be physically measured.

"In the beginning, everyone was looking for the best online analytical device, but now that there is a better understanding of process control, people realize that the data required already exist. With these tools, predictive modeling makes a lot more sense," says Steiner.

One of the biggest concerns for pharma has been regulatory attitudes toward continuous manufacturing. With some modernization programs in the past, such as PAT and QbD, there was high-level support within FDA, but it didn't always filter down to the troops performing inspections or reviewing products. Some companies may still be concerned about this happening with continuous says Docherty.

"It could be an issue if a lot of people were suddenly moving to continuous," says Hausner. "But the adoption rate has been gradual." Besides, he notes, FDA has recruited more engineers (including some C-SOP's graduates) and revamped its inspection program so that inspectors either specialize in food or pharma, but don't have to do both.

From accepting to advocating

Clearly, FDA is investing more resources in better understanding continuous processing, says Hausner, and, as more successful results have been demonstrated, the agency has gone from merely accepting the technology to actively supporting, even advocating for it, he says.

At the end of 2016, CONTINUUS began work with FDA, constructing an end-to-end continuous line that will be used to study and better understand phenomena that are critical for the regulatory review of continuous systems, such as RTRT and traceability, says Takizawa. C-SOPS has helped train FDA staff in continuous concepts and methods, says Hausner.

Meanwhile, EMA's approval of Janssen's continuous line in Puerto Rico may inspire more manufacturers. Regulators have already invited companies to discuss issues with them before implementing continuous and including it in a new drug application or a post-approval change request, Hausner says.

Because pharma is still at a relatively early stage in its exploration of batch alternatives, it faces a "chicken and egg" situation, says Hausner. Companies want more case studies to convince management to invest in continuous, while regulators want to see more applications before they issue specific guidance documents, he says, noting that lack of guidance can then deter some companies from filing applications with continuous.

Recently, the US Pharmacopeial Convention (USP) has become more involved in continuous. The group held a meeting on the subject in June and previously released a video on the topic on YouTube (10). Its involvement could help convince more companies to evaluate continuous more closely. In the meantime, a growing number of implementations suggest that more manufacturers are questioning the *status quo*, nudging OSD manufacturing out of its time warp and toward more modern approaches.

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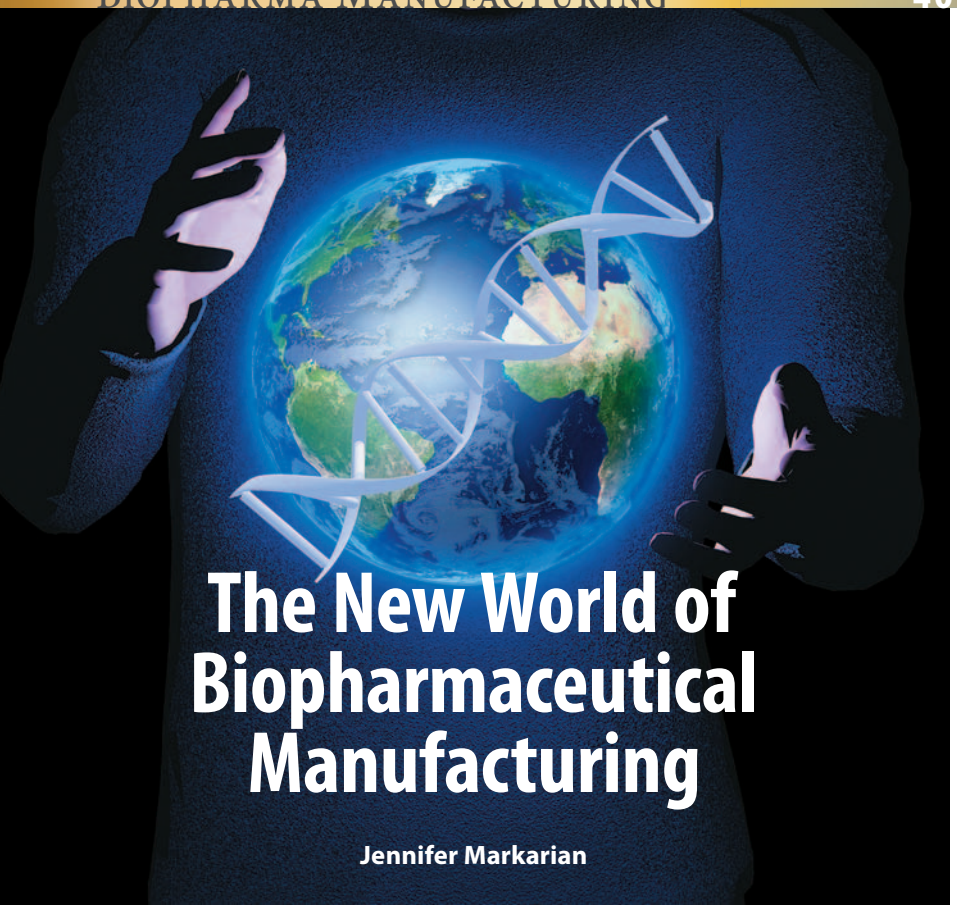

The New World of Biopharmaceutical Manufacturing

Jennifer Markarian

Industry experts discuss the single-use revolution and changes to upstream and downstream processing equipment.

Without question, biopharmaceutical manufacturing has changed dramatically since 1977, when it was in its infancy. The ball really began rolling 20 years ago and has picked up speed in the past five years. Without question, single-use (i.e., disposable) technology has been one of the most significant changes. Advantages of single-use technology include greater flexibility, reduced resources for cleaning and cleaning validation, and faster turnaround between products and batches, resulting in reduced capital costs and increased speed to market. Single-use technology has also precipitated changes in upstream and downstream processing.

Pharmaceutical Technology spoke with Eric Langer, managing partner at BioPlan Associates; John Boehm, chairman of the Bio-Process Systems Alliance (BPSA) and Colder Products Company Bioprocessing Business Unit manager; Eric Isberg, director of Life Sciences, Entegris and BPSA Board Member; Parrish M. Galliher, chief technology officer, Upstream, GE Healthcare Life Sciences; Sabrina Restrepo, associate director in the Sterile & Validation Center of Excellence, Global Technical Operations at Merck; Helene Pora, PhD, vice-president, Single-Use Technologies, Pall Life Sciences; Peter Levison, senior marketing director, Downstream Processing, Pall Life Sciences; Fritjof Linz, vice-president, Purification Technologies, Sartorius Stedim Biotech; and Eva Heintz, global market manager, Healthcare, at Solvay Specialty Polymers about advances the industry has made and the challenges that remain.

Single-use technologies

PharmTech: What have been the most significant advances in single-use systems for biopharmaceutical manufacturing in the past 40 years?

Langer (BioPlan Associates): Over the past 40 years, single-use systems have moved from simple blood and intravenous bags to simple media and serum containers, and to highly engineered, complex devices that are now mainstream technologies in bioproduction. Over the past five years, these devices have steadily made progress in bioprocess operations as their scalability has increased.

Galliher (GE): In the past five years, new advances include an increase in closed systems and in larger-scale, higher-throughput, high-duty applications, such as microbial fermentation and centrifugation. Single-use sensors have been developed for a variety of process parameters for downstream steps such as chromatography, tangential flow filtration, direct filtration, and fill/finish, as well as for smart mixers for measuring parameters such as temperature, PH, and conductivity.

Linz (Sartorius): In the past couple of years, we have seen just about every bioprocessing technology become available in a fully single-use format. Companies are implementing end-to-end single-use platforms for monoclonal antibody, antibody drug conjugate, and vaccine production. Flexible facilities are likely to become an important part of large biopharma's production network and allow much needed agility in operations.

Isberg (Entegris): I think the biggest advance in single-use technology in the past 20 years was the development of three-dimensional bags, which opened the door for large-scale mixing and cell-culture manufacturing. The industry was able to scale up volume while also creating systems equivalent in shape and volume to stainless-steel vessels. Equivalency is important because much of the engineering in areas like mass transfer was performed in stainless steel.

Pora (Pall): In the past 20 years, the sentiment has gone from, 'why use/trust these systems' to 'how do we best optimize/leverage these systems.' Overall, the ability of single-use technologies to offer sterile connections and operate a closed system, while still maintaining flexibil-

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ity, has been a game-changer. In the past five years, we have seen the technology go past acceptance to start maturing, with a range of market options and sizes to accommodate various needs.

Boehm (BPSA): First used for media and buffer prep, single-use manufacturing now applies from inoculum to final formulation and filling. An initial focus on small-batch clinical trials has expanded to full-scale cGMP commercial production. More recently, drug manufacturers are using fully closed systems to make multiple drugs in large ballroom suites.

Heintz (Solvay): The evolution of single-use containers from several decades ago to today's gamma irradiation-stable bioreactors has been one of the most significant transformations; it was the impetus to move all other components to single use to close the loop. In the past five years, we have seen many advancements in sterile connectors and sensors that are gamma irradiation-stable and non-ion migrating.

PharmTech: What are the most significant challenges that remain for fully optimizing single-use systems?

Heintz (Solvay): There are still challenges to single use in the final fill/finish and storage. From upstream to downstream, single-use components are gaining traction in development and use. Fill and finish technology still has room to grow, including the delivery systems of biopharmaceuticals.

Isberg (Entegris): I continue to hear that one of the biggest challenges is consistency and optimization of the materials used to manufacture single-use systems. Materials of construction have changed little in the past 20 years, with polyethylene and silicone dominating. I see the industry moving towards advanced materials like fluoropolymers, which solve most if not all of the challenges posed by other materials.

Galliher (GE): High-pressure resistant, high-temperature resistant, solvent resistant, better, and more extensive sensors and smart films are needed, along with systems that enable high-G centrifugation, elimination of seams for bags, and larger connectors for higher flow rates.

Restrepo (Merck): Single-use systems need to prove themselves to be a well-understood and robust technology. That might imply driving toward standardization from different perspectives: designs, interconnectivity, technical qualification packages, certificates, manufacturing practices, and product lifecycle management aspects (from user requirement specifications to management of supplier change notifications post-implementation). The establishment of industry standards such as ASTM E3051-16 or the ongoing joint efforts between the BioPhorum Operations Group (BPOG) and BPSA definitely contributes to move toward standardization. Being able to provide consistent information from drug manufacturers to health authorities around the globe will ultimately favor the prompt launch of more medicines to meet the needs of many patients.

Two other aspects to be considered are a broader spectra of integrated process analytical technology tools that can interface with many of the control systems available in the market and ergonomic designs or solutions for safe use by operators.

Organizations are setting more aggressive environmental goals, which will drive initiatives to show that single-use systems are environmental-friendly. Since the implementation of single-use systems involves a partnership with suppliers, robust and transparent supply chains to the customers are critical.

Linz (Sartorius): The industry still has more work to do to ensure all technologies are fully compatible with biological systems. Single-use systems must be tested extensively to ensure that their materials of construction do not inhibit cell growth or release chemicals into the product stream during bioprocessing. Biomanufacturers repeatedly cite the robustness of single-use technologies as

SINGLE-USE STORAGE CONTAINERS AND FILTERS PAVED THE WAY FOR SINGLE-USE SYSTEMS

How did single-use technologies get their start in biopharmaceutical manufacturing? *Pharmaceutical Technology* asked Chris Smalley, member of the International Society for Pharmaceutical Engineering's Disposables Community of Practice and an industry veteran with experience at Wyeth, Sanofi, Johnson & Johnson, and most recently retired from Merck, for a look back at how the single-use revolution began.

PharmTech: What were the first applications of single-use technology, and how has the technology changed in the past 40 years?

Smalley: Forty years ago, permanent filter housings with replaceable filter media were the norm. The filter housings were multiuse, inflexible in their use, time-consuming in their preparation, and frequently considered the 'cold spot' in the autoclave (i.e., the slowest to reach temperature). With the introduction of single-use filters, flexibility and responsiveness greatly increased, because the filter could be installed in a process stream and the entire system could be autoclaved or gamma-irradiated (providing a higher level of assurance by reducing post-sterilization manipulations) and stored prior to use. Single-use filters were easier to handle because they were lightweight, and they eliminated cleaning steps.

Forty years ago, the most prevalent container for intravenous (IV) sterile solutions was the colorless glass bottle that needed to be vented to allow the solution to drain, and most times the vent was not even being filtered. When a bottle was dropped by accident, it sounded like a shotgun blast, and of course there was broken glass everywhere. Slowly, single-use bags made from polyvinyl chloride (PVC) were accepted in hospitals across the country. They were robust and didn't need to be vented with the non-sterile air in the hospital room. The eventual broad use of bags for IV sterile solutions paved the way for expanding the use of other single-use systems in biopharmaceutical manufacturing. More systems were developed that have helped to revolutionize the applications of single-use systems in the past five years. In collaboration with suppliers, the expertise has been developed that enabled single-use systems to expand their use in challenging conditions (e.g., high temperatures, solvents, unique chemistries), which has allowed their evaluation and implementation in different applications. Before, low-risk applications (i.e., media/buffer preparation) adapted single-use systems. Now, the use of single-use systems has expanded to drug substance and drug product applications.

being a concern, and suppliers need to support their clients by helping improve process integrity. Most significantly, biopharmaceutical companies need vendors to commit to providing a high level of assurance of consistent supply with robust supply chains and highly characterized processes and raw materials.

Boehm (BPSA): The industry's greatest challenges are driving down drug costs to improve global accessibility and more quickly developing new therapies. Single-use technology plays a vital role in addressing these high-level opportunities. We must drive continuous improvement in education, standardization, and technology. Industry stakeholders (e.g., suppliers, users, regulators) must continue to exchange expertise and knowledge. Collaboration between stakeholders will also be critical to navigating the potentially conflicting goals of advancing standardization and technology innovation.

ADVANCES IN ADCs

Along with innovations in manufacturing equipment and facilities, improvements in starting materials, such as antibody selection, have made a difference in the efficiency of biopharmaceutical manufacturing. Catalent's SMARTag technology, for example, improves antibody-drug conjugate (ADC) manufacturability. *Pharmaceutical Technology* spoke with Jennifer Mitcham, director of Business Development, Antibody-Drug Conjugates at Catalent, about this new technology.

PharmTech: How does SMARTag improve manufacturability of ADCs?

Mitcham (Catalent): Although SMARTag is a chemoenzymatic method, the 'enzymatic' portion of the approach refers to a natural, endogenous enzyme that performs a co-translational modification during expression of the SMARTag antibody. We've observed that insertion of the enzyme's recognition sequence does not impact expression levels or target reactivity as compared to the native antibody, and standard purification methods yield antibody material ready to proceed directly into a one-step conjugation. This simplicity is key to robust, efficient scalability of the required manufacturing process for ADCs. We've currently scaled multiple SMARTag antibodies up through a number of 500 liter runs, observing productivity in excess of 75 pg/cell/day (yielding ~5 g/L) with essentially quantitative conversion to the aldehyde tag. Similarly, the aldehyde-specific chemistry, Hydrazino-Pictet-Spengler (HIPS), which is designed specifically to be well tolerated by proteins and to yield no off-target reactivity, has now been demonstrated to scale very efficiently for the generation of clinical material. Manufacture of SMARTag ADCs also offers an advantage in terms of release analytics since no off-target reactivity has been observed, and lots consistently produce highly homogeneous and stable ADC preparations. We expect the first SMARTag ADC to enter the clinic in early 2018.

Langer (BioPlan Associates): Although single-use systems have made great inroads at clinical scale, the advances at larger scale have been slower. Over the past eight years, the reasons biomanufacturers give for not expanding their use of disposables have been relatively consistent. Top concerns are the potential for breakage of bags/loss of production materials and leachables and extractables (L&E) issues. Part of this persistent concern for L&E issues is the increased use of disposables, which, in turn, has increased awareness of the uncertainties regarding related regulatory issues.

Pora (Pall): While single-use systems are starting to mature, automation and process monitoring (sensors) remain pain points. We have yet to see how we can fully take advantage of single-use technologies with automation—even though we now have bioreactors at every size.

Bioreactors

PharmTech: What have been the most significant changes in bioreactor technology over the past 40 years?

Pora (Pall): We have come a long way from the first stirred tank bioreactor—even the way single-use bioreactors look has changed—with a broad range of solutions from small to large scale. As single-use systems continue to mature, we are seeing more specialized applications and new innovations. Pall Life Sciences' square stirred tank bioreactor design has shown clear advantages over traditional round design. And Pall's iCELLis bioreactor system is an automated fixed-bed bioreactor, designed to simplify adherent cell-culture processes using single-use technology.

Galliher (GE): In the past 40 years, biomanufacturing facilities were primarily built using stainless-steel technology. That technology has grown in sophistication and scale required to produce large scale quantities of biotherapeutics (up to tons/year) and vaccines (hundreds of millions of doses/year). Steam-in-place (SIP) and clean-in-place (CIP) systems, with sophisticated automation, were technological advances in stainless-steel systems to ensure aseptic operation (where needed) and minimization of soil carryover from batch to batch or product to product.

PharmTech: What do you anticipate for the future of bioreactors?

Galliher (GE): Both stainless steel and single-use bioreactors will continue to get smarter (i.e., more sensing of process parameters and product quality) and will continue to get more productive via high cell-density techniques and sub-systems. On average, they will shrink further in scale as productivities further increase and peak. They will also be integrated into recovery/purification and be operated in semi-continuous or continuous mode. The number of drugs that are produced by non-mammalian expression systems, such as yeast and microbes, will continue to climb; these will require more highly engineered microbial bioreactors.

Pora (Pall): Single-use bioreactors present a real solution for today's drug manufacturer, and there is no doubt that the industry now accepts and understands this fact. Over the past few decades, we have been able to clearly establish the boundaries—for instance, we know that 2000 L is the maximum level that you

PERSPECTIVE: BIOLOGICS ADVANCE THE PHARMA INDUSTRY

Advancements in cell culture and protein technology have opened the door for new therapies, according to Wendy Saffell-Clemmer, director research at Baxter BioPharma Solutions.

Pharma industry advancements

PharmTech: During your 23 years in the pharmaceutical industry, how has it evolved? What advances have been made?

Saffell-Clemmer: At the start of my career, recombinant protein technology was limited to a few expression systems, mainly *Escherichia coli* (*E. coli*). Advancements in mammalian cell culture enabled production of glycosylated proteins and led to the explosion of recombinant monoclonal antibody (mAb) therapeutics and optimized mAb-based therapeutics, such as bispecific antibodies and antibody-drug conjugates (ADCs). The growth in biologics, particularly in mAb-based therapeutics, has resulted in changes in drug development and manufacturing. Increased analytical characterization is needed throughout development, particularly in the areas of aggregation and subvisible particle detection. Additionally, demand for lyophilization development services, particularly for ADCs, has increased. Changes have been required in the manufacturing environment as well, as concerns about shear sensitivity have driven biologics customers to move from piston pumps to peristaltic pumps for some pre-filled syringe products.

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Saffell-Clemmer: Recombinant protein technology, the sequencing of the human genome, and the ability to humanize mAbs have opened vast new targets and potential therapeutics for immunological diseases and the growing new field of immuno-oncology. These technologies have changed active pharmaceutical production from chemical process to biological process, driven demand for aseptic production, and required the introduction of new complex analytical technology into product development and quality control laboratories.

PharmTech: How have regulations advanced or hindered advances?

Saffell-Clemmer: Over the course of the past 20 years, the expectations have increased for the application of good documentation practices, data integrity, and other quality best practices such as quality-by-design. While development of quality-by-design approaches for process steps such as lyo-cycle development required significant research and proof-of-concept testing, the implementation has resulted in more data-driven and faster development timelines with improved process definition and lower risk.

The future of Pharma

PharmTech: What do you foresee for the next 10 years?

Saffell-Clemmer: In the next 10 years, rising incomes in countries such as India and China will fuel increasing demand for biologics and create new markets for biosimilars.

—*Wendy Saffell-Clemmer has been a member of Pharmaceutical Technology's Editorial Advisory Board since 2012.*

can leverage the advantages of single-use. Still, users are always looking for innovative ways to optimize the flexibility of single-use technologies, and we see this resonating in approaches like parallel processing, as well as the market drive towards bringing continuous processes to the upstream.

Downstream

PharmTech: What have been the most significant changes in downstream biopharmaceutical manufacturing in the past 40 years?

Linz (Sartorius): Downstream processing has changed dramatically because of the introduction of single-use technologies. Purification suites were once hard-piped with stainless steel, making them inflexible capital assets requiring utility plants to enable their cleaning and steam sterilization. Today, buffers are held in bioprocess containers and unit operations are connected with tubing. Chromatography columns can be disposable or can be replaced by single-use membrane adsorbers. In the past couple of years, single-use centrifuges have been introduced. These have application as cell retention devices as fully closed systems and can handle very high cell densities. They can also be used in viral vector and vaccine production and for the collection of the cells used in cell therapies.

Levison (Pall): Historically, bioprocesses were carried out with animal or plant products, introducing a great deal of challenges along the way. Today, we can express proteins in cell culture, so the approach to downstream processing is completely different. In the past five years, the biggest advances have been in the introduction, development, and general acceptance/interest in continuous downstream processes for biopharmaceutical production.

PharmTech: What challenges remain for optimizing/debottlenecking downstream separations?

Levison (Pall): The real bottleneck is in the upstream (cell culture), which is why there is so much interest in perfusion technologies for continuous cell culture. Bioprocesses cannot be fully continuous without further advances in upstream processing. Another bottleneck can often come from the cost of goods in implementing newer downstream processing technologies; this bottleneck will likely abate over time as these technologies become fully implemented.

Linz (Sartorius): Integrating downstream processes with continuous upstream steps such as perfusion remains a challenge. There are some options available, but they are at an early stage of development. Although downstream process intensification is possible, we are still quite a long way from having the continuous flow of product through a purification train and into the vial. That is one of the challenge for downstream processing engineers over the next decade. **PT/40**

Advances in Analytical Testing Tools for the Bio/Pharma Industry

A roundtable discussion moderated by Adeline Siew, PhD

Industry experts discuss how advances in analytical testing tools have helped address challenges in pharmaceutical analysis.

Analytical testing, which deals with characterization of raw materials and finished dosage forms, plays an important role in pharmaceutical manufacturing and all phases of drug development. In this roundtable article, industry experts discuss how advances in analytical testing tools have helped address challenges in pharmaceutical analysis. Industry experts include: Guillaume Tremintin, market area manager, Biopharma, Bruker Daltonics; Lisa Newey-Keane, marketing manager, Life Science Sector, Malvern Instruments; Gurmil Gendeh, marketing manager for Pharmaceuticals at Shimadzu; Kyle D'Silva and Simon Cubbon, both Pharma and BioPharma marketing managers at Thermo Fisher Scientific; and Geofrey Wyatt, president of Wyatt Technology Corporation.

Evolution of analytical tools

PharmTech: How have the tools for analytical testing of small molecules and biologics evolved over the past 10 years?

Newey-Keane (Malvern): Developments in analytical instrumentation for pharma have largely been addressing three key trends over the past decade. The first is the significant rise in small-molecule generic drug development. This development has increased the requirement for instruments that offer performance-relevant measurements and/or high informational productivity for deformulation and the demonstration of bioequivalence (BE).

The second important trend is the shift towards continuous manufacture (CM). The potential ease of scale-up of continuous processes and the ability to file on the basis of full-scale experimental data makes CM particularly interesting for pharma, but its realization relies on effective monitoring and automated control. Here, the ongoing transition of core analytical techniques to fully integrated, online implementation is enabling rapid progress.

Finally, in biologics, we've seen growing awareness of the importance and power of orthogonality when it comes to probing the complex nature of the proteins. Identifying the optimal set of biophysical characterization techniques is crucial to comprehensively elucidate critical aspects of behavior, such as stability. Significant progress has been made in this area, and there is now growing awareness of how to complement traditional techniques with newer/less well-established ones, such as differential scanning calorimetry (DSC) and Taylor dispersion analysis (TDA), to maximize understanding and add value.

Wyatt (Wyatt): The tools have gotten more sophisticated, specific, and in some cases, more expensive too. In the never-ending quest to learn more about small molecules and biologics, the FDA has encouraged the use of orthogonal testing techniques. As a result, greater insight and understanding of these molecules has been possible.

Tremintin (Bruker): What we have seen evolve is the increased usage of high-resolution accurate-mass instruments (i.e., moving from instruments where you have a limited level of insight to higher resolutions that gives users the ability to confidently determine the identity of a target molecule). On an ultrahigh-resolution quadruple time of flight (QTOF) mass spectrometer (MS), such as the Bruker maXis II, the accurate-mass and the precise relative intensities of the isotopes allows derivation of a molecular formula or a protein monoisotopic mass. On the Fourier transform ion cyclotron resonance (FT-ICR) MS side, such as solariX XR, one can even resolve the hyperfine structure of the isotopic pattern and directly read the molecular formula of the ion being measured. Building

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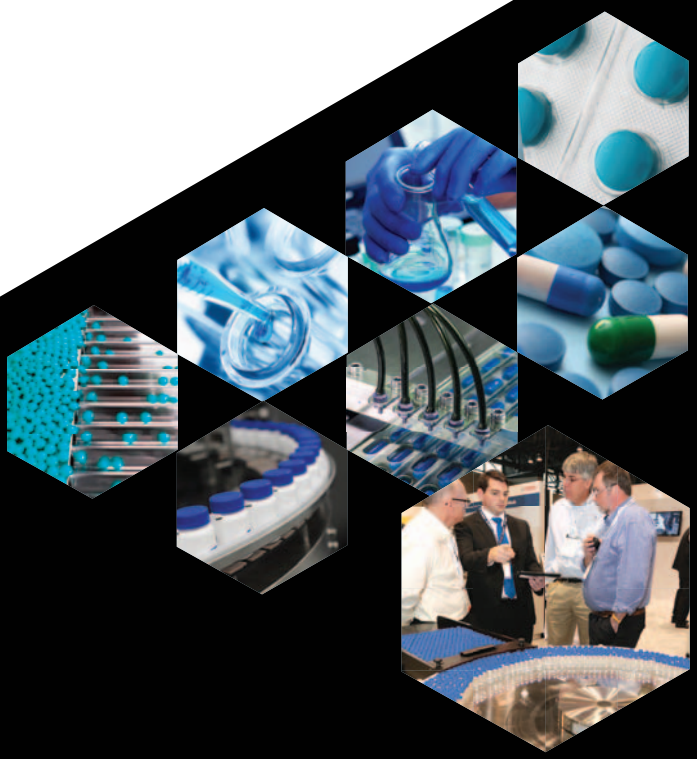

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confidence and getting deeper insights through high resolution has been the biggest change.

Cubbon (Thermo Fisher Scientific): Two key areas that have contributed to accelerated evolution of biologic characterization have been the widespread adoption of high-resolution accurate mass (HRAM) spectrometry and advancement of software tools that deliver meaningful answers to non-expert users. A decade ago, characterization of biologics demanded expert mass spectrometrists to both acquire and interpret data, typically done manually over days and weeks. Instrument variability and difficulty of operation meant that a high degree of skill was required for the results to be meaningful. Today, platforms such as the Thermo Scientific Q Exactive BioPharma with Thermo Scientific BioPharma Finder software have democratized mass spectrometry. Software tailored for drug quality attribute monitoring easily transfers this data to actionable knowledge with automated reports, reducing the demand for specialist operators. As well as being easier to use, the systems are also smaller and more affordable than a decade ago. Consequently, we see greater adoption of these technologies, not just in research laboratories, but also further down the drug pipeline in development; in chemistry, manufacturing, and control (CMC); and even in quality control (QC) environments as biologic manufacturers seek to implement multiple attribute monitoring (MAM) methods using HRAM mass spectrometry to replace a host of chromatographic testing methods performed for QC lot release.

Gendeh (Shimadzu): We have seen an increasing adoption of ultra-high performance liquid chromatography (UHPLC) and sub-2-micron column chemistries for both small and large molecule analysis that allows faster, better, and higher resolution chromatography. As both small molecule and large molecule become more complex, we have also seen the development and increasing adoption of higher resolution technologies, for example, two-dimensional liquid chromatography (2D-LC) and liquid chromatography combined with mass spectrometry (LC/MS/MS). High-throughput, automated, and streamlined sample preparation that is fully integrated into analytical workflows has been adopted. Moreover, data systems have been adopted that not only integrate LC and LC/MS but the complete portfolio of analytical instrumentation, including spectroscopy, with seamless data analysis and reporting that are in full compliance to existing standards.

Recent advances

PharmTech: What are the most significant recent advances in analytical testing tools that have helped speed up and improved the success rate of drug development?

Tremintin (Bruker): The most significant recent advances have been high-resolution measurements that enable users to accelerate their protein characterization tasks. Because of the simplicity of the assay, customers can perform measurements upstream in their development. They have better chance of identifying problems on a lead candidate earlier in the development, which avoids spending too much money down alleys that will lead to failure or costly remediation. Users of maXis II have been able to use this type of measurement to detect incorrect glycosylation sites very early in the development at a stage when they are still able to send the molecule back to the molecular engineering department to optimize the molecule before advancing it any further. There also is a renewed interest in MALDI ionization to perform simple characterization tasks such identity testing of a recombinant product without the need for a chromatography modality.

D'Silva (Thermo Fisher Scientific): When developing biologics, the biopharmaceutical industry look to achieve full structural insight into their candidate molecules, with high confidence, as fast as possible. They look to fail candidates fast. Technologies such as ion exchange chromatography using pH gradients were first proposed by Genetech in 2009 for profiling of therapeutic protein variants. Since then, unique patented products such as Thermo Scientific CX-1 pH Gradients Buffer Kits have led to a 10-fold reduction in analysis time over conventional salt gradients, dramatically accelerating drug development time.

Understanding the primary structure of a biologic candidate is critical step performed early in the development process, but also at every stage after. This was traditionally a labor-intensive and time-consuming, 24-hour process to prepare the sample for analysis. Today, we see biopharmaceutical developers able to perform protein sample preparation in 45 minutes and achieve 100% coverage when mapping their drug candidates. The software technology for analyzing peptide digests has also increased its throughput dramatically. The time for biopharmaceutical comparative modification data interpretation can be taken down from two weeks to one day.

Gendeh (Shimadzu): Mass spectrometers have definitely seen the biggest advances in terms of speed, resolution, and sensitivity gain over the past decade. The Shimadzu triple quadrupole mass spectrometer LCMS-8060, for example, delivers high sensitivity, fast scan speed, and fast polarity switching that enable collection of high-quality data and information. Having these features allows big pharma to fail candidates early, fast, and cheaply in preclinical studies, thus accelerating the pace of drug discovery and bringing safer and more efficacious drug candidates to market faster.

Wyatt (Wyatt): The tools we know best are those that we develop. Our DynaPro Plate Reader II (DynaPro PRII) is but one example. Until it came into being, the only way to make a dynamic light scattering (DLS) measurement was to use one-at-a-time, batch measurement techniques in small cuvettes. The measurement required an operator to prepare a sample, pipette it into a cuvette, then place the cuvette

in the instrument, close a lid, make a measurement, open the lid, remove the cuvette, and, as the saying goes 'lather, rinse, and repeat.'

The DynaPro PRII has taken industry standard well plates of 96-, or 384-, or 1536-well formats and enabled them to be used as massively multiple cuvettes. An entire plate of hundreds or thousands of small molecules or other biologics can be pipetted into the wells, the well plate inserted in the instrument, and … that's it. The technician can walk away and do other work while the instrument makes DLS measurements, ramps temperatures, etc. In fact, the DyanPro PRII enables researchers to perform tasks that were heretofore impossible. The daunting challenge of, for example, screening thousands of samples at different pH levels, or investigating promiscuous inhibitors, is no longer an impediment to making huge numbers of DLS measurements.

Newey-Keane (Malvern): Morphologically-directed Raman spectroscopy (MDRS) is a relatively new technique that combines the capabilities of automated imaging and Raman spectroscopy. It delivers particle size and shape data, along with chemical identification for individual particles in a blend, making it a powerful tool for deformulation as well as many other pharmaceutical applications. MDRS data was recently used to establish *in-vitro* bioequivalence, in lieu of clinical trial data, in the approval of a generic nasal spray application by Apotex, highlighting its value in the time-critical world of generic drug development.

A relatively new addition to the biophysical characterization portfolio is TDA, which provides ultra-low volume, solution-based molecular size measurement. Technology that combines TDA with Poiseuille flow for relative viscosity assessment has been shown to be valuable for robustly identifying drug candidates with a poor developability profile early in the drug development pipeline, thereby saving time and money. TDA extends label-free measurements into highly complex solutions and is able, for example, to detect and size monomeric insulin, even in the presence of its hexameric form.

Finally, our latest technology launch exemplifies the trend of enhancing instrumentation to make it easier for researchers to access robust data for secure and effective decision-making. The MicroCal PEAQ-DSC is a fully-automated differential scanning microcalorimeter that extends the use of DSC—the 'gold standard' for protein stability assessment—throughout the development cycle. Key features include: unattended 24-hour operation; automated data analysis; built-in automated cleaning; and self-validation protocols.

Data interpretation

PharmTech: With so many features and

functions on new analytical instruments (such as capabilities to measure various parameters using one equipment), does the industry or the people using them actually understand the concept behind these measurements, how the results are obtained, and how to interpret them correctly?

Wyatt (Wyatt): This is a frightening and very realistic possibility. Too often vendors sacrifice ease-of-use for 'black boxes'—instruments that simply produce numbers. The researcher has little indication of whether the numbers mean something or whether they may as well be random because there is something wrong in the measurement itself or with the sample preparation. At Wyatt Technology, our customers come to Santa Barbara, CA to participate in Light Scattering University, a course that demystifies light scattering by teaching some of the theory, practice, sample preparation, and data interpretation. The result is that we create a cadre of customers who have an understanding of the powers—as well as the limitations—of the measurements that the instrument makes.

Newey-Keane (Malvern): Given productivity pressures, well-documented skill shortages, and the ever-increasing number of analytical techniques routinely deployed, it's important to consider what level of understanding is actually optimal. For example, if you are carrying out routine QC, then a highly automated, standard operating procedure-driven, modern instrument with integrated method and data quality checking software can eliminate any need for understanding or interpretation, and will effectively remove any subjectivity in data analysis. Techniques such as laser diffraction have already matured to this point. Indeed, it could be argued that for many industrial applications, modern systems can now be more effectively differentiated on their ability to make their performance accessible than on their performance itself.

Conversely, if you are investigating a more complex concept, such as protein stability, then greater understanding is vital, and orthogonal testing is key. Here, the analytical instrumentation expert understands best the merits and limitations of the technology, but the researcher knows their sample and what information is most useful, so collaboration is vital. Interaction with applications specialists can be incredibly helpful, and the best instrumentation companies invest heavily to develop relevant in-house expertise. However, embedding expertise in instrumentation software is also an important and growing trend that has the potential to greatly enhance the support available to industrial users at the benchtop.

Tremintin (Bruker): It is the responsibility of the instrument manufacturers to deliver companion software solutions that harness the hardware capabilities and enable the users to gain the insights they need. For example, the recently released BioPharma Compass 2.0 software takes high-resolution protein measurements and translates them to actionable information such as a glycosylation profile or degradation levels. Similarly, the matrix-assisted laser desorption/ionization (MALDI) PharmaPulse solution takes 100,000s of measurements and derives possible active ingredients against a defined substrate. This substantially improves the library screening approach by providing high throughput while not requiring any labels.

Gendeh (Shimadzu): Analytical instrument companies such as Shimadzu continuously innovate not only new analytical instruments but also complete solutions that solve challenging real-world problems. Many of the early product and solution conceptualization and development are driven through partnership and collaboration with the industry. These new solutions are initially used by the industry partners or collaborators, who are often people that clearly understand the technology, the results, how to interpret the data, and more importantly, the value the data brings to their work. Over time, these new solutions are improved and packaged into 'analyzers' for the mainstream users. As an example, Shimadzu recently released one such 'complete analyzer' solution for the biopharmaceutical industry. The Shimadzu Cell Culture Profiling 'analyzer' combines optimized and validated UHPLC coupled with a triple quadrupole mass spectrometry method to simultaneously analyzes 95 compounds and metabolites in cell culture supernatant. The multi-parameter data from the LC/MS/MS platform is crucial in the cell culture process development and media optimization to promote cell growth; rebalancing media components and quantities by introducing new media components at variable levels to support continuous manufacturing; to monitor cell development to determine optimal harvest endpoints; or when it comes to development of cost-effective media.

D'Silva (Thermo Fisher Scientific): Traditionally, trying to understand a certain aspect of a complex biologic would require various techniques and painstaking analysis of any data—once you'd managed to acquire it, that is. Ensuring that manufacturers meet the ever increasing challenges that their customers face requires them to listen and develop instrumentation that simplifies analysis, alongside impactful software that drives scientists to their ultimate goal: results.

The Thermo Scientific Q Exactive BioPharma platform, for example, allows scientists to analyze complex biotherapeutics using a single system: from native, intact, and sub-unit mass analysis through to peptide mapping, with minimal training and maintenance. Combined with Thermo Scientific BioPharma Finder integrated software, you have a data collection and interpretation workflow that streamlines scientists' access to their results, allowing them to make rapid, informed decisions, rather than spend time setting systems up and learning complex software platforms. So, provided scientists have the right tools (no matter how complex they may be), the industry is in good stead to be able to acquire and interpret those all-important results.

Room for improvement

PharmTech: What areas are still lacking that make analytical testing challenging and what developments can we expect to see in this field over the next 5 to 10 years?

Tremintin (Bruker): Where you see the most movement is in terms of sample preparation and data processing. The big changes will be bringing more automation to streamline the sample preparation and make it more consistent and less dependent on the skill of the operators. On the back end, it would be to have smarter software that is able to process data faster, more effectively, thus allowing companies to compare larger data sets and derive trends and have feedback on the processes based on analytical results. Additionally, chromatography remains a challenge for some compounds, and so the improvements in ion mobility will add an additional dimension of separation that can help solve problems that challenge conventional chromatography techniques. For example, the Bruker trapped ion mobility separation (TIMS) has enabled the separation of isomers that until now could not be separated.

Gendeh (Shimadzu): Biologics are large and complex molecules, and sample preparation for their characterization and bioanalysis (e.g., absorption, distribution, metabolism, and elimination [ADME]/toxicology) has always been a challenge. We can expect to see more innovation and advancement not only in the automation but also in innovative chemistries to simplify the sample preparation workflows. The Perfinity platform from Shimadzu is one such example that fully automates tryptic digestion and brings sample preparation online with LC-MS.

contin. on page 112

PERSPECTIVE: COST CONSTRAINTS HINDER INNOVATION

While industry advances have made medicines safer, cost constraints have hindered innovation, according to Susan Schniepp, distinguished fellow at Regulatory Compliance Associates.

Pharma industry advancements

PharmTech: During your 38 years in the pharmaceutical industry, how has it evolved?

Schniepp: The industry has changed in many ways, and in many ways it has remained the same. When I started in 1979, there was a lot of focus on data integrity, complete investigations, and risk-based decisions. In 1993, we all read and absorbed the Barr Decision and rewrote the rules on investigations into out-of-specification (OOS) results. In the past year or two, we have seen the reemergence of these issues. FDA, the Medicines and Healthcare products Regulatory Agency [in the United Kingdom], and other regulatory agencies have published new guidances on data integrity, and trade organizations have formed taskforces to study the issues. In addition, one of the top FDA 483 observations for both the drug and device industries has to do with incomplete investigations. In many ways, it seems like the industry has come full circle.

PharmTech: What advances have been made?

Schniepp: There have been a number of advances in the biotech and device industries. I think the emergence of 3-D printing will become critical in advancing the industry towards creating personalized medicines and for some of the more routine surgical procedures like heart valve replacements.

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Schniepp: Medicines are safer due to the reduced exposure of the human to the product because of barrier technology. Dissolution testing, high-performance liquid chromatography, ultra high-pressure liquid chromatography, and rapid microbiological method advancements allow the industry to obtain more precise test results faster for determining the suitability of the product for release. The emergence of the biotechnology industry and the new manufacturing needed to produce these products has been the key in opening the pathway to achieving personalized medicines.

PharmTech: What were some factors that hindered advances in the industry?

Schniepp: There has been a switch in the industry in the past 40 years. The emergence of the generic industry, contract manufacturing organizations, and virtual companies has, in some ways, hindered advancements. While they have been good for consumers in these sectors, they have inadvertently hindered advancements because they need to be cost conscious and may be unable to risk revising or updating their manufacturing facilities or processes to meet today's expectations.

PharmTech: How have regulations and standards advanced or hindered advances?

Schniepp: The inability of the regulators to harmonize on post-approval changes has hindered advancements. The timelines for approval and the information required for approval varies around the world. In some cases, it may take up to five years for a company to globally implement a critical change to its product. The inability or unwillingness of the pharmacopeias to harmonize their monographs has also hindered the industry in its ability to offer the same medicine around the world. When the testing criteria in the pharmacopeias are different around the world, companies must meet and test to these different criteria. This costs time and money and is ultimately insignificant when it comes to judging the quality of medicines.

The future of Pharma

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Schniepp: I think the area of personalized medicine will continue to grow, and surgical advancements will be made because of the emergence of 3-D printing. I think manufacturing facilities will shrink in size and companies will manufacture small batches as opposed to the current large-batch manufacturing being done today.

—Susan Schniepp has been a member of Pharmaceutical Technology's *Editorial Advisory Board since 2007.*

Packaging Improves Medication Adherence

Hallie Forcinio

A staggering percentage of people do not take their medication correctly, but pharmaceutical packaging aims to improve patient compliance using new technology to address reasons for non-adherence.

Despite decades of effort to design packaging that helps people take the right dose of the right prescription at the right time, the number of prescriptions that are not taken as directed has been stuck around 50% since at least 1993 (1, 2). Sometimes the reason for lack of compliance, or what increasingly is referred to as "adherence" (see **Sidebar**), is financial. The patient can't afford the medication, so the prescription goes unfilled. But more often, lack of compliance is due to difficulty accessing and dispensing the proper dose and remembering dosing times.

"The severity of medication non-adherence has been so well documented that the healthcare industry is taking a much more serious look at how to improve patient behavior," reports Ward Smith, director of Marketing at Keystone Folding Box Co. "People are starting to recognize compliance is a really important factor in determining the outcome for the patient," agrees Graham Reynolds, vice-president and general manager of Global Biologics at West. Reynolds explains: "Non-adherence has significant financial consequences. The patient ends up in the hospital or back in the hospital and puts additional strain on the healthcare system. From a pharmaceutical company perspective, non-adherence is widely recognized as a cause for a significant loss of revenue; a number recently estimated at $600 billion."

Solid-dosage compliance packaging

To improve adherence, many compliance packaging designs have been introduced. The Pharma Compliance Pack from August Faller Group features an integrated sliding mechanism (see **Figure 1**). As doses are taken, perforated tabs are removed to provide access to the next dose(s) on the blister card. "The patient can directly see which tablets he/she already took," says Tanja Feldmüller, head of Marketing and Innovation at August Faller.

Keystone's child-resistant Key-Pak and Ecoslide-RX packaging also calendarize medication dosing. "This type of packaging has been documented to improve medication adherence," says Smith. He notes, however, that it appears to be less effective for patients on multiple medications. "…if a patient takes more than five medications; all of the packages (blisters and bottles) can become overwhelming," he explains.

Some patients on multiple medications resort to pill minders with compartments for each day and/or various times of day. However, this solution can be problematic. Filling errors can result in missed doses or overdoses. Sensitive medications can be exposed to detrimental environmental conditions, and product information is separated from the dose.

"No one solution seems to exist to solve non-adherence," says Smith. As a result, there's growing interest in more holistic approaches that integrate packaging with interactive devices, software, rewards programs, and personalized support.

An example of a more holistic approach is a smart, wireless pill bottle from AdhereTech. Used primarily for specialty medications like cancer drugs, each bottle contains a wireless cellular chip and numerous sensors. It collects

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adherence data in real-time, analyzes the information, and populates a secure dashboard. If a dose is missed, the system sends an automated alert via phone call or text message to the patient, caregiver, or pharmacist. The bottle itself offers alerts via blinking lights or audible chimes.

The smart bottles are child-resistant and supplied free to patients and pharmacies through programs sponsored by pharmaceutical companies. When the prescription is dispensed, the pharmacist inputs the necessary information into the system, and the bottle is ready for use. Sensors detect when the bottle is opened and reclosed and can monitor other attributes such as the contents of the bottle, battery level, and signal strength. "If the bottle is in an area with no cellular coverage, the bottle holds data on up to 180 doses for later transmission," says Josh Stein, CEO and cofounder of AdhereTech. The pharmacist can access the compliance dashboard and intervene if the patient needs help. Results to date show the wireless pill bottle boosts adherence up to 20%, while persistence (the time on therapy) jumps to 30%.

Another smart packaging option, the iCap closure from TimerCap, is Bluetooth-enabled with red, yellow, and green lights to visually indicate medication status. Each time the cap is opened, the onboard timer stops and returns to zero. The cap also collects data for real-time or email transmission. Compatible with Android, iPhone, and Apple Watch devices, the child-resistant, push-and-turn closure is sold as a kit with two caps, two bottles, two batteries, and the MediSafe iConnect app. Various colors make it possible to differentiate medications. The Medi-Safe iConnect app moves setup of the iCap closure to a Smartphone or other device, minimizing energy consumption and maximizing battery life. In addition to tracking adherence, the MediSafe iConnect app can monitor almost two dozen measurements including glucose levels and weight. The iCap not only helps patients take their medication as prescribed, but also can track and detect opioid abuse and diversion.

With the iCap, the pharmaceutical company sees firsthand when a patient takes a medication. "That knowledge helps fix side effects and other issues and determine why a drug works for some and not others," says Larry Twersky, CEO of TimerCap. As a result, healthcare providers have a better chance of knowing how a particular drug will work for a patient.

Smart labels equipped with a near-field communication (NFC) chip and/or QR code also can support adherence (see **Figure 2**). "NFC has multiple advantages compared to a QR code, such as a very high security level for authentication purposes, the possibility to individually change or protect specific information or the enhanced convenience to read the tag with your Smartphone," says Gene Dul, president of Schreiner MediPharm US. "However, the advantage of including both [code and chip] is that online information is also available to those users that do not have an NFC-enabled Smartphone available." Labels also can be equipped with other features such as anti-slip varnish, hologram for authentication, or a temperature indicator that changes color when a certain ambient temperature is reached.

Figure 1. August Faller's Pharma Compliance Pack uses a reclosable, five-page fanfold label.

Medication management tools from Compliance Meds Technologies (CMT) can be tailored to the needs of various settings such as senior care, addiction treatment, and clinical trials. Tools include the CleverCap LITE; the CleverCap PRO; an optional mobile app called Companion App CMT; and secure, cloud-based reporting/analytics portals. The devices are distributed through the pharmacy, incorporated into existing medication vials/bottles, shipped directly to enrolled patients, or given out by a participating doctor.

Moses Zonana, founder and CEO of CMT, described how the integrated technology works. "The CleverCap

ADHERENCE VS. COMPLIANCE

When it comes to patients and dosage regimens, the term adherence seems to be supplanting the term compliance. Although often used interchangeably, Ward Smith, director of Marketing at Keystone Folding Box, points to established definitions. He reports, "A document from the National Stroke Association states that medication adherence is the act of filling new prescriptions or refilling prescriptions on time. Medication compliance is the act of taking medication on schedule or taking medication as prescribed" (1).

Adherence tends to be viewed more positively. "Adherence encompasses changes in lifestyle and changes in behavior," says Andrew Dunning, vice-president of Strategic Development at AssistRx, the supplier of iAssist software, which streamlines prescribing, distributing, and administering of specialty medications. Teek Dwivedi, CEO of Ehave agrees. He says, "Adherence is about putting the power with the patient to follow the practices of medicine, whereas compliance is about following the doctor's orders. In the latter, there's a sense of subservience rather than the patients being in control of their actions and their health."

"Adherence is softer terminology that connotes a partnership with the patient toward better outcomes," adds Moses Zonana, founder and CEO of CMT. As a result, he believes, "Adherence has pretty much become the term of choice with the advent of engagement platforms that bring the patient into the equation."

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IMAGE IS COURTESY OF AUGUST FALLER

Figure 2. Smart labels from Schreiner Medipharm support adherence by sending data via a Smartphone.

PRO … detects when a pill is dispensed and can control the dose, ensuring the patient receives the right dose at the right time. The information is automatically transmitted through cellular 3G networks into the CMT Reporting, Analytics, and Engagement System. Devices can generate visual and sound alerts at predefined timeframes or operate under silent mode. The CleverCap LITE does everything the CleverCap PRO does except it doesn't actually track at the individual pill level of granularity or control dosage. It tracks when the vial/bottle is accessed or is not properly reclosed to provide an extra layer of security.

"We have observed regimen adherence levels of 95% using CleverCap PRO and regimen adherence levels of 96% using CleverCap LITE. In the majority of our programs, there is an intervention layer in addition to the technology layer, which allows us to obtain those types of successful results. These interventions may incorporate nurse support groups and incentives for better medication habits."

Smart and holistic systems

Adherence-enhancing smart systems for products other than solid-dosage forms also exist. Options include Eveon's IntuityJect self-injector (3). A digital monitoring system from Kali Care integrated with dispensing technology from Aptar Pharma supports ophthalmic clinical trials (4). A similar partnership between HealthFactors and Koronis Biomedical Technologies focuses on capturing and sharing inhaler use data in real-time to improve outcomes for people with respiratory conditions.

In some cases, changing the delivery format may improve adherence, particularly for diseases such as schizophrenia where 30–40% of relapses stem from non-compliance. A matchstick-size implantable device, recently patented by Delpor, enables the sustained release of antipsychotics and other molecules and thereby lengthens the interval between doses to several months. The sustained release results in a smoother pharmacokinetic profile and enhanced safety and tolerability. Initial applications for Delpor's Prozor technology are likely to be a six-month formulation of risperidone and a three-month formulation of olanzapine (5).

Holistic solutions often expand interaction with patients to include simulation, education, and incentives. "As treatment regimens become complex, using engaging technology will help with patient adherence," predicts Teek Dwivedi, CEO of Ehave, a provider of software that supports planning, treatment, and capture of patient- and clinician-reported outcomes. The patient interacts with Ehave Connect via a dashboard and a mobile app, which help track adherence, symptoms, and side effects. There's also an incentive component. Dwivedi explains: "The incentivization comes in two forms: a daily goal to complete a task and achievement badges. Our strategy is to treat patient-reported outcomes similar to how activity trackers motivate individuals to reach their exercise goals."

Improving outcomes via personalized coaching is the driver behind a partnership between Fit4D, a provider of diabetes patient engagement software, and Glooko, a global diabetes data management company. "Glooko's mobile app enables people with diabetes to automatically sync their blood glucose data from over 95% of the blood glucose meters, continuous glucose monitors, and insulin pumps available on formulary and then augment that data with food, exercise, and medication data," says David Weingard, CEO of Fit4D. "That data is then made available to Fit4D coaches through the Glooko Population Tracker."

The impact of the combined technologies can be significant. Weingard reports, "Patients who were engaged in the Fit4D program saw an increased incremental fill rate compared to the control group. Fit4D was able to improve adherence by 20% with non-adherent patients, resulting in better health outcomes and a 3X ROI [return on investment] for the client …. With the addition of data from the Glooko app, Fit4D certified diabetes educators will be able to improve adherence even more because they can reach out to patients proactively based on blood sugar levels to give them timely and relevant guidance."

Something already in many homes, the Amazon Echo smart speaker, could become an adherence tool. A partnership between Orbita, a provider of voice-first software for connected home healthcare, and ERT, a developer of the EXPERT technology platform for clinical trial data collection, processing, and analysis, is improving how data are captured from participants. "We're excited … to give patients the power of voice—an important, emerging technology—to complete surveys, verify completion of care pathway tasks, and report health concerns, all of which enables pharmaceutical researchers to move ahead in their clinical development programs quickly and with confidence," says Andrea Valente, executive vice-president and chief development officer at ERT. With the combined solution, study coordinators can create and manage care plans, and patients and family members can review and manage care tasks via voice as well as mobile phone or web environments (6).

A Smart Injection Pad Training System from Noble, a specialist in biopharma onboarding and device training, helps patients learn how to use self-injectors correctly. A needleless device and pressure-sensing touch pad detect errors and alert the patient. The Smart Injection Pad also helps collect patient data via onboard NFC, Bluetooth, and wi-fi connectivity that enables interface with devices such as

IMAGE IS COURTESY OF SCHREINER MEDIPHARM

smartphones. These data can identify patients who need extra support. "The Smart Injection Pad improves the patient onboarding experience, which is often the most critical time period for establishing adherent behaviors and patient satisfaction," notes Joe Reynolds, research manager at Noble. The simulation overcomes anxiety associated with self-injection and reduces chances that a patient will avoid starting treatment or discontinue it.

West is collaborating with HealthPrize Technologies to integrate West's self-injection technologies with their Software-as-a-Service medication adherence and patient engagement platform. HealthPrize rewards can be monetary, educational, or appeal to the patient's competitive nature. Results can be dramatic. In one demonstration rewards improved refill rates by 50%.

Although rewards can have a positive impact on adherence, Reynolds notes good scores start with an understanding of the needs and concerns of the patient. "You really have to … design the whole system from the point of view of optimizing adherence," says Reynolds. Is the patient worried about the pain of self-injection? The complexity of the device? "The more the process can minimize stress, worry, and pain, the better the adherence is likely to be," he says. However, he notes, even the most adherence-enhancing design needs to be accompanied by training and onboarding.

A good example of whole system design is West's SmartDose platform. The wearable electronic injector delivers injections slowly to reduce injection-associated pain and can support lengthening the time interval between doses. A multisensory training system, being developed in collaboration with Noble, will talk patients through the process from carton opening to completion of the injection. "It's a good example of all factors coming together to provide a drug delivery system that meets the needs of newer drugs, addresses patient concerns, and hopefully help improve adherence," concludes Reynolds

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PERSPECTIVE: THE EFFECT OF PERSONALIZED MEDICINE

Maik W. Jornitz, CEO, G-Con Manufacturing, Inc., and member of *Pharmaceutical Technology's* Editorial Advisory Board, gives his insight on how the pharmaceutical industry has evolved over the years, especially with the move to personalized medicine.

Pharma industry advancements

PharmTech: During your 30 years working in the pharmaceutical industry, how has it evolved? What advances have been made? What were some factors that hindered advances?

Jornitz: A multitude of changes happened; from the dominance of small-molecule drug products to biotech-derived therapies and now the move into patient-based personalized medicines. These shifts also required the introduction of new process technologies, for example the conversion from re-usable stainless-steel processes to single-use process technologies. These processes will be further refined by patient-based therapies, as the volumes are much smaller and, in instances, cold sterilization methods like sterile filtration are not any longer applicable. With new processing technologies, cleanroom and facility designs shifted, and we see now smaller, standardized facility solutions, which are by far faster to deploy than the previous, often single-product lifecycle, large scale 'monuments'.

PharmTech: How have regulations and standards advanced or hindered advances?

Jornitz: It is primarily by the motivation of the industry to initiate technology advances, and we have seen so with new treatment solutions coming from our industry. Having said this, a globally unified post-approval change approach would most definitely support technology advancement decisions, which would help our industry greatly to become more efficient and deploy the newest technologies rapidly.

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Jornitz: [The following have changed the industry:]

- Mammalian cell-culture processes, as we gained a variety of new treatment options
- Single-use process technologies, avoiding the lengthy cleaning and set-up times for the multi-unit operations biologics processes
- Segregation and containment technologies like isolators or autonomous cleanroom units, which create higher safety for critical applications and protection of the product.

The future of Pharma

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Jornitz: We will see new patient-based therapies being more widespread introduced, and with this we will see very different process technologies and facility designs. Flexibility for multi-product, multi-purpose, and capacity scaling will become a prevalent need, but also the urge for a faster time-to-run for smaller footprint facilities. Such facilities will probably not any longer centralized systems, but deployed in-country/for country and potentially within a country on a regional level.

—Maik W. Jornitz has been a member of the Pharmaceutical Technology *Editorial Advisory Board since April 2016.*

Contract Manufacturing Through the Years

Jim Miller

How has the bio/pharmaceutical contract manufacturing industry evolved over the years and what does the future hold?

The 40 years during which *Pharmaceutical Technology* has served the bio/pharmaceutical industry have been years of momentous growth and change in the way drugs are discovered, developed, manufactured, and sold. Contract development and manufacturing organizations (CDMOs) have long played a part in the industry's growth, but it is only in the past 20 years that they have become a critical element in bio/pharmaceutical company operations. In light of *Pharmaceutical Technology's* 40th anniversary, it is appropriate to review the CDMO industry's evolution and outlook.

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Early days

Phase one of the CDMO industry includes the years prior to 1996. In those years, there were three primary participants in the CDMO industry: global bio/pharma companies that provided manufacturing services to each other; fine chemical companies providing intermediates; and a small number of dedicated service providers offering specialized capabilities.

It was quite common in this period for the major bio/pharma companies to manufacture products or intermediates for companies of similar stature, especially when it could be done without enabling competition. The business was conducted on a relatively informal basis; although, a few companies, including Schering Plough and Pharmacia & Upjohn, had formal units with dedicated sales teams.

Dedicated contract drug-product manufacturers were rare prior to 1996.

API and GMP intermediate manufacturing during this time was just a piece of the fine-chemical industry, alongside agrichemicals, food ingredients, and various specialized applications. The generic API business was still dominated by European companies, and custom manufacturing was a small piece of the business as the global bio/pharma companies had large internal laboratories and manufacturing facilities for process development and commercial production. There wasn't a biologics contract manufacturing sector, and early entrants such as Amgen and Genentech had to build their own facilities.

Dedicated contract drug-product manufacturers were rare prior to 1996. Those that existed generally offered specialized capabilities: R.P. Scherer offered proprietary softgel technology; Ben Venue Laboratories was the principal provider of lyophilized injectable product manufacture; Vetter offered bulk syringe filling; DPT had semi-solid and liquid capabilities; and Custom Pharmaceuticals, the forerunner of Patheon, manufactured primarily over-the-counter (OTC) products.

The modern CDMO industry emerges

The CDMO industry really took off in the late 1990s. Starting in 1996, Custom Pharmaceuticals became Patheon and began acquiring facilities in Europe

from global bio/pharma companies. Lonza, already a major player in the contract small-molecule API manufacturing business, acquired Celltech and began establishing its position as a leader in contract biologics manufacturing. Cardinal Health, looking to diversify beyond its core wholesale distribution business, acquired R.P. Scherer, the first piece of what became today's Catalent. In Europe, a number of new drug product CDMOs were established with private equity backing including Nextpharma, Haupt, and Famar.

Three factors contributed to the industry's launch during the 1996–2007 period. The first was the shedding of excess capacity by global bio/pharmaceutical companies as older products went off patent and as the establishment of the European Union and North American Free Trade Agreement enabled freer cross-border trade of bio/pharmaceuticals. Facilities were usually sold to CDMOs, many of which were formed for the specific facility being sold, at a nominal price and with contracts for legacy products. That enabled the bio/pharmaceutical companies to rid themselves of the assets without negative publicity and costly labor settlements.

A second factor was the explosion of early stage bio/pharma companies, thanks to the maturity of biotechnology and the availability of external funding. Emerging bio/pharma companies rode the coattails of Internet companies to gain access to venture capital and the market for initial public offerings (IPOs). Those early stage companies were unable or unwilling to establish their own manufacturing operations and became core customers of the emerging CDMO industry. To this day, major bio/pharma companies that came of age in that era such as Vertex, Gilead, and Shire remain committed to outsourcing all or part of their manufacturing requirements.

The third factor boosting the CDMO industry was the success of clinical research organizations (CROs). Companies such as Quintiles, Covance, and PPD established themselves as key suppliers of data management, site monitoring, and laboratory services in the late 1990s to both established and emerging bio/pharma companies. Their success validated outsourcing as an effective alternative to in-house capacity for critical development activities, and the relationships with CROs enabled bio/pharma companies to develop critical experience and practices for establishing and managing contract services relationships.

Bouncing back from the financial crisis

The years immediately following the global financial crisis and flood of patent expirations were difficult for the CDMO industry. Emerging bio/pharma companies, one of their core customer groups, suffered a large drop in funding, while mergers among the global bio/pharma companies slowed new drug development. Some CDMOs went out of business while others had to downsize and restructure their operations in order to survive.

The financial crisis created an opening for an important group of players in the CDMO industry—private equity firms.

The financial crisis created an opening for an important group of players in the CDMO industry—private equity firms. Low valuations and low interest rates combined to provide savvy investors the opportunity to get into an industry whose long-term prospects looked very attractive. The private equity firms brought new capital and financial expertise to the industry, along with the concept of the "roll-up" (i.e., making an initial acquisition in the industry and then build out is capabilities and scope with additional acquisitions). Most importantly, however, the private equity firms were able to recruit top-tier people to run those CMOs, former senior executives from leading bio/pharmaceutical companies as well as experienced operating managers. Big name private equity firms such as Black Rock (Catalent), KKR (Capsugel) and JLL Partners (Patheon) became important presences in the industry.

External funding for emerging bio/pharma companies began to flow again in 2013, and the CDMO market was ready. Since 2013, CDMO development services revenues have grown at 10–15% annually, as have the revenues of API manufacturers.

The success of small-molecule API manufacturers has been particularly noteworthy during this period, as the industry was practically left for dead in the late 2000s, while biologics became a bigger part of the pipeline. The small-molecule API CMOs have benefited from three positive developments. One is the growth in funding for early stage companies with their pipelines of early phase candidates: nothing in drug development happens without API and small-molecule compounds still make up the majority of drug candidates. A second factor has been the willingness of global bio/pharma companies to outsource more of their small-molecule API requirements. This reflects the fact that the small-molecule API technology and supply base are quite mature, so the global bio/pharma companies can confidently hand off their small-molecule needs to CMOs while they focus their internal resources on biologics. More recently, concerns about compliance problems at emerging-market API manufacturers have resulted in more opportunities going to North American and European manufacturers.

The robust environment for contract drug development has fed a frenzy of merger and acquisition activity in the CMO industry as new investors look to break into the industry and current participants look to expand their capabilities. An average of 35 deals per year was done in the 2014–2016 period involving drug product and substance

manufacturers, packagers, formulators, and analytical services providers. The pace seems to have picked up in 2017, especially for large deals like Thermo Fisher's intention to acquire Patheon, the acquisition of Albany Molecular Research (AMRI) by a major private equity firm, and the consolidation of the biologics manufacturing industry by several Japanese strategic investors.

The future

The CDMO industry has established itself as a critical part of the global bio/pharma industry. In the United States, drug product is contract manufactured for nearly 50% of all new drug application (NDA) approvals, and drug substance is contract manufactured for more than 50% of all small-molecule NDA products. It can truly be said that the CDMO industry has enabled the rapid expansion of the emerging bio/pharma company sector as 80% of drugs approved for those companies are manufactured by CDMOs. The same can be said for mid-size companies as at least 60% of drugs approved for those companies are made by CDMOs.

Still, the CDMO industry is very much in transition. Four developments in particular bear close watching.

One is the state of external funding available to emerging bio/pharma companies. The early stage bio/pharma sector has buoyed CDMO industry performance thanks to its dependence on CDMOs for pretty much all of its development and manufacturing requirements. However, their funding has historically been quite cyclical and anything that disrupts investor confidence will dent the flow of new funding to emerging bio/pharma and that could hit the CDMO industry hard.

A second development to watch is how the industry has bifurcated into two major segments as it has matured: innovation-driven CDMOs that offer the most sophisticated capabilities and get the lion's share of high value new product approvals; and capacity-driven CDMOs that have standard, undifferentiated capabilities and depend on older products and generic drugs to fill capacity. The innovation-driven segment includes less than 10% of the CDMOs in the industry but account for approximately 35% of industry revenues; they have the most advanced technologies, deepest development capabilities and most global regulatory and compliance experience. That gives them the most pricing power and makes them the most desirable strategic partners.

The capacity-driven CDMOs, by contrast, are forced to compete on price and are at risk as the generic-drug business becomes more commoditized. Their margins make it difficult for them to invest in capabilities and compete with the innovation-driven CDMOs. The capacity-driven segment is ripe for consolidation, especially in Europe where labor laws and government procurement practices have kept otherwise-unsustainable operations afloat. We expect to see a shakeout of capacity-driven CDMOs in coming years.

How to address the global bio/pharma sector is a critical strategic issue for CDMOs.

The third development worth watching is how the CDMO industry addresses the global bio/pharma companies (i.e., the 25 largest companies by revenues). Global bio/pharma companies have made more than $125 billion in capital expenditures for new plant and equipment in the past six years, much of it to support their biologics pipelines. Outsourcing of manufacturing by global bio/pharma companies has actually declined in the past 10 years as they have built up their internal capacity for the new generation of drugs. Thanks to the wide profit margins on new drugs, global bio/pharma companies are far more able to invest in new capacity than CDMOs.

How to address the global bio/pharma sector is a critical strategic issue for CDMOs: with the small and mid-size pharma sectors already highly penetrated, CDMO industry growth will depend to a significant degree on the industry's ability to gain a bigger share of global bio/pharma's manufacturing requirements. Big Pharma doesn't need capacity in the traditional manner in which CDMOs have supplied it, but they are open to new service models that emphasize flexibility, technology, and cost and risk sharing. A number of the innovation-driven CDMOs have crafted offerings that effectively deconstructed the traditional CDMO offering into its component parts like tech transfer know-how, shared overhead, and regulatory expertise, and are putting together customized packages of services that meet the individual company requirements. It will require these kinds of innovative arrangements to get significant penetration into global bio/pharma's supply chains.

Finally, the impact of new therapeutic and manufacturing technologies bears close attention. New targeted therapies mean that the average volume per product is declining; even when more sophisticated processing commands a higher unit price, overall revenue per product is falling. Some technologies such as autologous cell therapy don't really fit into the traditional CDMO business model. Developments in manufacturing technologies such as vastly improved yields for biologics, single-use systems, and continuous processing simultaneously require CDMOs to invest in new technologies while making investment in captive capacity more attainable for many companies.

The CDMO industry is robust today and will remain a vital part of the bio/pharmaceutical industry. But significant challenges loom and individual companies will need strong leadership, vision, and operational discipline to succeed. **PT/40**

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History Guides Future CMO Strategies

Matthew Moorcroft

As pharma models changed during the past 40 years, contract manufacturing capacity and services evolved to meet demand.

The past 40 years have seen many changes and trends within the pharmaceutical contract manufacturing arena, from small-scale boutique operations, specializing in individual technologies or chemical processes, to the rise of one-stop shops, and the low-cost providers in India and China. Through interviews with industry veterans who have witnessed—and helped shape—these evolutions first-hand, the author explored the history of pharmaceutical manufacturing outsourcing and future trends.

The discussions revealed four distinct periods in API manufacturing during the past 40 years where contract manufacturing organizations (CMOs) and strategies by pharma companies changed as business needs evolved.

The dawn of CMOs and outsourcing: 1975–1980

Prior to 1975, pharma companies handled manufacturing in house with internal capacity; however, during this time, they began to look for partners to undertake individual steps that involved hazardous or dangerous chemistries, so that risks did not need to be taken with their own facilities.

At the same time, the blockbuster drug era began; the growth of high-volume manufacturing to meet the needs of the market led to a shortfall of in-house capacity. Although companies did not outsource entire processes, Big Pharma began to outsource early chemical steps before bringing the intermediates back in-house for the final manufacturing steps.

The blockbuster era: 1980–1996

With the advent of new technologies such as computational and combinatorial chemistry, high-throughput screening, and biotechnology, the pipeline of novel small-molecule therapeutics increased, as did the investment Big Pharma companies put into R&D. Blockbuster drugs filled capacity, which led to a shortage of GMP facilities. Alongside increased investment in new facilities by Big Pharma came a wave of CMO companies across the United States and Western Europe.

Multi-step outsourcing took off, but initially a lack of investment and expertise limited the number of CMOs that could undertake the challenges of multi-step chemical API manufacturing. Some investors in CMOs saw an opportunity to get rich quick in the industry, somewhat naïve to the slow timeframes in the pharmaceutical industry. When the reality of the timeframes became apparent, investors withdrew from the marketplace leading to a reduction of new entrants at the turn of the millennium, particularly in the United States.

Competition from the East: 1997–2010

The rapid entry of low-cost competition from India and China led to a decade-long period of volatility and uncertainty in the CMO market. At the same time, Big Pharma was grappling with the end of the blockbuster era, patents expiries, more complex drugs, and fewer FDA approvals.

Drug companies embraced low-cost manufacturing opportunities to balance soaring R&D costs, and an influx of CMOs offering services predictably led to over-capacity around the globe, matched by a race to the bottom on price. Risks associated with quality, supply, and experience were put to one side with the aim of saving money, and historic relationships with established

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partners were severed. Western companies were left fighting to promote their value above and beyond the bottom line of cost, and many were left to wonder what would happen to the industry that had boomed only a few years before.

The turnaround: 2010–Present day

A number of factors have combined to bring about a stabilization and resurgence in the CMO industry, most notably a steady increase in FDA approvals of new chemical entities, particularly in high-value disease targets such as oncology and orphan indications.

An increase in wages in China has reduced the competitiveness of China-based CMOs compared to Western CMOs. FDA warning letters to manufacturers based in India and China jeopardized the reputation of companies within the region as a whole. The risk/reward balance—overlooked previously when prices were dropping—is now being reassessed by Western pharmaceutical companies.

While quality is a driver, the focus for pharma companies is identifying partners with specific capabilities and assets; merely having spare capacity is not a sufficient selling point.

In response, the Chinese Food and Drug Administration has pro-actively and aggressively tightened up on drug product approvals, as well as CMO quality and compliance levels. As a result, a significant number of Chinese CMOs failed to meet the new levels and exited the market. Many drug master files have been deregistered, contributing to the reshoring of pharmaceutical companies' supply chains back to Western CMOs.

What does the future hold?

Continued evolution of the CMO market is inevitable, and while looking back is easier than looking forward, there are opportunities for CMOs that wish to grow and capitalize on the resurgence currently in progress. History does teach that staying static it is not a viable business model or strategy; adapting to the changing needs of the industry is essential.

Ensuring that the CMO's assets matches demand is vital. After the blockbuster era, demand for very high volumes has dropped, and Cambrex research indicates that the average annual US demand for a small-molecule API has dropped from around a hundred metric tons to tens of metric tons.

Investing in the "right" facilities, along with offering differentiator technologies, will go some way to ensuring a CMO has a place in the industry. Many CMOs are looking at how to get into projects sooner in the developmental stages, with a view to maximizing the potential should a project be a commercial success. Although the low-cost competition has been diminished, competition for these projects remains high.

How history will define the next era of the CMO industry will become apparent in time. Client relationships are perhaps as crucial now as they have ever been. CMOs—as always—must meet the demands of the customer, delivering products on time, in full, and to the specification required. Trends will continue to be transitional; the much vaunted one-stop-shop strategy does not seem to have completely gone away, but pharma clients continue to show preference to pick and choose expertise where it is necessary. Fulfilling demand and being recognized as experts in areas within the industry seems to be the strategy that will stand companies on the most solid ground. **PT/40**

PERSPECTIVE: INNOVATIONS AND REGULATORY IMPLICATIONS

Russell Madsen, president, The Williamsburg Group, and member of the *Pharmaceutical Technology* editorial advisory board, shares his thoughts on how technology innovations and regulatory oversight have influenced advances in the bio/pharmaceutical industry.

Innovations foster control

PharmTech: What are the top three innovations that have changed the industry the most over the past 40 years and why?

Madsen: In my opinion the top three innovations are: Information technology/PC networks/Internet, advanced aseptic processing technologies, high performance liquid chromatography (HPLC)/genetic mapping/protein mapping.

These innovations have resulted in more and better control of pharmaceutical development, approval, manufacturing, distribution, and patient safety than had been available prior to their implementation, allowing elucidation of drug and biopharmaceutical structure and comparison of generics and biosimilars to innovator products.

Regulations help—and hinder—advances

PharmTech: How have regulations and standards advanced or hindered advances?

Madsen: A case can be made for both scenarios. Regulations and standards have clarified regulatory expectations and have resulted in improved drug quality and consistency. On the other hand, regulatory expectations have tended to hinder advances in emerging technologies such as restricted access barrier systems (RABS), isolators, and closed-vial filling systems, either through lack of understanding or implementation of stringent sterilization and environmental monitoring programs that may not be suited to these technologies.

Looking ahead

PharmTech: What do you foresee for the next 10 years in pharma innovations, regulations, and/or markets?

Madsen: There will be more 'personalized medicine' and more large-molecule or biotechnology-based products. Costs will continue to increase, leading to more regulatory oversight to control prices. Markets will become more international, and regulatory authorities will continue to harmonize regulations and filing requirements.

—Russell Madsen has been a member of Pharmaceutical Technology's *Editorial Advisory Board since 2005.*

LOOK BACK

LOOK FORWARD

Jingjun Huang, PhD
Chief Executive Officer
Ascendia Pharmaceuticals

ASCENDIA: DELIVERING SOPHISTICATED FORMULATIONS

Ascendia Pharmaceuticals is a speciality contract development and manufacturing (CDMO) company dedicated to developing enhanced formulations of existing drug products, and enabling formulations for pre-clinical and clinical stage drug candidates. We specialize in creating formulation solutions for poorly-water soluble molecules and other challenging pharmaceutical development projects. Using our suite of formulation capabilities and nano-particle technologies, we can assess the feasibility of a broad array of formulation options in order to improve a drug's bioavailability. Ascendia formulates products for injection (IV, SC, or IM), transdermal, opthalmic, or nasal delivery, and both immediate-release and controlled-release products for oral administration. We execute rapid, comprehensive, and cost-effective programs for our clients.

Ascendia provides complete development services—analytical testing/validation; pre-formulation development and modeling, formulation proof-of-concept, development, and optimization; and cGMP manufacturing/release of clinical trial materials (CTM). Our projects range from discovery-stage molecules, to life-cycle-management projects, to generic product development—always creating formulation solutions with enhanced biopharmaceutical properties suitable for clinical scale-up.

Our areas of formulation expertise include nano-particle engineering (milled crystals and solid-lipid particles), stable oil-in-water nano-emulsions (using no organic co-solvents), amorphous solid dispersions (both hot melt extrusion and spray drying), oral controlled-release (via fluid-bed coating), and production of liposomes.

We provide contract cGMP manufacturing services for our clients, quickly transitioning projects from formulation optimization to proof-of-concept for a first-in-man study. We conduct turnkey development of control documentation, and product release requirements as necessary to meet our client's specifications.

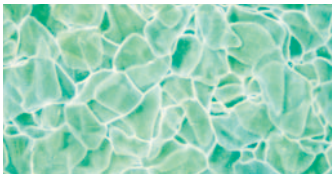
Ascendia also has developed and patented a proprietary pipeline of pharmaceutical product candidates for out-licensing, including ASD-002, a novel, injectable form of the anti-thrombotic drug clopidogrel, and ASD-004, an improved nano-emulsion form of cyclosporin for dry-eye syndrome. Ascendia has a state-of-the-art pharmaceutical research center located in North Brunswick, NJ, and also operates a formulation research and development facility in Xiamen, China.

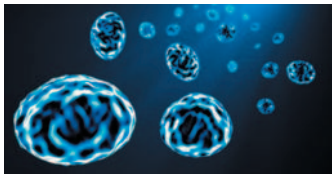
ABOUT DR. HUANG

Dr. Huang founded Ascendia in 2012 after a career in pharmaceutical R&D and management at Pfizer, Baxter, AstraZeneca, and Roche. Dr. Huang holds a PhD in Pharmaceutics from the University of the Sciences in Philadelphia.

ABOUT ASCENDIA PHARMACEUTICALS

Ascendia Pharmaceuticals specializes in the invention and development of specialty pharmaceutical products and novel formulation technologies. We provide formulation, analytical, and manufacturing solutions to create advanced medicines.





ASCENDIA PHARMA

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Baxter BioPharma Solutions

YOUR PREMIER CMO FOR SPECIALIZED STERILE INJECTABLES

Baxter's BioPharma Solutions business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. BioPharma Solutions is a premier CMO with a focus on injectable pharmaceutical manufacturing designed to meet complex and traditional sterile manufacturing challenges. Backed by more than 85 years of Baxter experience in parenterals, BioPharma Solutions can support your pharmaceutical needs with a broad portfolio of sterile fill/finish production capabilities. Our reputation is built on the high-quality products we manufacture for our clients in a cGMP environment. From formulation and development, through commercial launch, our extensive, customized support services can help guide you through marketplace complexities, helping you achieve the full potential for your drug molecule. Baxter BioPharma Solutions' state-of-the-art, award-winning, contract manufacturing facilities are located in Halle/Westfalen, Germany, Round Lake, Illinois and Bloomington, Indiana.

Bloomington, Indiana, USA—The Bloomington facility is a leader in sterile contract manufacturing and offers form/fill/finish services and solutions for injectables. As a full-service contract manufacturer, this facility serves client needs with clinical through commercial launch, including: manufacturing, packaging, quality systems, experience with worldwide regulatory agencies, and our Lyophilization Center of Excellence, an industry-leading resource center focused on the development of high-quality freeze drying.

Halle/Westfalen, Germany—Recognized as a premier CMO that specializes in parenteral pharmaceuticals, Baxter BioPharma Solutions' Halle (Westfalen), Germany facility has completed a capacity expansion designed for oncology drugs, and further expands our leadership position as one of the largest capacity CMOs for lyophilized cytotoxic parenterals, and supports the growing needs of cytotoxic manufacturing.

Round Lake, Illinois USA—Baxter is the world's leading provider of manufacturer-prepared IV solutions and our Round Lake facility is a best-in-class aseptic solution manufacturer. Baxter's portfolio of premixed drugs is the broadest in the industry, and the only CMO offering a manufacturer-prepared, commercial-scale aseptic filling process for premixed drugs in flexible IV bags.

ABOUT BAXTER BIOPHARMA SOLUTIONS

BioPharma Solutions, a business unit of Baxter, collaborates with pharmaceutical companies to provide contract manufacturing form/fill/finish for sterile injectables. Our expertise includes oncology products, biologics, ADCs and vaccines; and we offer a variety of sterile dosage forms, including prefilled syringes, liquid vials, lyophilized vials, cartridges, and cost-saving diluents for reconstitution.

Baxter

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LOOK BACK

LOOK FORWARD

Elliott Berger
Vice-President, Global Marketing and Strategy
Catalent Pharma Solutions

TEN YEARS OF INNOVATION

Catalent is built on several great heritage technology businesses including offshoots of Glatt Technologies in oral solids, Weiler Engineering in blow-fill-seal and, of course, the RP Scherer Softgel encapsulation manufacturing technology pioneered in the 1930s. 2017 marks Catalent's tenth year since the company was born out of Cardinal Health and three years since its IPO on the New York Stock Exchange.

Over the past five years Catalent has invested more than $1 billion to expand its global network of facilities to more than 30, employing more than 10,000 people across five continents and building the industry's broadest set of drug delivery technologies to solve the most complex development and manufacturing challenges. Every year, Catalent launches nearly 200 new Rx, consumer health, and biologics products with its customers, including three first-in-class medications this year, and manufactures over 70 billion oral, sterile, and inhaled doses, for patients in over 80 countries.

Catalent provides its customers with solutions to help solve their most challenging development and manufacturing challenges, with the right technology and expertise. This has been achieved by establishing the broadest toolkit of technologies and solutions to overcome challenges, such as poor bioavailability, stability, scalability, and manufacturing complexity. Catalent's mission is to forge successful partnerships and help our customers to develop better, patient-centric treatments to help improve real world outcomes. Focus on patient needs is at the heart of our culture and everything we do.

Catalent consistently innovates. Challenges still exist in areas such as the oral delivery of biologic drugs and oral and thermostable delivery of vaccines, where Catalent has looked to evolve its technologies to meet these demands; as well as in the development of next generation antibody-drug conjugates to provide more efficacious and safer drugs in therapeutic areas such as oncology.

In the clinical trial space, Catalent's demand-led supply model has the potential to increase efficiency in the clinical supply industry, ensuring global sites can have access to patient kits within a matter of days instead of weeks, and waste from trials can be reduced from more than 200% to less than 20%.

Catalent continues to invest in capabilities and capacity required by our customers to serve their patients globally. Our biologics site in Madison, oral solid site in Winchester, and others are currently undergoing significant expansions to provide more expertise and flexibility to produce better treatments.

ABOUT ELLIOTT BERGER

Elliott Berger was deeply instrumental in developing what we now recognise as Catalent's brand. He has played a pivotal role in launching multiple technologies for the company.

ABOUT CATALENT

Catalent is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products. More products. Better treatments. Reliably supplied.

Catalent®

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Coating Place

COATING A PATH TO THE FUTURE

Coating Place was founded in 1976 by Harlan Hall through the purchase of intellectual property and prototype equipment designed and engineered by the University of Wisconsin Alumni Research Foundation (WARF). The Wurster fluid bed coating technique mastered by Coating Place was invented by Dale Wurster PhD in 1958. Since that time, Coating Place has continued to improve the design to increase speed, efficiency, and consistency of the coating process. Coating Place has continued to be a leader in the Wurster coating industry through sustained research and expansion on what is possible with a Wurster coating unit.

In 1999, Coating Place was purchased by Tim Breunig who has been at the forefront of the business development for the company ever since. His years of experience have propelled the company forward to reach new customers, locations, and standards. Coating Place has formed a solid foundation that will allow us to remain prevalent in the pharmaceutical community and an apex in fluid bed coating.

Last year, Coating Place celebrated 40 years of outstanding service to the pharmaceutical industry. Over the past 40 years, Coating Place has expanded from a single unit facility, to a manufacturing site spanning roughly 300,000 sq. ft. with 20 Wurster units designed and built by CPI. Additionally, we have added milling, blending, granulation/extrusion/spheronization, capsule filling and tablet compression.

Coating Place is currently in the middle of an expansion that includes a new executive office space at roughly 21,000 sq. ft. and a warehouse expansion that increases storage capabilities by 25,000 sq. ft. as well as tripling controlled substance storage. With two manufacturing locations, the company stays busy in both the pharmaceutical and specialty chemical industries.

Coating Place is in the process of validating two new model 4600 Wurster units for GMP production to be ready in quarter three of 2017. These units can produce batches up to 800kg, increasing our overall facility manufacturing capabilities. The Formulation Department at Coating Place is currently researching ways to enhance the nozzle and air distribution designs of our Wurster units to allow for faster coating application and create more uniform coatings. Coating Place continues to develop and push the envelope on what is possible with a Wurster fluid bed coating unit.

ABOUT COATING PLACE

Coating Place is the leading Wurster fluid bed coating services supplier in the industry with more than 40 years of experience in formulation development, technical transfer, and commercial manufacturing.

COATINGS
Coating Place
Innovative Controlled Delivery

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LOOK BACK

LOOK FORWARD

Contec, Inc.

CONTEC, INC.

Contec, Inc. was founded in 1988 in Spartanburg, South Carolina as a distribution company focusing on the needs of the cleanroom manufacturing industry. The company is still owned by the two original owners; who are as passionate about contamination control now as they were then. Contec is responsible for many advances in critical cleaning, but our biggest milestone is the development of presaturated wipes for contamination control use. Contec, Inc's presaturated wipes were first introduced into cleanrooms at IBM in 1992, to reduce solvent use and increase convenience in hand wiping. Contec manufactures presaturated wipes in large quantities in a validated process which allows our life science customers to purchase fully validated wipes ready for use. This is a big cost and time saving to the industry.

Contec continues to grow alongside the life-science industry as our customers continue to embrace our innovative new products. In addition, our VertiKlean® MAX™ Sealed Edge Mop is proving to be widely accepted as the best mop for the cleaning and disinfectant application of all critical surfaces. The company has also introduced a full line of low endotoxin products for the most critical pharmaceutical applications. This line comprises dry and presaturated wipes, IPA, and a cleaning solution with hydrogen peroxide, all with guaranteed low endotoxin levels.

Contec continues to be at the forefront of innovation in contamination control consumables and hardware, launching many new products each year. With manufacturing, R&D, and technical and sales support on three continents, Contec is expanding to be a global supplier to the global pharmaceutical industry. As regulations and standards evolve and tighten, Contec will continue striving to exceed customer's needs and expectations through product development, education, and support. We will continue working with pharmaceutical customers to help find solutions to their cleaning challenges, and if necessary, develop custom solutions for specific customer's problems.

CONTEC®

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Siddhartha C. Kadia, PhD
President and CEO
EAG Laboratories

EAG LABORATORIES

EAG Laboratories was founded as Charles Evans and Associates in 1978, became Evans Analytical Group in 2005 following a series of acquisitions, and rebranded its 20+ laboratories under the EAG Laboratories trade name last summer. EAG has served the pharmaceutical industry with a variety of materials testing, surface analysis, extractables and leachables studies, and impurity investigations for decades. The acquisition of ABC Laboratories in 2015 added a full suite of cGMP analytical and GLP capabilities. The company also gained deep development and regulatory know-how, which is critical to serving the industry's growing number of small and mid-sized pharmaceutical companies.

EAG is growing, and has invested heavily in both capacity and technical expertise. We've increased ICPS/MS capacity to address new regulations related to trace element analyses, and continue to holistically build our biopharmaceutical capabilities—most recently with the addition of many seasoned biopharma scientists, qualification of several new pieces of advanced instrumentation, and the expansion of our cell bioassay laboratory. We've also built a proficiency in complex Antibody Drug Conjugate (ADC) analysis. There are dozens of ADC programs in the industry pipeline but few CROs have the experience to address the unique analytical challenges they present.

EAG Laboratories' mission is to answer complex scientific questions through creative problem-solving, objective analyses, and expert data interpretation. We will continue to build a legacy of scientific excellence, but with an equally important focus on HOW we deliver service to our customers. We believe there is a tremendous opportunity to improve on the current state of pharma-CRO relationships, and have made an organization-wide commitment to deliver the best customer experience in the industry.

ABOUT SIDDHARTHA C. KADIA, PHD

President and CEO of EAG Laboratories, Siddhartha previously served as President of the Life Sciences division of Life Technologies. Prior to that, Siddartha held various executive roles at Life Technologies, notably as President of the Greater China region and President of the Japan region, as well as McKinsey & Company. His career has seen him live and work in United States, Japan, China, and India. He holds a PhD in biomedical engineering from John Hopkins University.

EAG LABORATORIES | WE KNOW HOW™

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LOOK BACK

LOOK FORWARD

Rupert Taylor
Global Category Manager Healthcare & Personal Care
Essentra PLC

GLOBAL END-TO-END HEALTHCARE SOLUTIONS

Essentra is one of the leading global providers of packaging and support services to healthcare customers. Established in the 1940s, we've grown from a small division to being listed in the FTSE 250 index, with a revenue of £1.1 billion GBP in 2016.

We're growing in developing markets and have strong, long-term relationships with many blue chip companies. This is due to working innovatively to come up with solutions to rapidly changing industry requirements. We're flexible and competitive in our response to our customer's issues, and our end-to-end solutions help drive cost-efficiency and embed value.

We provide an unrivalled range of innovative packaging solutions to meet the requirements of the pharmaceutical and health and personal care markets worldwide. Working in effective partnership with customers and strategic suppliers, we're committed to creating quality, flexible, and creative packaging.

Our diverse product range includes:

- Cartons
- Leaflets
- Self-adhesive labels
- Printed foils used in blister packs.

A key challenge for the pharmaceutical industry is counterfeiting, particularly in the developing world. The World Health Organization estimates that up to 15% of all pharmaceutical drugs globally are counterfeited. To counter this there needs to be a focus on monitoring and maintaining the integrity of the supply chain by paying more attention to detail and having proper protocols in place.

To help combat this issue and give manufacturers flexibility in their packing lines, we've created a range of solutions covering pre-serialized cartons and labels, such as Glued Cartons and Tamper Evident Labels.

We see many exciting developments shaping the future of our industry. Through consumer and market insight, we can determine what solutions our customers will be looking for so we can be ahead of the curve, and offer innovation in a proactive way.

One area we're focusing on is Bio-Pharma, where implications include temperature controlled logistics. We're developing protective packaging, which give an indication of when a product has suffered temperature abuse, as well as structural protective packaging so that the product reaches the patient in the best condition.

Patient adherence is another key area of interest for our customers. Roughly $300 billion USD a year is spent as a result of patient non-adherence. And approximately 50% of patients with chronic diseases in developed countries do not take medicines as prescribed. One reason for this is a lack of knowledge. Our range of packaging solutions is designed to aid patient adherence, through the clear display of information.

ABOUT RUPERT TAYLOR

Rupert's role at Essentra is to identify customer and consumer needs in the market place and deliver those solutions through the Essentra portfolio of packaging, components, special technologies, security, and authentication.

ESSENTRA

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Timothy S. Oostdyk, PhD
Chairman
Eurofins Lancaster Laboratories, Inc.

LOOK BACK

LOOK FORWARD

MARKET LEADING OUTSOURCING AND INSOURCING SOLUTIONS FOR BIOPHARMA LABORATORY TESTING

Founded in 1961 in Lancaster, PA, Eurofins Lancaster Laboratories began as a 2500-square-foot-laboratory with three employees. After 12 major facility expansions, expanded service models and many scientific innovations, we have become a global leader in bio/pharmaceutical laboratory services with more than 2,500 employees and facilities totaling more than 500,000 square feet.

During the course of 56 years, we have made investments in state-of-the-art instrumentation and technology and developed vast expertise in Biochemistry, Molecular & Cell Biology, Virology, Chemistry, and Microbiology.

Through the years, we also evolved our service delivery methods and began to offer clients the flexibility to manage testing programs more efficiently through a choice of three unique service models, including standard Fee-For-Service, as well as our award-winning Professional Scientific Services® (PSS) insourcing solutions and Full-Time-Equivalent (FTE) service models.

As part of Eurofins BioPharma Product Testing, the world's largest network of GMP laboratories with more than 1 million square feet of laboratory space and 4,000 employees worldwide, Eurofins Lancaster Laboratories continues to expand our facilities, enhance our capabilities and service models, and continually invest in Information Technology (IT) to support our steadfast commitment to data quality and data integrity.

The Lancaster site recently completed construction of a new, 17,000-square-foot GMP stability storage building to further enhance our comprehensive programs for clinical and marketed products. We also added a new laboratory dedicated to both primary and secondary package testing. And our Eurofins group is undergoing major facility expansions at our Lancaster, Ireland, and Munich facilities.

From the development of our secure, online data access portal, LabAccess.com in 2007 to our recent efforts to develop and deploy our global Laboratory Management System (LIMS) and Electronic Laboratory Notebook (ELN) platforms, we continually develop solutions that further enhance data quality, data integrity, and data accessibility for our clients.

As the largest site in the Eurofins BioPharma Product Testing network, Eurofins Lancaster Laboratories is a leading force in the global harmonization, expansion, and technology exchange for the group. And we are deploying a new in-house-developed LIMS platform across the network of 26 facilities worldwide, which will provide our global clients with an unmatched platform for harmonization, data integrity, and data access.

We also continue to aggressively make investments to enhance and expand our market-leading biologics capabilities across our global network of Eurofins BioPharma Product Testing laboratories, as well as continuing to drive geographic expansion. All of this focused on serving our clients with the world's largest and most comprehensive group of harmonized GMP laboratories.

ABOUT TIMOTHY S. OOSTDYK

Timothy S. Oostdyk, PhD is chairman of Eurofins Lancaster Laboratories and group senior vice-president of Eurofins BioPharma Product Testing. Since 1985, Dr. Oostdyk has ensured the continued success and ongoing growth of Eurofins Lancaster Laboratories, as well as the entire Eurofins BioPharma Product Testing network of laboratories worldwide.

ABOUT EUROFINS LANCASTER LABORATORIES

Eurofins Lancaster Laboratories provides comprehensive testing services to support all stages of the drug development process and offers three flexible service models, including standard Fee for Service, Professional Scientific Services® PSS insourcing solution®, and Full-Time-Equivalent (FTE).

eurofins | Lancaster Laboratories

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LOOK BACK

LOOK FORWARD

Hamilton Company

COMPLETE PROCESS SENSOR SOLUTIONS–FROM PH TO CELL VIABILITY

The history of Hamilton Company begins in 1947 when its founder Clark Hamilton produced the first lead-shielded syringe out of his garage in Whittier, California. This idea enabled precision measurement and pipetting in the microliter range and is the basis for modern Microliter syringes widely used by chromatographers today. Since then, Hamilton Company has grown to include liquid-handling Robotics, ultra-low temperature Storage Technology, chromatography columns, and measurement solutions for Process Analytics. Hamilton process sensors have enhanced the pharmaceutical industry by providing reliable solutions for pH, ORP, dissolved oxygen, conductivity, and cell density (total and viable).

Today, Hamilton Process Analytics prides itself on disrupting the norms of process sensor measurements. When the VisiFerm optical dissolved oxygen sensor was introduced, it blew away the idea of long polarization times and heavy maintenance. In 2009, Hamilton revolutionized sensor communication by offering the first intelligent family of sensors (called Arc) with integrated micro-transmitters inside the probes. Bluetooth 4.0 moves process monitoring, sensor configuration, and calibration to your smartphone or tablet. Now, with online cell density measurements, cell viability can be monitored in real time without manual intervention. Without grab sampling and cell counting, contamination and man hours are removed and decisions can be made in real time, not based on data with many hour-long intervals. Used in combination with the other analytical parameters measured by Hamilton Process Sensors, online viable cell density is a powerful tool in optimizing any bioprocess.

In the future, Hamilton will continue to develop solutions to meet the needs of the pharmaceutical market. The goal for enhanced process understanding and control through sensor systems with open communication will continue to drive the innovation and advancement of Hamilton Process Analytics.

ABOUT HAMILTON COMPANY

Hamilton Company specializes in the development, manufacturing, and customization of precision measurement devices, automated liquid handling workstations, and sample management systems.

HAMILTON

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Alberto Vacchi
Chairman and CEO
IMA S.p.A.

IMA

Established in 1961, IMA is world leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceutical products.

In 1963 the Vacchi family purchased 52% of IMA, transforming it into a joint-stock company to best promote its industrial growth.

The '70s saw IMA enter the field of packaging machines for pharmaceutical products, with the launch of a blister machine. In those years, IMA began to evolve from a small business into a dynamic and innovative multinational Group. The goal of business growth was constantly pursued both internally and externally through acquisitions and alliances.

IMA has a high technological profile and the ability to offer tailor-made solutions to satisfy the most sophisticated requests of the pharmaceutical industry through three highly specialised divisions: IMA Active (Solid Dose Solutions), IMA Life (Aseptic Processing & Freeze Drying Solutions), and IMA Safe (Packaging Solutions).

Its position of leadership is the result of significant investments in R&D, regular and constructive dialogue with the end-users in its sectors, and the Group's ability to expand internationally, conquering new markets. Its history features a constant growth that has enabled the Group to close the year 2016 with consolidated revenues of 1,310.8 million euros, an increase of 18.1% over the previous year. Exports accounted for more than 86%.

In support of organic growth, IMA has continued to invest in research & development to meet the growing needs of a clientele made up of sector leaders that require machines and production systems that are increasingly intelligent and more and more customised.

In an increasingly competitive global market, IMA is proceeding in its policy of sustainable growth based on the enhancement of leading market brands. The industrial DNA of the IMA Group encourages its participants to seek constant improvement, which has a virtuous effect on the dynamics that regulate internal growth.

IMA Digital, launched during Interpack 2017, summarizes all of the projects that represent IMA's commitment to the evolution towards the Smart Factory, Smart Machines, Smart Organisation, and Smart Services. IMA's leadership in terms of innovation and technology imposes a highly competitive position also in the challenges of Industry 4.0.

ABOUT ALBERTO VACCHI

As a reference partner, Alberto Vacchi represents the ongoing commitment of the Vacchi family to the continuous growth of the IMA Group on worldwide markets.

ABOUT IMA GROUP

The IMA Group owns more than 1,400 patents and patent applications in the world and has launched many new machine models over the years.

IMA Sustain Ability

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LOOK BACK

LOOK FORWARD

Matthew Halvorsen
President & CEO
Lyophilization Services of New England, Inc.

LSNE CELEBRATES 20 YEARS OF CONTRACT MANUFACTURING

LSNE was founded in 1997 with a focus on providing lyophilization services to diagnostic and reagent companies. I was outsourcing a lyophilization project and was not happy with the service that I was receiving. This motivated me to purchase a lyophilizer of my own and start a new company. My previous employer was my first client and I am proud to say that, more than 20 years later, we are still manufacturing that product. Since 1997, LSNE has added many capabilities and we now have hundreds of clients in the diagnostic, medical device, and pharmaceutical industries.

The first big expansion at LSNE was in 2005 when LSNE added its second manufacturing site. This facility was used to manufacture sterile product, and it ran as a multi-use facility from 2005 to 2011 and produced material for clinical trials as well as for commercial use. In 2011, LSNE signed an agreement with one of its clients to convert this building into a dedicated facility for an approved commercial product. At the same time, as the need for additional sterile manufacturing increased, LSNE expanded to its third manufacturing site. This facility, located in Bedford New Hampshire, added additional process development labs, a second aseptic fill line, an aseptic formulation suite, and commercial scale lyophilizers. Our third manufacturing site has now been the site of hundreds aseptic fills as well the development of hundreds of lyophilization cycles and formulations. This site also offers two ISO 8 manufacturing suites for the production of bulk drug intermediates and non-aseptic processing. We are proud to announce that in the last year all three of our manufacturing facilities have been inspected by the regulatory authorities and we had no 483s issued at any of the sites. All three manufacturing facilities are now supporting commercial products.

In April 2017, LSNE was acquired by Permira Funds, a global private equity firm with a focus on the healthcare industry. This partnership will allow LSNE to move to its next phase of growth. LSNE will be expanding its manufacturing capacity and capabilities to continue to meet the ever changing needs of our growing customer demand. The first round of facility expansion will focus on adding a segregated facility for the fill/finish and lyophilization of potent compounds, ADCs, and cytotoxic material along with the expansion of the QC lab, which will allow LSNE to bring on additional QC Analytical and microbiological capabilities. The second round of expansion will include the build out for additional commercial high-speed vial filling lines. To support this growth, LSNE will continue to bring on qualified staff and industry experts.

ABOUT MATTHEW HALVORSEN

Mr. Halvorsen has over 25 years of experience in the pharmaceutical and medical device industries. He holds numerous patents in the field of lyophilization and continues to develop new technologies within the industry.

ABOUT LYOPHILIZATION SERVICES OF NEW ENGLAND, INC.

LSNE Contract Manufacturing is a CMO with expertise in process development, formulation, fill/finish, and lyophilization. Our FDA-inspected facilities are strategically positioned to provide uninterrupted material for clinical through commercial use.

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Website : www.lyophilization.com

MPI Research

MPI RESEARCH LOOKS FORWARD

Established in 1995 to meet the rising demands to outsource preclinical studies, MPI Research focused on toxicology research for pharmaceutical and emerging biotech companies.

Enlisting the scientific strength of well-respected industry leaders allowed the opportunity to expand its service offerings to better serve the ever-changing needs and requirements of the industry and its' regulatory agencies. These experts understand that every project is unique, and over time MPI Research had become known for its' flexible and customized approach, and its' wealth of experience in drug safety research.

The company saw tremendous growth, adding hundreds of talented staff and building the world's largest single-site preclinical facility, with more than one million sq. ft., in Michigan.

Amidst rapid growth, the company remained dedicated to keeping quality and animal welfare at the core of the business. MPI Research supports and endorses all of the regulations and standards required by the Food and Drug Administration (FDA), United States Department of Agriculture (USDA), National Institute of Health (NIH), Office of Laboratory Animal Welfare (OLAW), Public Health Service (PHS), and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

The future of MPI Research is looking brighter than ever. The company continues to grow, strengthen its' capabilities, and enhance specialty research programs to support therapies such as; ototoxicology, ophthalmology, and gene-cell therapies.

With more than 1500 dedicated employees, a robust animal care and welfare program, best-in-class scientists and board-certified pathologists, and a large historical control database, MPI Research has grown to become the preferred preclinical CRO and will continue to provide the best possible science, at the best total cost, for their Sponsors.

ABOUT MPI RESEARCH

MPI Research is a leading early stage drug development CRO dedicated to bringing safer and more effective treatments to the world. With a commitment to responsiveness, integrity, trust, and teamwork, MPI Research consistently delivers high-quality services to Sponsors across the globe.

MPI® RESEARCH

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Email : info@mpiresearch.com
Website : www.mpiresearch.com

LOOK BACK

LOOK FORWARD

Dale Natoli
President
Natoli Engineering Company, Inc.

NATOLI ENGINEERING COMPANY, INC

Natoli Engineering Company, Inc. was founded in 1973 on the belief that high-quality tablet compression tooling could be manufactured and delivered for a reasonable price while providing unwavering dedication to superior customer service. Natoli's ability to troubleshoot tableting deficiencies, followed by customized solutions, continues to be their catalyst for growth and is responsible for making them the undisputed global leader and premier tablet compression tool provider.

In the mid-1980s, as European tablet presses were imported to the United States, Dale Natoli chaired the TSM (IPT) committee to educate the tablet compression industry on the differences between European and American equipment and to establish standards satisfying both. Natoli Engineering has taken the lead with troubleshooting skills to engineer tooling options commonly used today by all tooling suppliers. Natoli has identified and maintains the largest selection of raw materials used in the fabrication of tooling. These higher quality materials offer more options for customers including longer tool life, minimized sticking and picking issues, and smoother press operation.

Natoli recognized the critical aspect of speed-to-market. Delivering customer service with transparency, honesty, and integrity is how Natoli revolutionized the industry. Natoli established a higher level of service and removed guesswork from tooling by expediting the manufacturing process of design to completion in days versus weeks.

Today, Natoli continues to advance the pharmaceutical industry and its emphasis on customer satisfaction. A notable tableting enhancement is the reintroduction of the multi-tip punch and the development of the multi-tip reject verification tool. This tool helps Natoli clients verify quality and consistency of tablet weights and sizes, which makes multi-tip tooling a viable option for manufacturers.

With unmatched determination and support, Natoli continues to expand through partnerships and acquisitions, providing value to international markets while demonstrating steadfast dedication to the global industry. Due to increasing demands, Natoli continues to evaluate manufacturing facilities and find innovative methods for greater efficiency, providing the highest value to its customers.

Natoli is known for leading the global marketplace in tablet compression tooling. By bridging gaps between R&D and full-scale production, Natoli improves quality, speed and accuracy for its clients and stands behind the quality of its products. Natoli values and understands the importance of partnerships and strives to exceed the ever-changing goals and demands of the industry with expertise, unmatched service, and leadership.

ABOUT DALE NATOLI

For over 40 years, published author Dale Natoli has been the driving force of global innovation for the most commonly used manufacturing tooling options today.

ABOUT NATOLI

Natoli Engineering Company, Inc., is the recognized global leader in tablet compression tooling manufacturing, providing the highest quality tablet tooling, presses, replacement parts, and impeccable customer service.

NATOLI

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OPTIMA Packaging Group GmbH

25 YEARS OPTIMA PHARMA

Hans Bühler took over the Optima Packaging Group in January 1980. Being the third generation, he pushed for the takeover of Inova, which lead Optima to enter into the market of filling and packaging of sterile liquid pharmaceutical products in 1992. Shortly thereafter, the product portfolio was extended to include washing machines and sterilization tunnels.

This, however, was just the beginning of a wise strategy. Klee, manufacturer of pharmaceutical freeze dryers was brought onboard in 2005, and in 2010 Metall + Plastic, manufacturer of pharmaceutical isolators, followed. Since then, pharmaceutical turnkey projects are a central part of the Optima Pharma portfolio. Medicon, a start-up launched in 2001, soon resulted in the new business unit Optima Life Science.

The importance of flexibility is a crucial issue today. In accordance with this, Optima Life Science offers modular and scalable systems for a smooth transition from developmental to production lines for transdermal patches (TDS) and oral filmstrips (ODF). New highly active and sensitive products require versatile technology within the pharmaceutical branch. Due to this, Optima Pharma developed the multiuse lines processing small batches efficiently according to the highest pharmaceutical safety and sterility requirements.

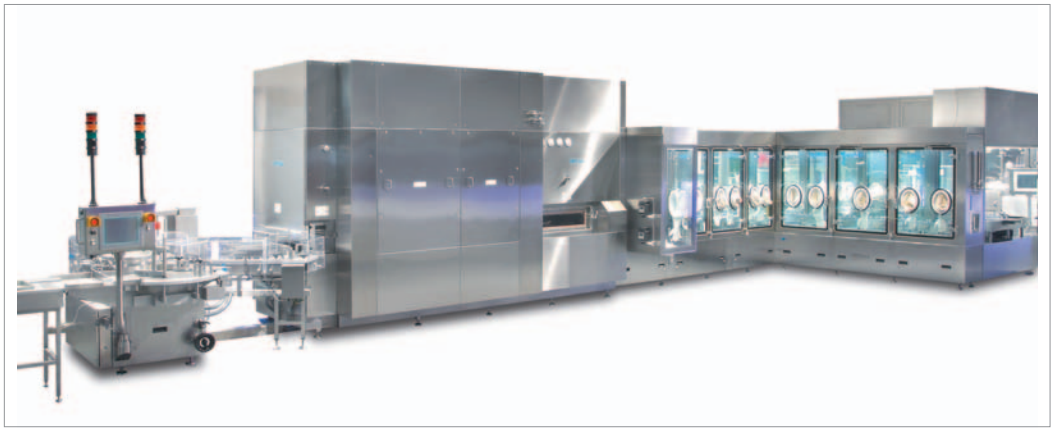
THE FUTURE BEING NOW

Another focus is the digitalization within machine production. It accompanies the lifecycle of production lines beginning with innovative training concepts that may take place in the Virtual Reality Center of Packaging Valley e.V. before the actual installation of the machines, all the way to customer service and retrofits of existing lines.

Software is also a part of this. “OPAL” connects the ERP level with the production level. Data are processed for an overall production control and can be transferred into the machine controls of whole production lines. Detailed process (and error) analyses are also possible.

ABOUT OPTIMA PACKAGING GROUP

Today, Optima generates over 80% of its sales abroad. Optima, now in its 95th year of existence, employs 2150 employees worldwide—100 more than one year ago. Currently, Optima is planning an investment of 50 Million Euro. The company offers single machines all the way to complete turnkey lines for Pharma, Life Science, Consumer, and Nonwovens products.



OPTIMA
EXCELLENCE IN PHARMA

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LOOK BACK

LOOK FORWARD

Amanda Gowans
CEO
PSL (Powder Systems Limited)

IMPROVING PATIENTS LIVES AROUND THE WORLD THROUGH INNOVATIVE TECHNOLOGY

PSL started in 1989 as an original pioneer of containment, manufacturing isolators, and filter dryers for mainly UK pharmaceutical manufacturers.

In 1992, following a new strategy with international marketing and sales objectives supported by technological innovation such as the ChargePoint Split Valve, the company installed its first contracts in Singapore.

The global pharmaceutical industry was growing fast, and the demand for quality process equipment increased considerably from the United States, Japan, and Europe. To sustain such demand, PSL opened its first overseas office in 1997 in the US and started to establish partnerships with equipment providers in overseas markets such as Japan.

Throughout the years, PSL has opened five new overseas offices: Czech Republic, France, India, US, and Australia and in 2016 Singapore to directly support and service its Asia-Pacific markets.

New product innovations allowed the business to restructure from a turnkey engineering provider to a product-based manufacturer, and a network of agents and distributors started to grow to now reach 15 representatives based in South America, Asia and Europe.

The implementation of a new dynamic business structure has resulted in expansion from better engineering and manufacturing quality generating 95% growth and enabling export to over 30 countries.

In 2013 PSL launched the MicroSphere Refiner, winning the ACHEMA Innovation Award in 2015. PSL's innovative scale-up expertise enabled development from laboratory scale during product development up to large scale industrial manufacturing. For pharmaceutical groups, it is essential to have a proven technology used during process development that can be scaled-up.

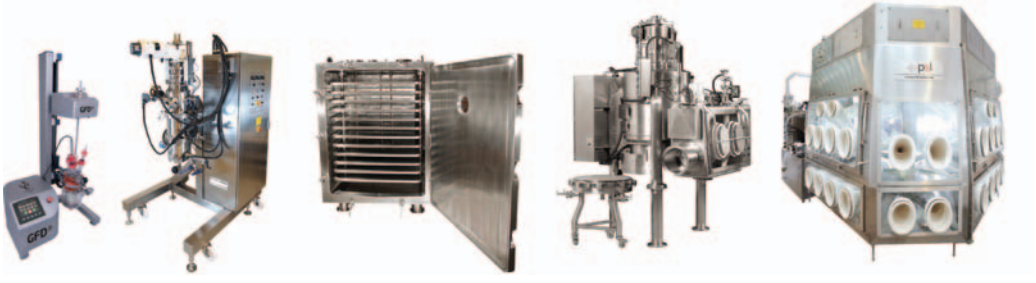
The organization has also established a subsidiary company, C.O.P.E (Center of Process Excellence) in the US, providing a synergy for the businesses and creating numerous innovative ways to increase and achieve the growth for a company as dynamic as Powder Systems Ltd.

ABOUT AMANDA GOWANS

Amanda's extensive background in finance and people management has proven to be the key to the company's new energized approach to business and client relationships.

ABOUT PSL (POWDER SYSTEMS LIMITED)

PSL is at the forefront of innovation in process equipment design and manufacture. Our technology changes peoples lives by bringing next-generation drugs into the market place faster.



psl

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Website : www.powdersystems.com

Hans Steiner
Managing Director
Rommelag Kunststoff-Maschinen Vertriebsgesellschaft mbH

LOOK BACK

LOOK FORWARD

PRODUCTS THAT IMPROVE LIVES COME FROM IDEAS THAT CHANGE THE WORLD

We built the first prototype bottelpack machine in 1962. It's been more than 50 years since we first came up with theperfect alternative to conventional liquid filling processes for our customers—particularly those in the pharmaceutical sector. Our aim? To make sure that every last precious drop is packaged more reliably, more-flexibly, and in a more user-friendly way. It is based on this principle that blow-fill-seal technology came to life: the world's first aseptic filling process of its kind for liquids, semisolids, and even some highly sensitive products.

Since then, we have continued to gather and hone our expertise in packaging solutions made of plastic, and also come up with special applications and develop specific packaging solutions. Our machines are primarily used in the pharmaceutical, chemical, and food industries. With its bottelpack systems and BFS technology, Rommelag sets standards in the aseptic packing of liquids and semi-solids.

What makes Rommelag so special? It's sure to be the fact that as the inventors of the blow-fill-seal process, we have the highest level of expertise when it comes to BFS filling operations. Add to that our experience from thousands of projects involving processing plastic films into anything our customers desire, from the possible to the almost impossible. And don't forget our absolute desire to take on your challenges and develop solutions that allow you to rest easy: from idea to market launch, and from standard to custom-made.

ABOUT ROMMELAG KUNSTSTOFF-MASCHINEN VERTRIEBSGESELLSCHAFT mbH

Rommelag is the inventor of blow-fill-seal technology (BFS) and the global market leader in the aseptic filling of liquids and semisolids with its bottelpack machines.

ROMMELAG ENGINEERING

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LOOK BACK

LOOK FORWARD

Gwenaël Servant
Director
Servier CDMO

COMMITTED TO THERAPEUTIC PROGRESS TO SERVE PATIENT NEEDS

Servier was created in 1954 in France by Dr. Jacques Servier. The group, now privately owned, invests 25% of revenue in R&D each year. Through organic growth, we expanded across Europe, and the world. We now have a turnover of 4 billion Euro, with 21,000 people and a global network of 11 facilities. In 2015, we created the business unit "Servier CDMO" to bring our expertise to third parties. In 2017 we will see the group expand its capabilities to biologics and cell therapies. We continue to defend our core value: "To be committed to therapeutic progress to serve patient needs".

Since 2014, the group is governed by a non-profit foundation. We continue to invest in new technologies (such as mAb manufacturing and cell therapies), partnerships with innovative biotechs, and maintain a strong focus on Oncology, in addition to our main specialties: Cardiology, CNS, Diabetes, and Autoimmune Disease. We also have a generic division (1 b€ income) expanding in various countries and launching biosimilars.

We are building our long-term vision by placing the patient and innovation at the heart of all our actions, and by fostering individual and collective commitment—the force driving our company.

An important goal is to guarantee our independence and our capacity for long-term investment and to be a company of global reach. Through our actions, we contribute to passing on to future generations a world that can ensure access to quality healthcare for all.

ABOUT SERVIER CDMO

Servier is a global pharmaceutical company that brings 60 years of expertise to its embedded CDMO business.

SERVIER CDMO

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How to Create Insights from Your Quality Data

On-Demand Webcast Aired June 13, 2017

Register for free at www.pharmtech.com/pt_p/insights

Event Overview:

Most quality departments are sitting on mountains of unmined data. Used correctly, this data can increase efficiency, lower risks, achieve compliance, and build better, safer products. So how can you unlock its full potential?

Key Learning Objectives:

- The difference between quality data and quality insights
- How to create actionable insights from your quality data
- How to use insights to improve your quality management
- Common data integrity issues and how to avoid them

Who Should Attend:

- Mid-sized and emerging Biotech, Pharma and Medical Device companies.
- Managers and leaders with quality and regulatory responsibilities.

Presenters

Jaseem Mahmmdla
Sr. Product Manager
Sparta Systems

Michael Edwards
Sr. Product Manager
Sparta Systems

Moderator:
Rita Peters
Editorial Director
Pharmaceutical Technology

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For questions, contact Ethan Castillo at ethan.castillo@ubm.com

Analysis of Total and Transferrin-Bound Iron from Serum Samples

Incorporating structural constraints into pharmacokinetic studies of iron sucrose formulations

James A. Koziol and Michael A. Grossman

Results from assays conducted independently of one another can produce findings that are incompatible with underlying physiologic constraints as a result of random errors. The authors investigate one such instance here, relating to assays of total iron and transferrin-bound iron concentrations in sera. A method of adjusting the observed total and transferrin-bound iron concentrations in these settings was outlined. The key of this approach was to satisfy the intrinsic physiologic constraint that the total serum concentration of iron is at least as great as the serum concentration of transferrin-bound iron. The adjustment method proposed by the authors can be readily applied in other settings that have physiologic constraints.

Submitted: Feb. 24, 2017
Accepted: Mar. 6, 2017

The FDA has issued a draft guidance for *in vitro* and *in vivo* studies of intravenously injected iron sucrose (1). One of the recommendations is that total iron and transferrin-bound iron concentrations are to be assessed simultaneously in sera from healthy male and female volunteers, prior to further determinations of area under the curve measures.

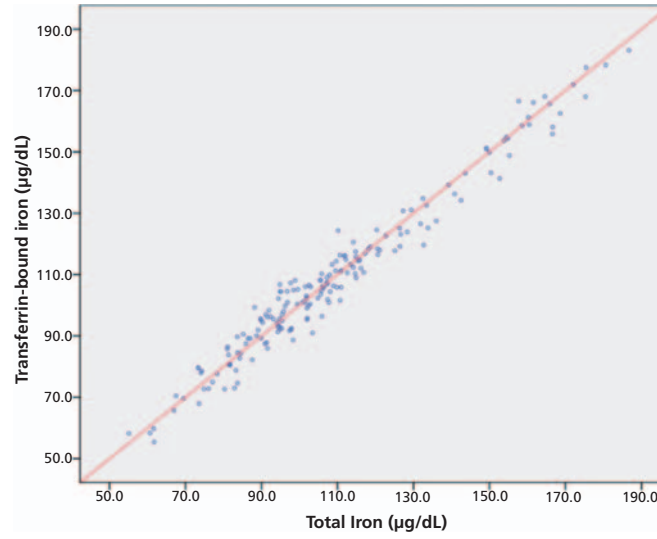
These recommendations are eminently reasonable, but practical implementation may not necessarily be straightforward. Assays of total iron and transferrin-bound iron concentrations are typically done independently, but can result in violations of obvious physiologic constraints. Suppose, for example, total iron is assayed in assay A, and transferrin-bound iron in assay B. Total iron should incorporate both transferrin-bound and non-transferrin-bound (e.g., free) iron, hence, one might expect that assay A should lead to a quantitative estimate of total iron no smaller than the amount of transferrin-bound iron calculated from assay B. This is not necessarily the case, however, as described in a study by Goggin *et al.* (2). These authors developed a spectrophotometric method for measuring total iron and transferrin-bound iron in human serum, and found a strong correlation (r=0.97) between the two measurements in naïve serum samples (n=341). On the other hand, they found a non-negligible proportion of paired values in which assayed transferrin-bound iron concentrations exceeded the assayed total iron concentrations. The purpose of this article is to outline a method of adjusting the observed total and transferrin-bound iron concentrations in such settings, so as to satisfy the intrinsic physiologic constraint that the total concentration of iron is at least as great as the concentration of transferrin-bound iron.

Methods

Let T and B generically refer to the serum concentrations of total iron and transferrin-bound iron, respectively, commonly in units of µg/dL. A serum sample was taken from a random individual; from this serum sample, assay

A reports X_T as the concentration of total iron, and assay B reports X_B as the concentration of transferrin-bound iron (both in units of µg/dL). If $X_T \geq X_B$, it would be accepted that X_T and X_B are valid estimates of the serum concentrations of total iron and transferrin-bound iron respectively in this individual. But if $X_T < X_B$, these observed values are at odds with the physiologic constraint that bound iron cannot exceed total iron. In this situation, the authors propose a likelihood approach for estimation of total and transferrin-bound iron concentrations. The approach is standard, but differs in the details, depending on what is known about the operating characteristics of the assays.

Figure 1: Total iron and transferrin-bound iron concentrations (mg/dL) from separate assays in n = 180 normal individuals. The reference line Y = X [transferrin-bound iron = total iron] is depicted in red.



Assay variances known

It is assumed that as random variables, X_T and X_B have normal (Gaussian) distribution with means μ_T and μ_B respectively, and variances σ_T^2 and σ_B^2. For now, it is assumed that σ_T^2 and σ_B^2 are known, as might be ascertained by reference to the assay manufacturers. There is the physiologic constraint that $\mu_T \geq \mu_B$, but otherwise these underlying means are unknown. If $X_T < X_B$ is observed, the authors propose maximizing the joint likelihood of (X_T, X_B) over $\{\mu_T, \mu_B\}$, subject to the inequality constraint $\mu_T \geq \mu_B$; and are used, with the values of μ_T and μ_B, respectively, that maximize this likelihood, as the estimates of total iron and transferrin-bound iron concentrations, respectively, in this situation.

In fact, these estimates can be easily derived using the method of Lagrange multipliers. It turns out that

$$\widehat{\mu_T} = \widehat{\mu_B} = \frac{X_T * \sigma_B^2 + X_B * \sigma_T^2}{\sigma_T^2 + \sigma_B^2} \qquad \text{[Eq. 1]}$$

Assay coefficients of variation known

Operating characteristics of assays are not necessarily reported in terms of variances or standard deviations (SDs); a common alternative is to report coefficients of variation (CVs) rather than SDs, especially if assay variability tends to increase linearly with mean levels. The authors outline how CVs can be incorporated into the likelihood formulation.

As before, it is assumed that as random variables, X_T and X_B have normal (Gaussian) distribution with means μ_T and μ_B respectively, and variances σ_T^2 and σ_B^2. However, now σ_T^2 and σ_B^2 are unknown, and instead two different parameters are given, which characterize variability in the underlying assays, namely, CV_T and CV_B, the coefficients of variation of the assays for total iron and transferrin-bound iron, respectively.

Again as before, if $X_T < X_B$ is observed, the authors propose maximizing the joint likelihood of (X_T, X_B) over $\{\mu_T, \mu_B\}$, subject to the inequality constraint $\mu_T \geq \mu_B$; in writing this likelihood, σ_T is replaced by $CV_T * X_T$, and σ_B by $CV_B * X_B$. With these substitutions in **Equation 1**, one can arrive at $\widehat{\mu_T}$ and $\widehat{\mu_B}$ as the respective estimates of total iron and transferrin-bound iron concentrations.

For those with a more numerical bent, Matlab code for this maximization procedure is given in the Appendix, which also includes further technical details.

Example

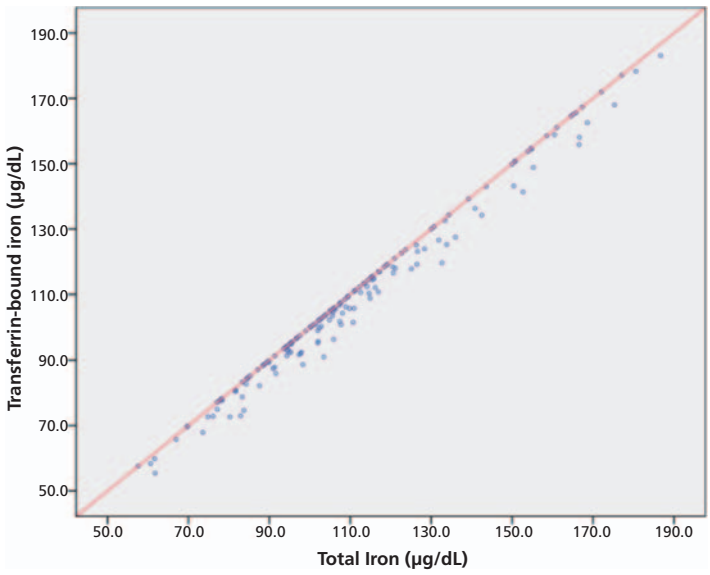
Figure 1 shows a plot of total iron concentrations and transferrin-bound iron concentrations from 180 individuals. The assays from which these concentrations were derived are not equally reliable; reported coefficients of variation are 8% for total iron and 5% for transferrin-bound iron. It is clear from **Figure 1** that for a non-negligible proportion of the 180 subjects, the observed transferrin-bound iron concentrations exceed the observed total iron concentrations. After applying the approach described by the authors, the "corrected" concentrations are shown in **Figure 2**—which is now tied data [total iron concentration = transferrin-bound iron concentration], but with no violations of the intrinsic ordering of total iron and transferrin-bound iron.

Discussion

On an individual level, tests and assays can yield inconsistent results, as with independent assays for serum concentrations of total iron and transferrin-bound iron.

FIGURES COURTESY OF THE AUTHORS.

Figure 2: Total iron and transferrin-bound iron concentrations in the 180 normal individuals from Figure 1, after adjustment of total iron and transferrin-bound iron concentrations to ensure that total iron ≥ transferrin-bound iron. The adjustment procedure is described in the text. The reference line Y = X [transferrin-bound iron = total iron] is depicted in red.



Summary statistics can obscure these inconsistencies, for example, by simple averaging of results over large cohorts of individuals. Nevertheless, the individual consistencies remain, and the suggestion in this article is to address these inconsistencies in a logically coherent manner prior to data summarization. The authors illustrate an approach in the context of independent assays for serum concentrations of total iron and transferrin-bound iron, but the approach remains valid in analogous settings with intrinsic structural (physiologic) constraints. For example, ligand binding assays are commonly used to assess concentrations of monoclonal antibody drugs in plasma or serum samples (3). These assays are designed to measure the total or free forms of monoclonal antibody and the target ligand. Total monoclonal antibody is the sum of bound and unbound forms of the monoclonal antibody drug, hence, the value must exceed that of the free form. This constitutes a physiologic constraint on the assay determinations, completely analogous to the scenario outlined in this note.

It is implicitly assumed that the tests or assays are accurate, that is, there is no systematic bias impinging on the test or assay outcomes. In the setting described by the authors, the assays for serum concentrations of total iron and transferrin-bound iron have been appropriately vetted for accuracy, and the inconsistent findings can be attributed to random error. Nevertheless, in other settings, it may be worthwhile to rule out the possibility of systematic bias.

In practice, summary statistics may give no inkling of individually inconsistent results, and corrections to individual data may be inconsequential. Nevertheless, it can be argued that data analyses and submissions ought to be based on rigorously validated data, and the proposal described in this article is made in this spirit.

Appendix

The following outlines the Matlab code for estimation of the concentrations of total and transferrin-bound iron, in the scenarios described earlier. The authors' methodology invokes the Matlab command fmincon, which minimizes a multivariate function (the objective function) subject to inequality constraints. In the following examples, the objective functions are saved as Matlab M files in the working directory.

Global variables are used to pass parameter values to the objective functions. The global variables are denoted:

- tval observed value of total iron concentration
- bval observed value of transferrin-bound iron concentration
- sig2t variance of total iron assay (if known)
- sig2b variance of transferrin-bound iron assay (if known)
- cvt coefficient of variation of total iron assay (if known)
- cvb coefficient of variation of transferrin-bound assay (if known)

It is assumed that assay reproducibility is expressed either in terms of variances (or standard deviations) of replicate measurements, or with coefficients of variation.

The likelihood approach outlined previously is predicated on the assumption of normality for replicate assay results. Let

$$f(z;\mu,\sigma^2)=\frac{1}{\sqrt{2\pi}\sigma}\exp\left[-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2\right]$$

represent the probability density function of a normally distributed random variable with mean μ and variance σ^2. Then, the joint likelihood L of (tval, bval) is the product of the two underlying normal densities

$$L = f(tval;\mu_T,\sigma_T^2) * f(bval;\mu_B,\sigma_B^2)$$

and the goal is to maximize this joint likelihood over $\{\mu_T, \mu_B\}$, subject to the simple linear constraint $\mu_T \geq \mu_B$. This maximization is equivalent to the minimization of the negative log likelihood - log L, for which fmincon is invoked.

The objective functions specified in the Matlab M files below are proportional to the negative log likelihoods (but with extraneous constants omitted), and maximization of the likelihoods is equivalent to minimization of the objective functions.

```
objfunc1.m
function z = objfun1(x)
% Objective function to be minimized if sig2t and sig2b
are known
%
global tval bval sig2t sig2b
z = (x(1) - tval)^2/sig2t + (x(2) - bval)^2/sig2b;
return
end
```

```
objfunc2.m
function z = objfunc2(x)
% Objective function to be minimized if cvt and cvb
are known
%
global tval bval cvt cvb
z =(x(1) - tval)^2/(cvt*tval)^2 + (x(2) - bval)^2/
(cvb*bval)^2;
return
end
```

For completeness, the objective functions are provided if sig2t and cvb, or cvt and sig2b are given.

```
objfunc3.m
function z = objfunc3(x)
% Objective function to be minimized if sig2t and cvb
are known
%
global tval bval sig2t cvb
z =(x(1) - tval)^2/sig2t +(x(2) - bval)^2/(cvb*bval)^2;
return
end
```

```
objfunc4.m
function z = objfunc4(x)
% Objective function to be minimized if cvt and sig2b
and are known
%
global tval bval cvt sig2b
z =(x(1) - tval)^2/(cvt*tval)^2 +(x(2) - bval)^2/sig2b;
return
end
```

Here is a prototypical Matlab progam for the maximization procedure:

```
main.m
global tval bval sig2t sig2b cvt cvb

% Specify the observed tval and bval values, and the
measures of variability % of the two assays, here

%  The linear constraint μ_T ≥ μ_B is rendered in Matlab
as A*x ≤ b, % where x denotes the vector (μ_T; μ_B)

A =[-1   1]; b=[0];
%  The vector x0 contains starting values for the mini-
mization procedure
% through fmincon. We have found the following start-
ing values to work
% well.

x0 = .5*(tval+bval)*[1; 1];

% Here is a simple call;
% in practice, the appropriate objective function should
be called.

[x] = fmincon(@objfunc1,x0,A,b)
% Matlab will return the vector x here. x(1) is μ̂_T, and
x(2) is μ̂_B.
end
```

Notes:

1. One can invoke fmincon regardless of the ordering of tval and bval. If in fact tval ≥ bval, the linear constraint is not active, and fmincon will return x = (tval; bval).
2. If bval ≥ tval, the linear constraint is active, and fmincon will return the value specified in text equation (1) for x(1) and x(2).
3. If minimization is a one-off operation, then anonymous functions might be an appropriate approach for the minimization problem in Matlab. Separate function files are used, with parameters passed into the functions via global variables, for clarity.

References

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2. M.M. Goggin et al., *Bioanalysis* 3 (6) 1837-1846 (2011).
3. J.W. Lee et al., *AAPS Journal* 13 (1) 99-110 (2001). **PT**

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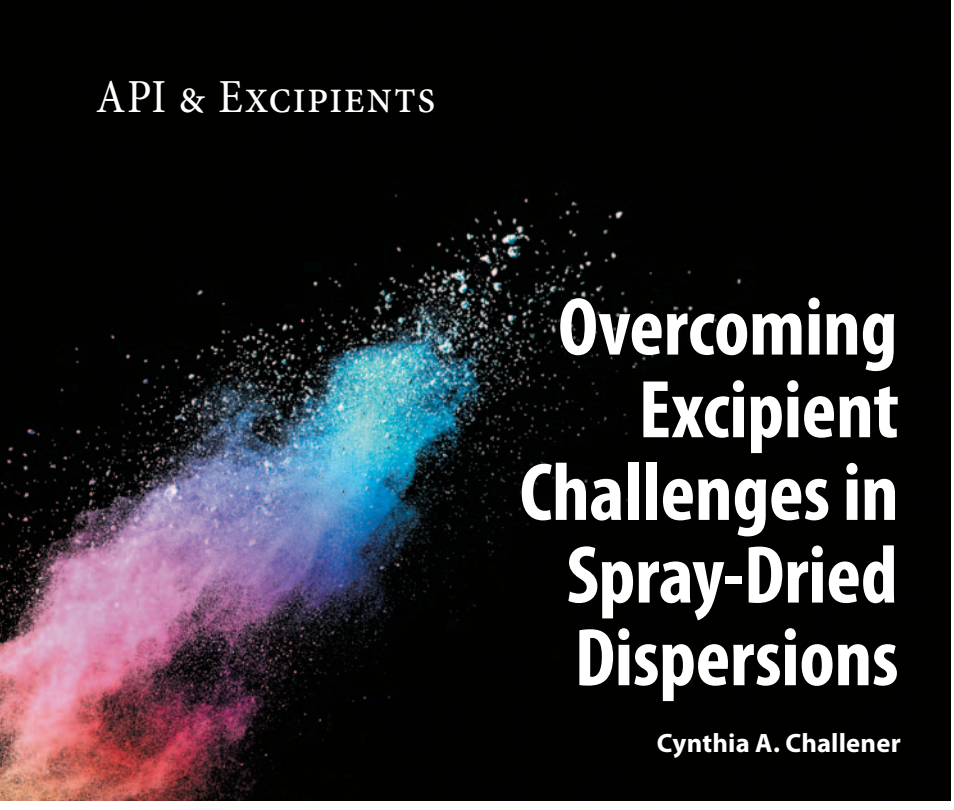

Overcoming Excipient Challenges in Spray-Dried Dispersions

Cynthia A. Challener

Polymers and surfactants impact stability and long-term performance.

Access to high-throughput synthesis and screening technologies has enabled the discovery of novel classes of small molecules that exhibit high potency. Unfortunately, many of these compounds suffer from poor solubility and bioavailability when administered in conventional solid-dosage forms, the preferred route of administration due to convenience and ease of use. Formulation as amorphous solid dispersions (ASDs)—most commonly via spray drying (SD) or hot-melt extrusion (HME) and more recently co-precipitation (CP)—is increasingly used to improve the performance of poorly soluble drugs. The choice of excipients for spray-dried formulations has a direct impact on the stability and efficacy of these ASDs.

Risking metastable forms

ASDs involve incorporation of the API in a metastable form within a polymer matrix. Spray-dried ASDs are prepared by dissolving the API with the polymer and other excipients in a solvent (or solvent mixture) and then removing the solvent through a rapid flash-drying process. "Metastable, amorphous forms have greater solubility and bioavailability, but because they are in a higher energy state, they desire, as do all things in nature, to move to a lower energy state, in this case via crystallization," notes Márcio Temtem, associate director for particle design and formulation development at Hovione.

The challenge is to avoid or at least delay for a sufficient length of time (the shelf life of the product) this change in the metastable state. The key excipient in ASDs—the polymer—forms a matrix that provides this needed stabilization. The matrix disperses the API molecules, preventing any interactions between them that could lead to crystallization. API molecules trapped within such a matrix also have reduced molecular mobilities, which further reduces their potential for crystallization.

Formulation considerations

Several key factors must be considered when formulating spray-dried ASDs, such as the selection of the best ingredients to increase the "supersaturation effect" and the API/polymer ratio and the impact it may have on the stability and performance of the selected system. According to Temtem, "the API and polymer must form a true solid solution in which the polymer and API cannot be distinguished from one another and are mixed in such a way and in the right proportion that the mixture is thermodynamically and/or kinetically stable and the two compounds prefer to be together rather than apart." Finding this "sweet spot" is achieved using various computational, high-throughput screening, and other experimental tools combined with knowledge and experience.

Processing conditions

Spray drying is just one method for preparing ASDs and may not be ideal for certain APIs or target formulations. Each method—spray drying, hot-melt extrusion, and co-precipitation—produces dispersions with different morphologies, surface areas, particles sizes, and other attributes that impact product release profiles. The manner in which the API is entrapped in the matrix is very different and thus also results in different levels of "disorder," or in other words energy levels, according to Temtem.

Process conditions during spray drying may also impact the chemical purity of some APIs. "Although the drying technique is gentle and takes place rapidly with the API droplets protected by evaporation of the solvent, it is necessary to assess an API for degradation during drying," Temtem observes. He adds the use of solvents can also result in the plasticization of the amorphous solid dispersion, increasing the molecular mobility and thus the potential to crystallize.

Challenges of excipient selection

The first challenges to maintaining stability in ASDs, according to Meredith Perry, associate director of pharmaceutics with Pharmatek SD, Catalent, is the need to use a polymer that is chemically compatible with the API while also being miscible and improving the supersaturation of the API in aqueous media. "Although most polymers are relatively inert, some are hygroscopic or acidic and therefore inappropriate for compounds prone to hydrolysis or acid degradation," she states.

The second challenge is to select a solvent that provides sufficient solubility and chemical stability for both the ac-

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tive ingredient and the chosen polymer. "A wide range of organic solvents can be safely spray dried, so usually it's possible to find a combination of solvents, such as polar protic and polar aprotic solvents, that meet these objectives," Perry says.

The next challenge with ASDs is excipient selection in the solid state. Any instability previously noted in the crystalline form of the API will likely be more pronounced in the amorphous state, according to Perry. "Specifically," she observes, "hygroscopicity is typically worse in an amorphous form due to the hygroscopicity of some polymers and the high surface area of the ASD particles. Reactivity with acids, bases, and oxidizing agents is also generally worse due to the high energy state of the amorphous material."

Common excipients

The pharmaceutical industry favors the use of excipients that have been previously approved and have data supporting their use in humans. As a result, there are three main families of polymers used to form spray-dried ASDs, according to Temtem: cellulose-based polymers, polyvinylpyrrolidone-based polymers, and acrylate-based polymers.

Common cellulose-based polymers used in spray-dried dispersions (SDDs) include hypromellose acetate succinate (HPMCAS) and hydroxypropylmethyl cellulose (HPMC). Widely used pyrrolidone polymers include polyvinylpyrrolidone (PVP, also known as polyvidone or povidone) and copolymers of PVP with vinyl acetate. A polyethylene glycol, polyvinyl acetate, polyvinylcaprolactam-based graft copolymer has also been used extensively in ASDs. Copoylmers of methacrylates with acrylic acid in different ratios make up the third family of polymers used to form the matrices within SDDs.

"Polymer selection is the primary tool for chemically and physically stabilizing the API in an ASD because the two compounds are mixed at a molecular level," notes Perry. For instance, HPMC capsules are often preferred over gelatin for hard shell capsules because HPMC has a neutral pH, low moisture content, and low hygroscopicity. Mannitol as a tablet excipient also meets these requirements.

In third-generation SDDs, surfactants, typically d-α-Tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) or sodium lauryl sulfate (SLS), are often added to prevent precipitation of the API during dissolution. "Surfactants help to maintain supersaturation of the API by forming micelles and/or other 3-D structures during drug product dissolution. The API is kept in solution by preventing interaction of API molecules with one another," Temtem explains.

Surfactant use is only effective at relatively low levels (< 5–10%); when used at higher levels, surfactants often undergo phase separation in the SDD. Due to their low melting points and sometimes low glass transition temperatures, when added to formulations in large quantities, may hinder product accumulation inside the units and result in physical and chemical stability challenges.

For compounds that are pH-sensitive, excipients with pH buffering capacity, such as citric acid and sodium bicarbonate, can have a stronger stabilizing effect on ASDs than on crystalline APIs, according to Perry. In addition, solid-dosage forms can be coated for further moisture protection. Materials such as polyvinyl acetate-based (PVA-based) coatings provide a good barrier, and can be coated more thickly than film coats to provide further protection.

Excipient developments

Excipient suppliers are taking various approaches to the development of new products for use in SDDs. Most efforts are directed at developing improved versions of existing, approved excipients given that drug manufacturers are hesitant to risk attempting to get a new drug approved with a truly novel excipient; novel excipients do not have a separate approval pathway and are only approved when a drug-product formulation in which they are used receives approval.

Thus, suppliers are looking to develop new grades of existing matrix polymers or to develop modifications to existing excipients. For instance, HPMCAS until recently was largely supplied by Shinetsu. The company's patent protection is expiring, and other suppliers such as Ashland and Dow are working to add this polymer to their portfolios. In addition, excipient suppliers are developing polymers with different combinations of acetate and succinate substituents to provide more options for drug developers. "These new excipients open new windows for formulators, particularly from a quality-by-design standpoint. Formulators now have many more polymer with a broad range of properties, allowing for the development of more effective products," Temtem asserts.

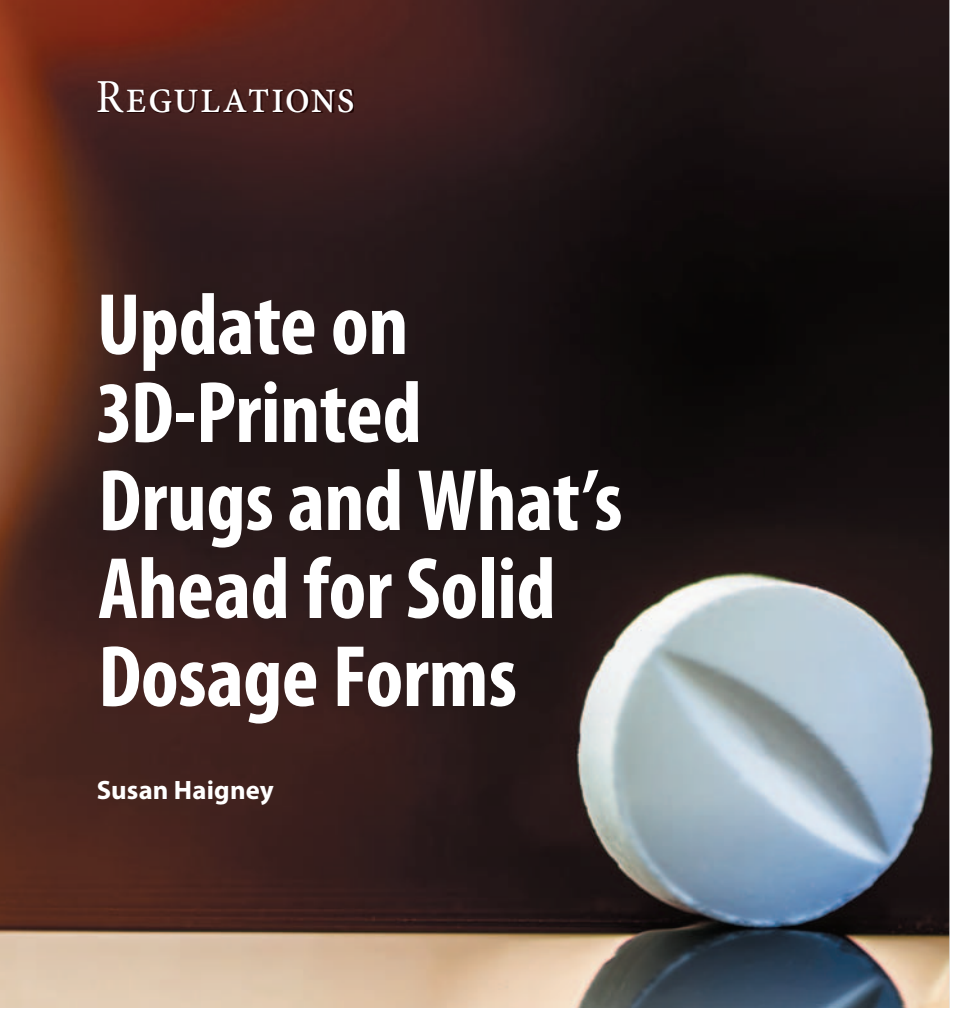
Another approach is the development of higher-performance versions of existing excipients that help manufacturers optimize their production processes. Temtem notes that Dow, for instance, is developing excipients for the pharmaceutical industry that have lower viscosities and thus allow for higher solids concentrations in SD formulations and/or the ability to process spray-dried systems under milder conditions.

The development of novel excipients, or new chemical entities, is not as common but is ongoing despite the challenges in obtaining their approval. BASF, for example, is developing a new excipient with a good balance between the hydrophilic and hydrophobic moieties that provides good stabilization of APIs in solid dispersions while also maintaining supersaturation for an extended period of time, according to Temtem.

Mesoporous silica is also a substance attracting significant interest from the pharmaceutical research community as a potential excipient for ASDs. Mesoporous silica has small pores and a high surface area and has been used for many years as a catalyst in chemical processing and for various applications in the food industry. "For ASDs," observes Temtem, "the size of the pores in mesoporous silica is ideal for trapping API molecules and preventing them from interacting. The material is advantageous because silica powder has good characteristics in terms of its flowability, which leads to improved downstream processing. Silica is also an inert material, and thus, there is no potential for interactions with the API or the GI tract." **PT**

Update on 3D-Printed Drugs and What's Ahead for Solid Dosage Forms

Susan Haigney



FDA is working with manufacturers to encourage industry innovation.

Innovation is key to any growing industry, and pharma is no different. Processes in the manufacturing of solid-dosage forms have stayed relatively the same for years. Innovations such as continuous manufacturing, however, have been making strides. In August 2016, FDA stated it was "working with drug makers in a new way to help the industry adopt scientifically sound, novel technologies to produce quality medicines that are consistently safe and effective—with an eye toward avoiding drug shortages" (1). As part of its commitment to fostering innovation, FDA created the Emerging Technology Program (2), which includes the Emerging Technology Team (ETT). The ETT has been working with companies on continuous manufacturing processes such as continuous aseptic spray drying and model-based control strategy. It has also been part of the development of ultra-long-acting oral formulations.

One novel approach that entered the market a couple of years ago was 3D printing of solid-dosage drugs. It has been said that 3D-printed drugs may be useful for orphan drugs and/or personalized medications that require smaller production lots (3). The first 3D-printed drug approved by FDA in August 2015, however, is produced in commercial scale. Aprecia's Spritam (levetiracetam) uses a specially developed platform to produce rapidly disintegrating high-dose drugs that are easy to swallow (4, 5).

But has FDA seen more from manufacturers on 3D printing, continuous manufacturing, or other technologies? *Pharmaceutical Technology* spoke with FDA's Center for Drug Evaluation and Research (CDER) to catch up on what the agency has been seeing regarding solid-dosage manufacturing.

3D-printed drugs

PharmTech: Since the approval of the first 3D-printed drug in 2015, has FDA developed any further regulations or guidelines for the development of 3D-printed drugs?

CDER: FDA's Center for Drug Evaluation and Research established an Emerging Technology Team (ETT) to examine and advance applications for new technologies, including 3D printing. What makes this approach novel is that this dialogue can occur during early technology development prior to the submission of a drug application to FDA. Such early engagement enables FDA to proactively identify and address potential roadblocks and helps eliminate potential delay in the adoption of promising new technologies.

FDA issued a draft guidance in December 2015 entitled, *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base*. While not specific to 3D-printing, the guidance document provides recommendations to pharmaceutical companies on effective ways to work with FDA's Emerging Technology Team. The document explains the ETT and provides specific recommendations to drug manufacturers for obtaining important early feedback from FDA regarding their efforts to develop novel manufacturing technologies. With respect to 3D printing more generally, in the context of medical devices, FDA issued a draft guidance document in May 2016 entitled, *Technical Considerations for Additive Manufactured Devices*.

PharmTech: Has the agency seen any problems regarding the manufacture of 3D drugs?

CDER: FDA inspects drug manufacturing to verify that operations are in control and adhere to the approved application methods and control strategy. Drug manufacturing is not without risk and, like other manufacturing operations, must be well-managed and maintained to ensure production and

availability of high-quality drugs. FDA collects and evaluates a variety of information about drug quality, and to date we have not seen any noteworthy manufacturing problems with a drug produced by 3D technology.

Drug manufacturing is not without risk and, like other manufacturing operations, must be well-managed and maintained to ensure production and availability of high-quality drugs.

Advances in solid dosage

PharmTech: What other new technologies in solid-dosage drug development or manufacture has ETT dealt with?

CDER: The ETT also worked closely with the manufacturer of Prezista, a solid oral-dosage drug for treatment of HIV-1 infection, as they worked on a switch from batch manufacturing to continuous manufacturing technology. The company's efforts were facilitated by the use of the *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base* guidance.

PharmTech: Data integrity has been a hot topic in the past year or so. Are there any other areas FDA is focusing on when inspecting solid-dosage manufacturing facilities?

CDER: Solid oral and semi-solid drugs account for most of the dosage forms consumers take. Thus, facilities that make them still remain the subject of a large percentage of FDA inspections. In addition to attention on data integrity issues, common themes in compliance actions that FDA is observing related to solid-dosage manufacturing include insufficient quality agreements between the sponsor and contract manufacturing organizations, or drug substance manufacturers and quality control labs; and management of the component (active and inactive ingredients) supply chain.

PharmTech: What can you tell us about some of the new and planned guidance documents in regard to solid-dosage products, such as the variety of ANDA guidance documents and *Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products; Revised Draft*?

CDER: As reflected in CDER's 2017 Guidance Agenda (6), the agency is diligently working to issue a revised draft guidance on *Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products*, as well as a number of guidance documents with respect to generics. When the documents are published, stakeholders will have an opportunity to review the guidance documents and provide comments to the dockets. In addition, FDA recently published a draft guidance for comment on *Extending Expiration Dates of Doxycycline Tablets and Capsules in Strategic Stockpiles*. Other guidance documents listed in the agenda, such as the guidance on drug products that contain nanomaterials, may also include recommendations relevant to solid-dosage products.

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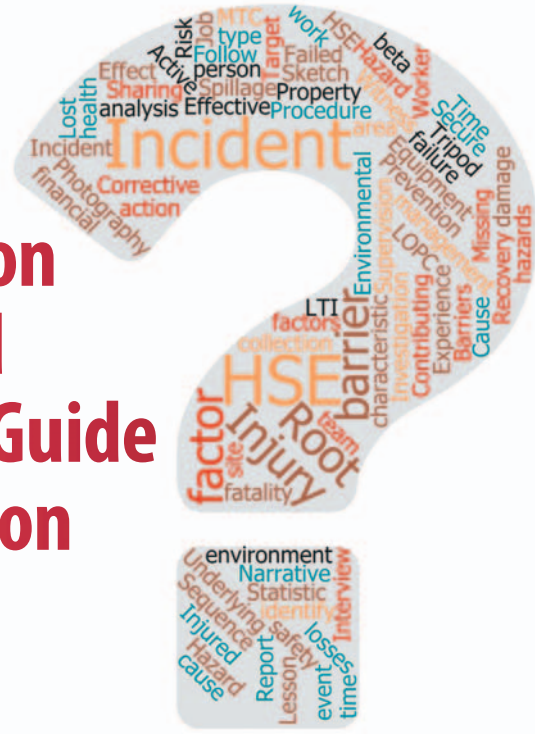
Deviation Investigation Format and Content: A Guide for Inspection Success



Pawel Drapala

This article presents a general strategy for authorship of deviation investigations, with primary focus on regulatory inspection success.

The primary purpose of a deviation investigation report in a GMP environment is to clearly and concisely demonstrate that the root cause of the deviation has been identified; corrective actions have been taken; and that safety, integrity, strength (potency), purity, and quality (SISPQ) of the product has been ensured.

The investigation report should house the details of the investigation in a manner that provides appropriate level of background and ensures the level of investigation is thorough and commensurate with level of risk. To achieve these objectives, an investigation report is recommended to contain the following sections:

1. Executive Summary
   - 1.1 Deviation event
   - 1.2 Root cause
   - 1.3 Product impact
   - 1.4 CAPAs
2. Process or equipment overview
3. Deviation event description
4. History review
5. Root cause investigation
6. Product impact assessment
7. Corrective actions.

Executive summary

The executive summary is the most visible section of the deviation investigation report. A well-written executive summary is one that satisfies the reader (e.g., regulatory agency inspector) by presenting a complete and concise synopsis of the deviation investigation. To achieve this, the executive summary should contain the following subsections:

- *Deviation event*: Two to four introductory sentences describing the deviation. Although the deviation event itself will likely be already know to the reader, the event should be restated such that the investigation report and the executive summary may serve as stand-alone documents during the inspection.
- *Root cause*: Subsection begins with "The most probable root cause of deviation # is …." followed by the concluding statement taken directly from Root Cause Investigation section (described below). It must be made clear to the reader that a formal investigation tool was used to arrive at the most probable root cause.
- *Product impact*: This subsection clearly and concisely repeats the product impact concluding statement taken directly from Product Impact Assessment section (described in the following). If no product impact has been confirmed, then this section should state at that onset "There is no expected product impact resulting from this deviation as confirmed by … (e.g., quality attribute testing, in-process controls, quality risk assessment, etc.)"
- *Corrective actions*: This subsection begins with "The following CAPAs [corrective actions and preventive actions] have been implemented to address the root cause of this deviation," followed by a bulleted list of the CAPAs and/or change controls. Regulatory agencies will expect corrective actions be taken in response to deviations, so a strong emphasis should be made by the manufacturer to demonstrate that a proactive approach has been undertaken to correct the deviation root cause.

Background (process and/or equipment overview)

If the reader proceeds pass the executive summary and into the main body of the investigation—and because the

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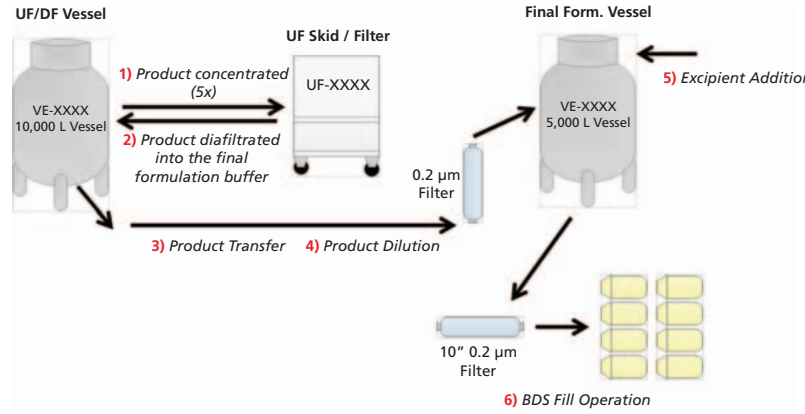
reader may only have a high-level understanding of the event—a process or equipment overview is necessary for complete background information of the deviation event.

While it is important to give an adequate level of detail, emphasis should be placed on clarity. Deviation investigations likely deal with a series of complex events that are site-specific such as manufacturing equipment malfunctions, production process aberrations, or assay techniques. To clearly visualize complex processes, the use of flowcharts, process flow diagrams, or parts and assembly drawings is highly recommended in this section (see example in **Figure 1**).

The process or equipment overview section should reference all pertaining documents, including internal documents (standard operating procedures [SOPs], batch records, engineering test plans, validation master plans, etc.) and external references (peer-reviewed journals, vendor reports or manuals, certificates of analysis [CoAs], etc.). It is up the regulatory agencies to request these documents if deemed appropriate.

Figure 1: Example of a process flow diagram within a process overview section of a deviation investigation.



Deviation event description

Once a sufficient process or equipment overview has been provided, the next step is a detailed description of the nonconformance that caused the deviation event. Depending on the complexity of the event, the use of tables, timelines, or flow charts may be warranted. Emphasis is placed on clarity of the sequence of events leading up the deviation.

The goal of the deviation event description section is to not only to describe the deviation event in detail, but to outline the immediate actions that were taken. A justification for initial classification of the deviation event (e.g., minor, major, critical) should be provided with reference to documentation for classification justification (e.g., deviation management SOP).

History review

The history review section is intended to provide the reader with an overarching historical context of the deviation event. This section typically includes a query of the quality management system with specific words and phrases pertaining to the current deviation event with the goal of identifying similar and/or related events.

If the deviation event is a first-time exclusive event, then it should be stated that a query was performed with no previous instances identified. Conversely, if the investigation encompasses several events, it may be necessary to depict the historical context in an outline, timeline, or Gantt chart. Emphasis should be placed on clarity for a first-time viewer.

Depending on the size of the organization, it may also be necessary to perform a global assessment of the deviation event to confirm to the reader that corrective actions will be implemented throughout the organization and the supply chain.

Root cause investigation

The root cause investigation section is intended to demonstrate to the reader that a systemic and logical approach was undertaken to arrive at the most probable root cause as stated in the executive summary. Numerous formal root-cause-analysis tools may be used, depending on the scope and complexity of the deviation. Examples of common root-cause analysis tools that are applicable to pharmaceutical manufacturing include fishbone diagrams, 5-why analysis, fault tree analysis, and failure modes and effect analysis (FMEA).

Under ideal circumstances, the pharmaceutical manufacturer should have SOPs dedicated to root-cause analysis. These SOPs should be referenced and executed as part of the deviation investigation write-up. At minimum, it is recommended to categorize all potential root causes or other factors into what is commonly referred to as the 5Ms: manpower, method, machine, materials, mother nature (environment).

Once categorized into the 5Ms, the potential root causes may be further subdivided based on likelihood as one of the following categories: ruled out, unlikely (non-ideality), contributing factor, and most probable root cause. **Figure 2** depicts an example of the type of output that may be generated using this form of cause-effect analysis. As with all sections, emphasis should be placed on clarity such that the reader may easily relate the most probable root cause to the deviation event and the resulting corrective actions.

Product impact assessment

The primary purpose of the product impact assessment section is to determine the extent (if any) that the devia-

FIGURES COURTESY OF THE AUTHORS.

Figure 2: Example of cause and effect analysis table within the root cause section of a deviation investigation.

Table 1: Summary of Potential and Probable Root Causes and Associated CAPAs

Potential Root Cause	Category	Likelihood	Justification / CAPA if applicable
Maintenance or calibration activities adversely affected the agitator seal.	Manpower	**Ruled out**	Change control and preventive maintenance review indicates that only temperature and pressure transmitter calibrations were performed since last inspection.
Agitator shaft loosened upon excessive torque or under reverse agitation.	Machine	**Ruled out**	The agitator was maintained under validated state and cannot run in reverse direction (see IQ/OQ, mixing studies).
CIP abnormalities.	Method	**Ruled out**	No abnormalities were reported. All CIP cycles were reported as passing. The agitator rotation during CIP is 75 rpm (manufacturer recommendation is 50 to 100 rpm).
Failure of O-rings internal to agitator bearing.	Material	**Most Probable Root Cause**	O-ring failure led to a breach resulting in liquid entering agitator bearing, traveling down the shaft and into the agitator seal. **CAPAs:** • CA-17-XXXX Replace the SMO agitator O-ring with an alternate design (the SMA agitator)

Table I: A severity, occurrence, detection (SOD) impact assessment is a qualitative risk analysis performed by ranking the severity, occurrence, and detection as high, medium, or low.

	Severity (S)	Occurrence (O)	Detection (D)
Low (1)	Not noticeable/ cosmetic	Highly unlikely	Almost certain to detect failure
Medium (2)	Noncritical aspect of product or process impaired	Occasionally	Fair chance of detecting failure
High (3)	Patient safety or regulatory compliance endangered	Repeated/almost certain	Highly unlikely to nearly certain not to detect failure

tion event affected the pharmaceutical product SISPQ, for lot(s) tagged with the deviation event. A secondary purpose of this section is to determine the risk to process or equipment, which might affect future lots. Ideally, this section should demonstrate to the regulatory agency that SISPQ of the product has been ensured.

SISPQ impact may be assessed by the following:

- Impact to critical quality attributes (CQAs) and critical process parameters (CPPs)
- Severity, occurrence, detection (SOD) assessment of any additional physical, biological, or chemical risks.

The CQAs and CPPs must be within an appropriate limit, range, or distribution to ensure the desired product quality. If the deviation resulted in a CQA out-of-specification (OOS), as determined in the root cause section, then there's sufficient evidence of product impact to merit lot rejection. Conversely, if there is no demonstrated impact to the CQA and CPP, a further assessment of any additional risk may be performed using a SOD assessment.

The SOD assessment may be applied to any potential physical, biological, or chemical risks identified as part of the root cause investigation. SOD assessment is a method used to quantify potential risks to product quality by ranking the severity (S), occurrence (O), and detection (D) as low (1), medium (2), or high (3) (see **Table I**). The output of a SOD assessment is termed a risk priority number (RPN), and is defined as a multiplier of severity, occurrence, and detection (S × O × D). An RPN of 9 or less typically indicates negligible patient risk and may be used to demonstrate to the reader that there is no product impact as result of this deviation event. The product impact assessment should conclude with a clear and concise list all potential risks associated with the deviation event and the corresponding RPNs, if an SOD assessment was performed.

Corrective actions

The purpose of the corrective actions section is to provide a list of CAPAs and change controls in response to the root cause and all of the contributing factors (if any) that were identified in the root cause section. It should be clearly emphasized to the reader that a proactive approach has been taken to rectify the deviation event and prevent reoccurrence.

Depending on the scope of the deviation event, it may be appropriate to subdivide the corrective actions based on priority (e.g., immediate corrective actions, long-term corrective actions, etc.). All corrective actions should include the following sections:

- Proposed due date
- Brief background
- Actions
- Deliverables
- Effectiveness check (if required).

After all of the corrective actions have been listed, the deviation investigation should conclude with a clear statement that the problem has been corrected and that the deviation is not expected to reoccur.

Conclusion

To achieve regulatory inspection success in a GMP environment, a well-written deviation investigation requires balance between conciseness, completeness, and adequate level of detail. Emphasis must be placed to clearly communicate to the reader (the inspector) that a deviation root cause has been identified, that the corrective actions have been undertaken, and that the quality of pharmaceutical product has been ensured. **PT**

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BASF Ups Ibuprofen Capacities in Germany and North America

On June 28, 2017, BASF announced plans to build a new world-scale plant to produce ibuprofen in Ludwigshafen, Germany. "It will be the first world-scale ibuprofen plant in Europe," Markus Kamieth, a member of the Board of Executive Directors, BASF SE, said in a press statement. Production is expected to begin in 2021.

BASF is also expanding its ibuprofen capacities at its production site in Bishop, Texas, to fill current supply gaps for ibuprofen in the market. The expansion is on track for completion in early 2018. With approximately €200 million ($226 million) invested in both projects, BASF aims to ensure reliable supply security for its customers and meet growing global demand.

According to Melanie Maas-Brunner, president of BASF's Nutrition & Health business, both investments will enable BASF to close supply gaps and efficiently support its customers' growth plans.

"We are one of the originators of a sustainable and high-quality ibuprofen value chain and chemistry," Francois Scheffler, vice-president of BASF's Global Segment Management Pharma Solutions and Human Nutrition, told *Pharmaceutical Technology* in an exclusive interview.

Scheffler highlighted that as a non-steroidal inflammatory drug (NSAID), ibuprofen has seen ongoing growth over a long period of time. "Ibuprofen is one of the best painkillers available on the market," he said. "It's not just because it has the least side effects but it also has anti-inflammatory action."

Commenting on the drivers behind the increasing demand for ibuprofen, Scheffler said, "On one hand, we have a growing population who want access to Western-type medicines, especially in eastern Europe and Asia, and this includes Western-type painkillers. On the other, there is a cultural change where people today are generally less willing to put up with pain. Whether it's children, or adults, or the ageing population, we are seeing a much bigger need to find solutions for pain."

"Another factor supporting the massive growth of painkillers is in the area of sports," Scheffler explained. "When people do sports or when they do activities, they don't want to have pain, so they start taking painkillers on a more regular interval."

Scheffler pointed out that at the moment, there is a significant shortage of supply of ibuprofen. "It puts our customers in a very difficult position because they have to meet the growing demands of the market and from their patients," he said. "This is why BASF decided to invest in the new world-scale plant ibuprofen manufacturing plant."

The investment at Ludwigshafen is also partly for sustainability reasons, according to Scheffler. "We are very concerned about how some of the chemical pathways carry risk for the environment, and how some procurement methods do not sufficiently take into account the environmental consequences, be it on the health of workers, or directly on the environment in terms of waste in the air or in the water. Therefore, as a leading supplier for ibuprofen around the world, we felt that we need to be the one showing the way."

BASF has been manufacturing ibuprofen at its FDA-audited, cGMP-certified production site in Bishop for more than 20 years. BASF operates an eco-efficient production process that ensures high product quality levels.

Analytical Testing— *contin. from page 71*

Shimadzu also recently introduced a nano-technology based antibody bioanalysis sample preparation solution called the nSMOL Antibody Bioanalysis Kit. This kit performs selective proteolysis of the antibody Fab region and greatly simplifies and streamlines antibody bioanalysis sample preparation. We expect to see many more similar innovations in nano-technology and micro-fluidic based sample preparation for the biopharmaceutical industry in the next five to 10 years.

Newey-Keane (Malvern): For biologics, the informational need is still being refined, particularly when it comes to biosimilars and the demonstration of BE; and analytical requirements are evolving in tandem with this. Getting more information from each sample remains crucial as this enables information gathering earlier in the drug development pipeline. Robustly identifying the best candidates as early as possible clearly cuts the time and cost of biopharmaceutical development.

The application of orthogonal techniques is bringing significant challenges in terms of data handling. The quantity of data is one issue, but a more taxing one is how to handle what can appear to be divergent data sets. Software platforms that integrate and rationalize data from an optimal set of techniques will be the way forward.

In terms of online implementation, we already have techniques such as laser diffraction particle size analysis that have successfully completed this transition but, over the coming years, others will follow suit. Such instrumentation will need to deliver exemplary reliability as CM matures, but will also be judged on ease of integration as automated control becomes a more routine feature of pharmaceutical processing.

Cubbon (Thermo Fisher Scientific): The list of molecular characterization assays demanded by regulators for biologic drugs is extensive. Typically, more than 30 individual chromatographic or immunoassays are performed to test for critical quality attributes of drug candidates by biologic manufacturers, which is both labor- and time-intensive.

Over the next five years we will see technologies emerging to amalgamate multiple assays into one and simplify the process. An area where this is already being implemented in the area of multiple attribute monitoring (MAM) using HRAM—a single workflow capable of replacing multiple individual steps. Several companies already have drug candidates in late-stage development using this workflow. In 10 years, this technology will move from a laboratory process off-line, to being beside the bioreactor at/on-line to inform the manufacturer immediately of the structural properties of their candidate molecules.

Wyatt (Wyatt): I believe artificial intelligence (AI) will lend its benefits to our industry in the not-too-distant future. With more data being generated, it may become harder to distill information from the data. AI holds the promise of aiding the data interpretation and becoming wiser, the more data to which it's exposed. **PT/40**

MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

Ad Index

Inspections: The Value of the Opening Presentation

The opening presentation gives the company a chance to put their best foot forward, according to Siegfried Schmitt, principal at PAREXEL.

Q: Our manufacturing facility is inspected regularly by various agencies. There are differences between these inspections, but one constant is that we always kick off with an opening presentation. Do you have any suggestions how we can make our opening presentations most effective?

A: This is an astute observation, and it is indeed important to give the opening presentation much thought. In fact, the opening presentation is the only time when a company is in control during an inspection and is the opportunity for the company to present the information that they consider important.

Let us consider what makes an opening presentation stand out and achieve its objectives. The main objective should be to present the company and facility being inspected in a positive light. Think of the inspectors as customers; ask yourself the following so you may provide the essential information they seek: What do they want to know? Why are they here?

The following are some practical suggestions to prepare for the presentation:

- The presentation should be complete, reviewed, and approved weeks before the inspection. Trying to improve it minutes before the inspectors arrive is never a good idea. Mostly companies use programs such as Microsoft PowerPoint, which works well, so long as presentations do not become overwhelmed by unnecessary transitions or effects.
- The length of the presentation should not exceed 30 minutes, if possible. It is not uncommon for inspectors to cut presentations short if they think that time is being wasted. One should allocate three minutes per slide, considering time for potential questions to be addressed. While additional slides can be prepared, they should be kept as backup.
- Technology should be thoroughly checked the day before the inspection to ensure that all is in working order. A back-up copy of the presentation should be ready on a portable device, just in case.
- The presenter can be the head of quality, the site manager, or the sales manager. The exact title or role of the chosen presenter is less important than their competency and confidence when discussing the contents of the presentation. Far too often, presenters click through a slideshow without portraying passion or genuine interest. Presenters should communicate that they are proud of their plants, quality systems, and place of work. Inspectors will pick up on a lack of enthusiam and that often impacts inspection results.

It is key that only essential, pertinent facts and figures are included in the slides shown.

After the inspectors have arrived, the presentation can begin. A color copy of the slides (one slide per page) should be printed and be available for inspectors so that they can take notes and make annotations.

A presentation's contents should include a site layout plan, one to two key organizational charts, key operations on site, and inspection history. But what about the quality system? As one inspector put it: 'usually the level of quality is inversely proportional to the number of times quality is mentioned in the opening presentation.'

In recent years, inspectors' time is at a premium. It is key that only essential, pertinent facts and figures are included in the slides shown, presenting a company's commendable aspects, people, and systems. If your presentation follows these suggestions, respecting the time and needs of inspectors, you should see happy inspectors beginning their work, which will ideally lead to a positive inspection. **PT**

Your opinion matters.

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

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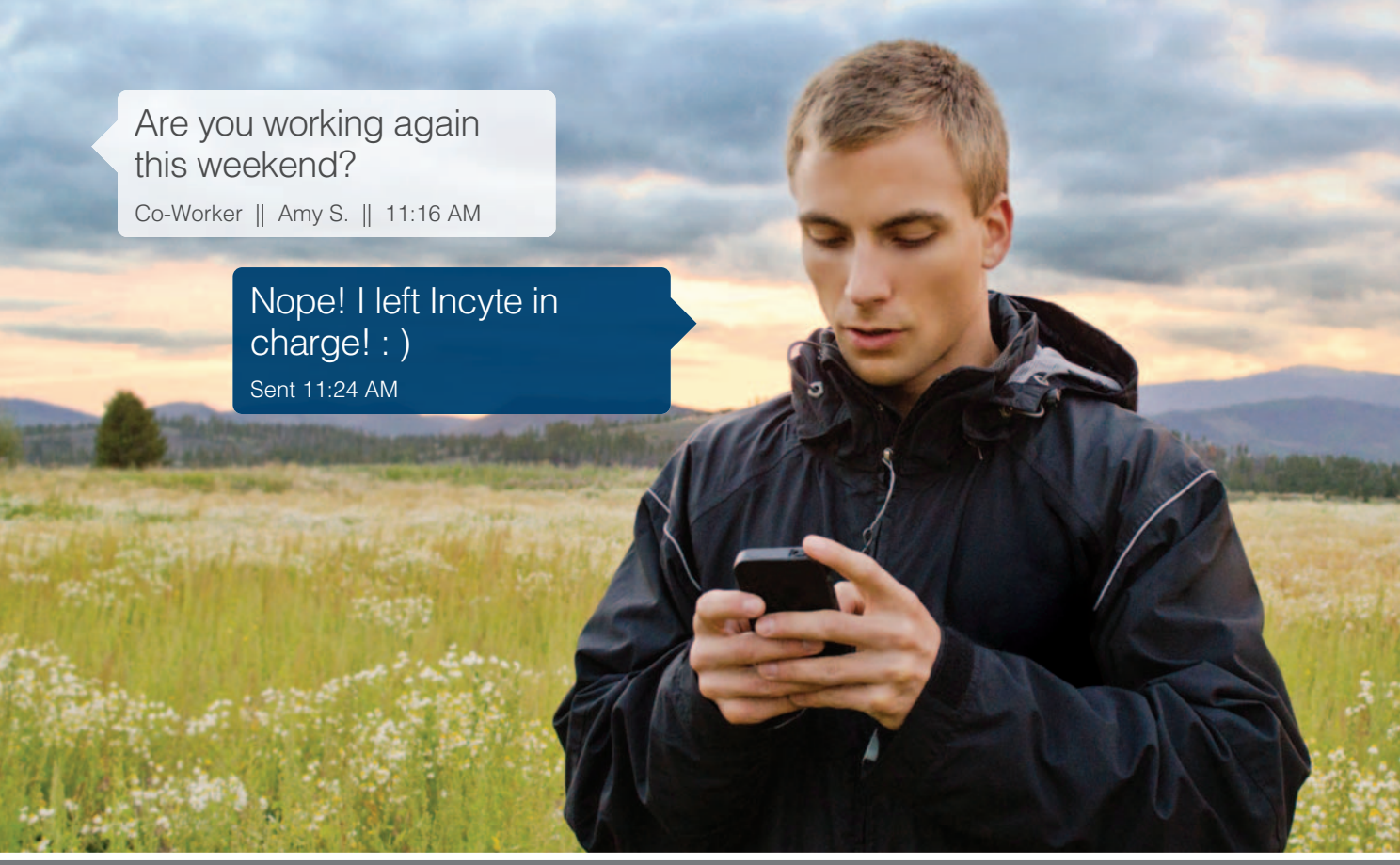

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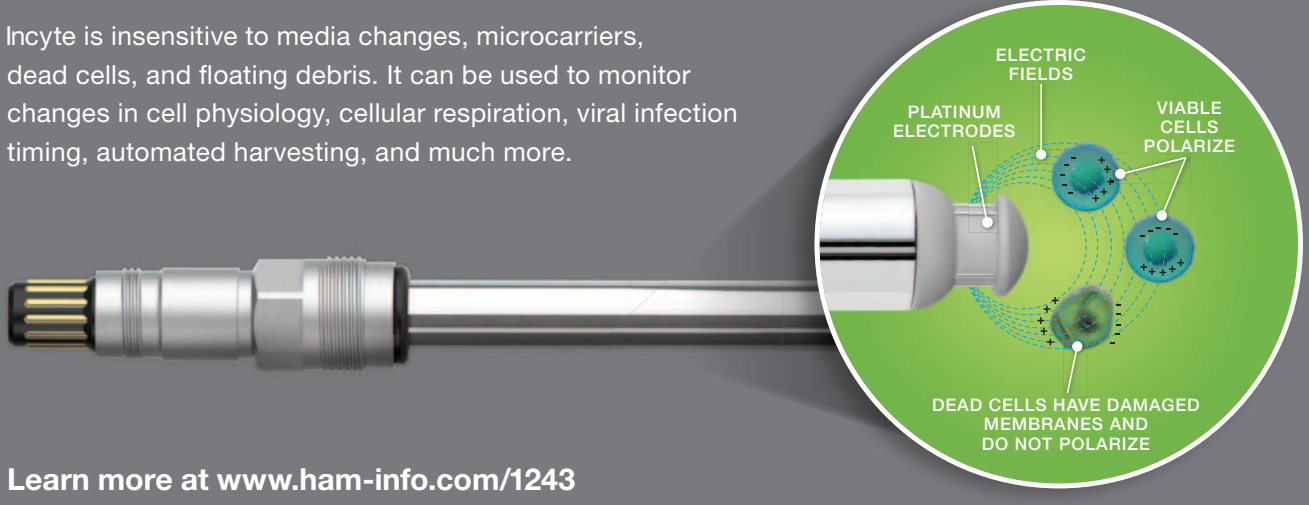

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