Advancing Development & Manufacturing

PEER-REVIEWED
An Investigation of the Anomeric Stability of Lactose Powder Stored Under High Stress Conditions
Phytochemical APIs and Botanical Extracts

APIs  Atropine, Digoxin, Homatropine, Pilocarpine, DHEM and N-Butylbromide Scopolamine.

R&D  Route scouting and lab-scale synthesis of complex organic molecules.

CMO  Manufacturing services for APIs and Botanical Extracts.

Centroflora CMS is the key sponsor of the “Partnership for a Better World” program that ensures a sustainable, traceable & fair-trade harvesting of phytochemical and botanicals used for pharmaceutical APIs such as Pilocarpine. The program contributes to the development of local communities and the preservation of the Brazilian biodiversity.

WE WELCOME YOUR VISIT AT DCAT 2017
ENVISION A PARTNER WITH MORE.


Take a closer look at MPI Research to find more of what you're looking for. You deserve a strategic, responsive and efficient partner for your early stage drug development. MPI Research offers that and more.

With an impressive breadth of discovery and preclinical scientific knowledge and services, our team of highly trained research scientists and world-class facilities provide the insights to see your project through. We do everything we can to make your vision a reality.

When you want more from your CRO, look to MPI Research.

- DRUG SAFETY EVALUATION
- DISCOVERY SCIENCES
- BIOANALYTICAL & ANALYTICAL
- MEDICAL DEVICE STUDIES
- DMPK
- SURGICAL SERVICES
For more than 30 years, VAI has pioneered the design and manufacture of hundreds of clean room solutions.

- Cleanest wipe in the industry
- Asepti-Fill® closed filling system
- Laundered in Class 1
- Saturated wipes are made with WFI
- Lot Specific Documentation for all wipers
- Laser cut sealed edges

Quadruple Bagged using the ABCD Introduction System®

No other company offers this broad a range of wipers...

- DAS-Wipe®
  Stainless Steel cleaning and lubricant wipe
- STEEL-BRIGHT® Wipe
  Stainless Steel Cleaning wipe
- ALOH-Wipe®
  Saturated with DECON-AHOL® WH 70% USP Isopropyl Alcohol
- DECON-Clean® Wipe
  Removes residue from disinfecting agents
- HYPO-CHLOR® Wipe
  Saturated Sodium Hypochlorite Wipe
- STERI-PEROX® WIPE
  Saturated Hydrogen Peroxide Wipe
- PROCESS® WIPE
  70% USP IPA in Water for Injection saturated wipe
- WIPEDOWN
  Dry cleaning wipe

www.sterile.com
1-888-4-STERILE
Since 1992, Marchesini Group USA has been one of the leading companies supplying the most technologically advanced packaging solutions to the North American pharmaceutical and cosmetic industries.


BOOTH 3125
Jacob Javits Center, NY | March 21-23, 2017

© 2017 UBM. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical including by photocopy, recording, or information storage and retrieval without permission in writing from the publisher. Authorization to photocopy items for internal/educational or personal use, or the internal/educational or personal use of specific clients is granted by UBM for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Dr. Danvers, MA 01923, 978-750-8400 fax 978-646-8700 or visit http://www.copyright.com online. For uses beyond those listed above, please direct your written request to Permission Dept. fax 440-756-5255 or email: maureen.cannon@ubm.com.
Ross Planetary Mixers are versatile. While suited to handle a wide range of processes, they are uniquely built to take on viscous applications. Mix gels, pastes, putties and shear-sensitive materials up to 6 million cP.

With laboratory sizes starting at 1/2-pint, up to 1000-gallon units for large-scale production, Ross has the Planetary Mixer to fit your process line.

Learn more at mixers.com. Call 1-800-243-ROSS or try our free online Knowledge Base & Product Selector web app at Mixers.com/web-app.
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.

COVER STORY

18 Achieving Manufacturing Excellence
Moving to the next level of productive, reliable performance in bio/pharmaceutical manufacturing requires a willingness to make changes and create a quality culture.

Cover Design by Dan Ward
Images: valdis torms/shutterstock.com

FEATURES

API SYNTHESIS & MANUFACTURING
24 Oral Delivery of Biologic APIs: The Challenge Continues
Effective solutions for overcoming the high molecular weight, hydrophilicity, and instability of large biomolecules have yet to be identified.

FORMULATION
30 Key Considerations in Capsule Filling
Capsule filling is a complex process, and the product to be encapsulated must be well developed to ensure mass uniformity.

PROCESS CONTROL AND AUTOMATION
46 Integrating Industrial Internet of Things and Pharmaceutical Manufacturing Processes
Industry experts discuss IIoT and its impact on pharmaceutical manufacturing.

QUALITY: RISK-BASED PREDICTIVE STABILITY
52 Risk-Based Predictive Stability—An Industry Perspective
A survey on risk-based predictive stability tools reveals how pharma companies are leveraging advanced stability approaches throughout the drug development process.

QUALITY AGREEMENTS
58 Quality Agreements: Managing Global Relationships
A robust quality agreement and good communication scheme can help avoid and alleviate regulatory concerns.

DATA INTEGRITY
62 Harnessing Advances in Informatics to Ensure Data Integrity
Although best practices are key, advances in integrated informatics platforms and automation can make it easier to ensure data integrity and improve overall lab efficiency.

FACILITY MODERNIZATION
70 GMP Facility Modernization: Opportunities for Successful Implementation
The DME Facility Focus survey revealed best practices for coping with the challenges of aging facilities.

TRACK AND TRACE
74 Serialization Hits the Home Stretch
As the November 2017 deadline nears, a surprising number of companies still don’t have a serialization plan in place. New programs aim to get them compliant in time.

PEER-REVIEWED RESEARCH

ANOMERIC STABILITY OF LACTOSE POWDER
36 An Investigation of the Anomeric Stability of Lactose Powder Stored Under High Stress Conditions
This study investigated the stability of solid lactose stored under high temperature and humidity conditions.
Non-sterile ointments, creams & liquids that come through our facility get the same high level of scrutiny and quality oversight that sterile products do.

Specialized capability to support multiple dosage forms

...Transfer and manufacture of complex formulations
...Available capacity for large scale manufacturing
...Potent products (up to SafeBridge 5)
...Milling and totally enclosed vessels
...Oxygen sensitive compounds
...Light sensitive products
...Explosion proof room
...Controlled substances
...Hormones
NEWS & ANALYSIS

FROM THE EDITOR

12 Strategizing a Shortcut to Market
Drug type, potential sales, and ownership factor in the race to get drugs to market.

TROUBLESHOOTING

80 Understanding Containment
The new ISPE Containment Manual is a summary of the process involved in the manufacture of highly active or highly hazardous pharmaceutical substances.

OUTSOURCING OUTLOOK

84 Will Pharma Manufacturing Move Back to the US?
Moving global manufacturing operations may be more complicated than it appears.

REGULATION & COMPLIANCE

US REGULATORY WATCH

16 International Trade Issues Threaten Global Pharma Operations
Manufacturers face uncertainty over imports, regulatory policies, and field inspections.

ASK THE EXPERT

106 Covering Global Regulations in a Quality System
Siegfried Schmitt, PhD, Principal Consultant at PAREXEL, discusses how to mitigate risk in a global regulatory environment.

DEPARTMENTS/PRODUCTS

14 Product Spotlight
88 Pharma Capsules
90 INTERPHEX Exhibitor Guide
105 Showcase/Marketplace
105 Ad Index

Pharmaceutical Technology is selectively abstracted or indexed in:

- Biological Sciences Database (Cambridge Scientific Abstracts)
- Biotechnology and Bioengineering Database (Cambridge Scientific Abstracts)
- Business and Management Practices (RDSI)
- Chemical Abstracts (CAS)
- Current Packaging Abstracts
- DEHEMA
- Derwent Biotechnology Abstracts (Derwent Information, Ltd.)
- Excerpta Medica (Elsevier)
- International Pharmaceutical Abstracts (ASHP)
- Science Citation Index (Thomson)

Pharmaceutical Technology is proud to be a member of IPEC and PDA.
From processing to packaging, we’ll show you the way

Products with unique needs require carefully-engineered solutions, not a limited menu of options. That’s why MG America brings unrivaled expertise in processing and packaging machinery to help custom-craft a solution that is perfect for your individual product needs.

Innovation? We’ve got that too, from our groundbreaking MultiNET™ Weight Control System to our state-of-the-art packaging lines, we’re advancing into exciting new areas to meet your growing needs.

Put your vision in our hands...and start seeing things in a whole new way.

MG AMERICA
A partnership for success
Fairfield, New Jersey
973-808-8185 • 866-962-3090
mgamerica.com

See us at Interphex Booth #2221
FROM THE EDITOR

Strategizing a Shortcut to Market

Rita C. Peters

Drug type, potential sales, and ownership factor in the race to get drugs to market.

During the past 20 years, the overall median total time required by FDA to approve a new molecular entity (NME) new drug application (NDA) or biologic license application (BLA) dropped from 12 months in 1996 to 7.8 months in 2016 (1). In that same time, FDA’s Center for Drug Evaluation and Research (CDER) accelerated the median total approval time to approve a standard NDA or BLA from 17.8 months to 10.1 months. The median total approval time for priority review applications was relatively steady during those 20 years; however, the 2016 time of eight months was less than half of the 20.5 months required in 1993 (2).

While FDA has reduced approval times, a recent report by Quintiles-IMS (3) revealed other factors that may contribute to the time required to bring a drug to market. The study authors examined time trends for two segments of a drug product’s lifetime. The first segment—where those professionals involved in drug development have an impact—is the time from the patenting of a new drug molecule to the time it first reaches patients. The second segment—when the drug owner can recover its investment in the research and development of the drug product—is the time the molecule has exclusivity on the market thanks to patent or other protections.

The study was based on 667 innovative small- and large-molecule drugs launched in the United States between 1996 and 2015. More than 300 groups filed original patents that became the basis for the 667 drugs. Large Pharma accounted for 60% of new drugs; companies classified as mid-pharma and small pharma each represented 20%. Oncology, orphan, biologic-based, and specialist-driven therapies all increased market shares during the time studied.

**Patent to market**

The filing of a patent is a business decision and can occur years in advance of, or close to, a launch date. The mean time from initial patent filing to launch for all molecules for the US market in the 20-year period was 12.8 years, the study reports, with an upper quartile of 16.3 years and lower quartile of 8.2 years.

The shortest time from patent to launch was 128 months in 1998; the longest was 211 months in 2008 when FDA approved fewer drugs (19) than any other year during the study. While some in industry attributed the drop to a more conservative approach by FDA following the withdrawal of Vioxx from the market in 2004, FDA cited a drop in new drug applications. Since 2008, the time from patent to launch has steadily declined to an average of 158 months for the five most recent years, a drop of four years or 25%. This increase in speed brings time to approval back to levels experienced in 1996–2000.

**Organic growth speeds process?**

An analysis of drug type showed that oncology drugs, on average, launched 34 months faster than other drug types. Drugs that achieved at least $1 billion in US sales by 2015 reached the market 27 months faster than drugs with lower sales.

The dynamic licensing, partnering, and acquisition nature of the bio/pharma industry, however, may be a greater factor in delaying the introduction of a new drug, the study suggests. Nearly three-quarters of the patented molecules were launched as drugs by a company that was different from the one that originally filed the patent. Those drugs launched by the same company that filed the original patent, however, took an average of 36 months less time to be launched than those that changed ownership, the authors reported. The transfer of a molecule from one company to another for development funding, technical expertise, or corporate strategy may ultimately get a drug to market. The path, however, may be longer than desired.

**References**

ENGINEERING MEDICINES TO LIFE

Capsugel’s unique capabilities and expertise in product design and particle engineering can prove crucial for enhancing the bioperformance of inhaled therapeutics. We design and optimize formulations using an array of specialized tools, including micronization, spray dry processing and nanocrystal technologies. Combined with formulation expertise for both small and large molecules, specialized DPI capsules, and finished product manufacturing capabilities to commercial scale, Capsugel is the right partner to bring your product from concept to market.

© 2017 CAPSUGEL BELGIUM NV ALL RIGHTS RESERVED.
Tabletop Pill Counter Automatically Counts and Fills Solid Oral-Dose Products

The Pharmafill TC4 Tabletop electronic tablet counter from Deitz Co. automatically counts pills, tablets, capsules, softgels, caplets, lozenges, and other solid oral-dose products and fills them into bottles. The Pharmafill TC4 counts translucent, transparent, and opaque solid oral-dose products at up to 2000 per minute. The Tabletop TC4 is a computer-controlled operation, and measures 34 inches across, 21 inches deep, and 30 inches in height. The TC4 entry level counter includes an air guide system that automatically separates and aligns the pills on a single layer, a vibratory hopper feeder that automatically regulates the flow of tablets into the counter, and an optional smart bottle sensing system that automatically stops operation in the event of a problem with the bottle.

Deitz
www.deitzco.com

Intelligent Stand for Pipette Management

The Rainin SmartStand from Mettler Toledo includes four pipette holders. The stand includes an LCD screen that displays its status in a clear visual language: green is good, yellow indicates that service is required soon, and red signals that the pipette is beyond its service or calibration date. A more detailed view of the pipette’s service and asset record can be viewed when the pipette is removed from the stand. Each Rainin SmartStand holds up to four manual or electronic Rainin XLS pipettes and automatically charges electronic pipettes when they are placed on the stand.

The included EasyDirect Pipette Asset Management software is a flexible, scalable Windows-based pipette asset management tool that can connect to multiple SmartStands simultaneously via Bluetooth. When a pipette is serviced or calibrated, users place the pipettes on a SmartStand to transfer new service data from their radio-frequency identification chips into EasyDirect. EasyDirect maintains a profile with 11 customizable fields for each pipette, so lab managers can assign unique information, such as the user and lab, applications and ID/inventory number, to a pipette and record it to its RFID chip. EasyDirect can also help users find pipettes by identifying which SmartStand they’re hanging on. EasyDirect graphically indicates which pipettes are due for service, making them instantly recognizable. By capturing usage data through the SmartStand, EasyDirect helps lab managers reduce asset costs and eliminate pipettes that are no longer in use.

Mettler Toledo
www.mt.com

Loading Bench for Cold-Chain Management

The OCEASOFT Loading Bench is an innovation for cold-chain monitoring management for transportation and high-volume shipment. The bench programs temperature datalogger missions with sensor reading intervals and alarm limits. The bench also performs a series of tests to verify hardware and battery level on dataloggers. The tool offers the ability to set how and when temperature monitoring begins, at a specific temperature, date or time, or manually. The loading bench includes an application for configuring missions and storing templates. The bench also transfers each datalogger’s configuration information to the cloud automatically. The loading bench will be available in Q2 2017.

OCEASOFT
www.oceasoft.com

Mixers for Blending Applications

Ross, Charles & Son offers a variety of mixers for mixing and blending applications. The dual-shaft mixers (pictured) are suitable for mixing 50-, 100-, and 200-gallon batches and are equipped with two independently-driven, variable-speed agitators, and a high-speed disperser and a two-wing anchor. Both agitators provide adjustable shear and efficient turnover of low- to high-viscosity materials including pastes, gels, suspensions, slurries, and fine dispersions up to several hundred thousand centipoise. The mixers come standard with an air/oil hydraulic lift, vacuum capability, jacketed mix vessel, stainless steel wetted parts, and inverter-duty motors.

The company also offers a Portable High Shear Mixing System designed for powder dispersion into liquid, emulsification, and homogenization in a closed, temperature controlled vessel. The 200-L mixing system featuring stainless steel 316L wetted parts, sight/charge ports, ASME dimpled jacket rated for 85 psig, chloride-free insulation with stainless steel sheathing, high accuracy weighing scale, and NEMA 4X gas-purged controls. The mixer is mounted on the cover in a vapor-tight sealing arrangement. Its four-blade rotor runs up to 3600 rpm within a close tolerance slotted stator, delivering mechanical and hydraulic shear. The mixer is driven by a 5 HP stainless steel wash-down duty explosion-proof motor.

Ross, Charles & Son
www.mixers.com
As American as the All-Star Game.
Your All-Star in Lactose — GranuLac® 200.
Made in the USA.

Cutting-edge quality was never easier to get. MEGGLE, Europe’s leading expert in excipients, finally moved to where the action is. Our most popular product GranuLac® 200 is now produced in the USA. Enjoy the best of both worlds: German tradition and American precision, right in your backyard. Get in touch and find out.

GranuLac® 200 lactose monohydrate — proven quality, readily available.
Made in the USA.
International Trade Issues Threaten Global Pharma Operations

Manufacturers face uncertainty over imports, regulatory policies, and field inspections.

The Trump Administration has proposed to create more jobs in the United States by pressuring manufacturers to reduce overseas production and to shift operations back home. This poses serious problems for pharmaceutical manufacturers around the world, as the US imports approximately 50% of finished drugs from Europe, Asia, and other regions. Moreover, up to 90% of APIs for US production of finished dosage forms come from overseas, largely from China and India, according to FDA. A tax on such imports, as has been proposed, would be devastating to both US and European-based companies, raising costs that would undermine efforts to lower prices for prescription drugs.

At the same time, Trump’s ban on travel and immigration from several Muslim countries ignited a firestorm among biotech firms, educators, and the biomedical research community. Even though the courts rejected the policy, US companies advised workers to minimize overseas travel, while meeting organizers looked to shift programs from the US to avoid entry problems. Although leading pharma manufacturers sidestepped the issue, more than 150 biotech executives, academics, and venture capital leaders voiced strong objections to the restrictions in a letter published in Nature Biotech (1). The signers state that the travel ban “has compromised years of investment” in the vital US biotech industry as it raises the sense that “America is no longer welcoming of any immigrants.”

The corporate annual meeting season brought these issues to the fore. Novo Nordisk CEO Lars Fruergaard Jørgensen lowered his earnings forecast for 2017, noting a “volatile” market situation in the US and concerns about a 20% border tax on imports (2).

Overseas inspection challenges

The rise in imports of both APIs and finished drugs has focused attention on FDA efforts to ensure the quality and safety of foreign-made medical products. FDA conducted more foreign inspections of drug establishments in 2015 than of domestic facilities, and that trend appears to be continuing, as FDA uncoverers foreign operations with unsanitary manufacturing conditions and inadequate documentation of operations to ensure adherence to GMPs.

“Globalization has complicated FDA’s oversight of drugs marketed in the US,” according to the Government Accountability Office (GAO) in its latest report on continuing shortcomings in the agency’s overseas offices and foreign inspection programs (3). FDA still has not inspected nearly 1000 of 3000 foreign establishments in its data base, GAO said, nor does it have sufficient information on the roles and value of its foreign offices in China, Europe, India, and Latin America. The analysts note persistent high staff vacancy rates in its foreign offices, and continued reliance on US-based investigators under FDA’s Office of Regional Affairs (ORA) to visit facilities listed in market applications for new drugs.

One response is for FDA to rely more on inspection reports from competent regulatory authorities in Europe, Japan, Canada, Australia, and other nations with well-established drug inspection and compliance programs. FDA officials and colleagues from the EU and other inspectorates have been examining and evaluating each other’s inspection procedures and capabilities for several years and hope to finalize agreements that would reduce the need to send investigators to facilities already inspected by local authorities.

Inspection overhaul

Just how the new administration deals with global pharmaceutical production issues is unclear. At the White House meeting with pharma executives several weeks ago, President Trump promised to speed up processes for approving drug production plants as one way to accelerate approvals of new drugs (4).

One opportunity is to implement a proposal for a major reorganization of ORA’s 5000-person field inspection force, which involves adopting a commodity-based, vertically integrated inspection program with specialized inspection cadres for drugs, biologics, medical devices, food, and other regulated products. While the agency’s current plan is to “stand up” this much-anticipated Program Alignment (PA) initiative by May 15, a new FDA commissioner and other top staffers most likely will want to reassess such a major organizational change.

This reorganization initiative was announced in 2014, and FDA centers issued PA Action Plans in 2015 to implement the extensive changes involved. The plan is for ORA to maintain 20 district offices across the US, with some concentrating on certain product areas, such as food or drugs, and additional specialists covering other areas. It also will incorporate a more automated and streamlined program for examining and vetting imports of regulated products, which have mushroomed in recent years. The initiative emphasizes the need for specialized, highly trained investigators able to identify and respond effectively to “questionable conditions.”

ORA has named senior-level program directors at FDA headquarters in Maryland to oversee operations for six main product areas: food, biologics, drugs, medical devices, bioresearch monitoring (BIMO), and tobacco, plus operations involving imports and ORA laboratories. Ginnette Michaud is program director for biologics, which includes blood products, tissues, vaccines, and other products overseen by the Center for Biologics Evaluation and Research (CBER). Alonza Cruse
is pharmaceutical quality program director and leads PA collaboration efforts for drugs regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine. Additional program directors head similar efforts to coordinate inspections for medical devices, tobacco products, and animal and human food, along with bioresearch monitoring for all medical products. Each district office will have a director, plus program managers to head inspection cadres at that location. ORA plans to roll out more details and organizational information over the coming weeks, explained Michaud at the WCBP Symposium sponsored by CASSS in Washington, DC in January.

A key goal of the PA reorganization is to enhance communications and collaboration between field inspectors and center product specialists. CDER’s Office of Process and Facilities (OPF) in the Office of Product Quality (OPQ) works closely with ORA pharmaceutical inspectors to provide an integrated quality assessment from a preapproval inspection. OPF has three groups of specialists to assess information in new drug applications on facilities, processes, and microbiology. Data in an application can facilitate an inspection, while inspection information can support application review, commented David Doleski, OPF deputy director, at the WCBP symposium. OPF also is developing a New Inspection Protocol to standardize and define elements that enable scoring and comparison of drug facility inspections. This initiative will expand to cover more inspections and manufacturers.

OPQ’s Office of Surveillance similarly collaborates with ORA on GMP inspections at plants. Staffers review inspection reports and other data, including a facility’s inspection history and type of products produced, to help determine the need and timing and extent of a surveillance inspection.

References
Moving to the next level of productive, reliable performance in bio/pharmaceutical manufacturing requires a willingness to make changes and create a quality culture.

In any industry, manufacturing or operational excellence can be thought of as efficiency, productivity, and reliability, with minimized downtime and few product failures. But excellence is an ever-moving target. “Manufacturing excellence is not just the best way to do it today, but continually improving to the next level,” suggests Hal Baseman, chief operating officer at ValSource LLC.

In the pharmaceutical industry, manufacturing excellence also encompasses the need to serve patients by providing safe and effective medicines without an interruption in supply. Regulatory quality requirements—current good manufacturing practices (cGMPs) and product testing, for example—are designed to ensure safety and efficacy, but opinions vary as to whether compliance necessarily leads to excellence. “Compliance is important, but it is not where a firm should focus the majority of its resources and efforts. The bio, pharmaceutical, and medical device industries must transform to embrace quality beyond compliance,” advises Martin Van Trieste, chairman of the board at the Parenteral Drug Association (PDA).

Some have the misconception that profitability and quality are mutually exclusive; compliance is costly, and quality is just too costly. In reality, “quality processes are more profitable. They are more reliable and error free. Yields are higher, rejects and defects lower,” says Baseman. Proponents of operational excellence in pharma hope that the industry will move from a compliance to a quality culture.

**Elements of excellence**

What is needed to achieve manufacturing excellence? To perform at six sigma quality levels, says Van Trieste, a manufacturer must:

- Understand and characterize its raw materials, manufacturing processes, and products
- Be fully engaged in identifying, monitoring, and controlling variation
- Have systems and processes in place that ensure flawless execution during manufacturing
- Deliver products in a robust and reliable supply chain.

Robust process design, highly qualified personnel, a reliable supply chain with second sources identified for critical components, and well maintained, reliable equipment, are all crucial, adds Sue Schniepp, distinguished fellow at Regulatory Compliance Associates. “In addition, there must be a functioning quality system underlying the entire process that is proactive in identifying issues and risks to the supply chain by using metrics and information that inform the company of potential problems,” she says. The three metrics proposed in FDA’s November 2016 guidance (lot acceptance rate, product quality complaint rate, and invalidated out-of-specification rate) (I) are three basic measures, but companies also need to develop and use their own metrics beyond FDA’s program (see Sidebar).

Traditional quality measures in pharma focus on product measures or end results, but “smart” devices and equipment provide more data about the equipment during the process that can be analyzed. “Automation, data collection, and data handling are part of the informatics movement that is one of the fastest growing areas in manufacturing. Compared to other industries, pharma is well behind the curve in this respect and it represents a huge improvement opportunity for the entire industry,” suggests Marc Bonner, senior director of operations at Mayne Pharma USA.

Automation and process analytical technology (PAT) help to reduce human error and support data-based decision making, adds Frank Generotzky, plant manager for Baxter BioPharma Solutions’ Halle, Germany facility. “These are helpful tools to handle and statistically evaluate data to identify process variations in a
It’s OK. We all make mistakes. You thought the discounted tablet press would perform just as the salesman promised. And then the problems started. Lots of problems. But don’t despair. There is a solution.

FETTE’s team of highly-trained specialists is standing by to get you through this difficult time. As a global leader, they have unmatched expertise, premier customer service…and they are really good listeners.

Life can be full of regrets, but your tablet press shouldn’t be one of them. Call 973.586.8722. Counselors are standing by.

FETTE COMPACTING AMERICA
400 Forge Way
Flockaway, NJ 07866
sales@fetteamerica.com
www.fette-compacting-america.com
Manufacturing Excellence

timely manner. Quick decisions for optimization can be made based on technical/scientific data leading to an environment of continuous improvement.”

Achieving manufacturing excellence requires process understanding, risk-based thinking and decision making, science, and common sense, adds Baseman. “The bio/pharma industry tends to focus too much on what we think regulators want to see, rather than what we actually need to do to improve the process.”

Practical steps for improving
One of the first steps in moving toward excellence is the willingness to look for areas that need improvement and the courage to make changes, whether that means better use of existing technologies or using new technologies or systems that can bring a process’ performance to the next level.

Often operators and staff have many ideas for what could be improved. Leaders must prioritize where to start. “My advice is to start with a project that is creating the most pain for operators in manufacturing and make significant improvements quickly,” recommends Van Trieste, who points out that this action is a good way to gain needed support from the plant floor. “Success breeds success. Only take on new projects that can be accomplished with the existing resources, and only start another project after one has successfully completed,” he suggests.

Different approaches. Continuous manufacturing and PAT, for instance, create opportunities for improving process efficiency and productivity. The focus on improved process understanding that comes with implementing these technologies is likely a significant driver for process improvements, says Thomas Friedli, professor of management at the University of St. Gallen’s Institute of Technology Management, who has been studying pharmaceutical manufacturing practices since 2004. Data indicate that the most successful companies “have a higher focus on true root cause analysis and also have more PAT implementation,” he says.

“Embracing new technology often requires new and different ways of thinking,” notes Baseman. “For example, continuous manufacturing is a great way to increase process efficiency, but existing strategies for batch control, validation, and testing don’t always align well with it. People have to get past the concerns over batch definitions and traditional means to test and monitor processes.”

Industry experts weigh in on FDA’s Quality Metrics program.

As FDA has noted, the same quality metrics used by the bio/pharmaceutical industry to evaluate manufacturing and fuel continuous improvement efforts “can also be useful to FDA to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the Agency’s ability to predict, and therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing.” This potential was highlighted in FDA’s most recent draft guidance on this topic (1).

FDA’s Quality Metrics program for pharmaceutical manufacturing is clearly a work in progress, and FDA’s November 2016 revised draft guidance, Submission of Quality Metrics Data, calls for a voluntary reporting phase through which “FDA expects to learn more about a limited set of quality metrics, associated analytics, and improve the FDA quality metrics reporting program” (2).

Operational excellence programs at many manufacturing facilities already measure, review, and implement metrics, and “developing synergistic quality metrics that will have wide-ranging acceptance by the industry makes tremendous sense,” wrote Thomas Friedli, professor of management at the University of St. Gallen’s Institute of Technology Management, and consultant Prabir Basu in the 2016 CPhI Annual Industry Report (3). Friedli, Basu, and Nuala Calan of the Dublin Institute of Technology are working on an FDA-funded quality metrics research project that was awarded to the University of St. Gallen in July 2016.

The research involves using the group’s database as a scientific basis to propose potential quality metrics, explains Friedli. The three initial metrics to be collected by FDA do not adequately reflect a company’s internal processes, and other key indicators are needed, said Basu in an interview with Pharmaceutical Technology published in January 2017 (4).

“Companies need to review and analyze the information the FDA is asking for, as well as other metrics they are collecting, and identify potential problem signals so that they can solve issues and self-correct before regulatory inspections,” adds Sue Schniepp, distinguished fellow at Regulatory Compliance Associates. The metrics that FDA will collect are not primarily intended to help individual companies achieve manufacturing excellence, but are a limited, standardized set of a metrics to help FDA identify companies that may have problems that affect the supply chain. Manufacturers shouldn’t have a goal of simply meeting these minimum requirements. “If we are not careful, the temptation may be to manage to the metrics. And in the end, managing quality to minimal regulatory expectations is never a good idea,” cautions Hal Baseman, COO at ValSource LLC.

Such metrics can be a starting point, however. Proactive companies might use this initiative to give new momentum to their own quality and excellence programs, suggests Friedli.

“One way to encourage firms to develop and improve their quality culture and product quality is to establish an effective use of publicly available quality metrics, leading to product, plant, and company grading. I believe that quality metrics combined with a grading system will revolutionize the approach to quality within our industry, significantly improving product quality,” says Martin Van Trieste, chairman of the board at the Parenteral Drug Association, who has developed such a grading system and a scorecard for pharma quality (5).

“However, it will not be easy to develop or implement a quality metrics program. If it is to succeed, the right metrics must be chosen, industry skepticism must be overcome, and there must be checks and balances within the system,” he says.

References
A tendency to focus and rely on testing and monitoring rather than process improvement can hinder change. “The pharma industry is good at collecting data, testing, and monitoring, but needs to be better at listening to what that data tells them,” says Baseman.

Aging facilities. The regulatory burden of post-approval changes for existing processes is a real concern, but this barrier must be overcome to achieve excellence. While PDA’s new Post Approval Change Innovation for Access to Medicines (PAC iAM) taskforce is working to create awareness and find broader industry solutions to this challenge (2), companies are finding ways to improve their facilities where the benefits outweigh the costs and risks (3). Modernizing aging manufacturing facilities requires long-term benefit analysis. “It is often a matter of progressive process improvement. One step may result in only a 10% increase in productivity by modernizing, but that step will set you up for another 10% improvement when you make the next change, and so on,” suggests Baseman.

Reluctance to upgrade manufacturing equipment and facilities is a barrier to excellence. “Older equipment can be unreliable and hard to maintain, resulting in unforeseen downtime,” notes Schniepp. Another problem is older products that are not up to today’s standards. “Many of these products were developed with different standards than those required for new products. The transitioning to today’s standards can be a time-consuming process and could potentially result in supply chain interruptions. If the industry can work with regulatory authorities in determining a path forward to updating these products, then this obstacle could be overcome,” she suggests.

Continuous improvement programs
Various methods are available to help manufacturers improve quality and set up continuous improvement programs, including Six Sigma, Kaizen, lean manufacturing, and operational equipment effectiveness (OEE), and many companies use pieces of these depending on the problems that need to be solved. “I see more companies using an internally branded, blended approach to solving problems and implementing effective change that sticks,” adds Jerry Rosenthal, director of continuous improvement for US Pharma Commercial Operations at GlaxoSmithKline (GSK). “A balanced combination of project management, change management, and continuous improvement (Lean and Six Sigma) seems to be on the way to becoming the most common way for pharma manufacturing to achieve their goals.”

“There is no one-size-fits-all program. Every approach should start with an analysis of the company’s current status,” says Friedli, who advises that teams tackle any underlying equipment or process instability issues before trying to reach other objectives, such as taking out waste and driving down inventories. The Univer-

---

**SCALEABLE**

**Fluid path solutions**

We can work with you at every process step

Our scalable technology with constant contact materials minimizes validation. We deliver repeatable, consistent and accurate performance.

Peristaltic pumps • High purity tubing • Liquid filling • Fluid path components

Weirless Radial diaphragm valves • Sanitary gaskets • Reinforced silicone hoses

wmftg.com/biopharm

800-282-8823

---

**Pharmaceutical Technology** MARCH 2017 21
Manufacturing Excellence

ity of St. Gallen’s Operational Excellence (OPEX) Benchmarking program aims to help analyze a company’s starting point on a scientific basis. For the past three years, Friedli’s team has also been moder-
ing an industrial OPEX exchange group to facilitate conversation about best prac-
tices and experiences.

Japanese quality gurus such as those who developed the Toyota Production System describe the need for senior management to be in touch with people actually doing the work, in the “Gemba,”
Japanese for the place where truth will be found. Gemba walks—getting onto the plant floor to see problems first-hand, and try to get suggestions from workers to help solve them directly—have the advantage of allowing managers to take action to solve the problem at its source, rather than just measure and monitor, notes Baseman. At the same time, improvement programs should have measurable, objective metrics. “Understanding the performance of pro-
cess and equipment is the first step to improve-
ment. One cannot improve without objective methods to assess and evaluate manufacturing,” says Baseman.

OEE is used by many to improve productivity. “We measure and review OEE daily to understand what is affect-
ing our equipment availability, performance, and quality and put action plans in place, following the Deming cycle ‘Plan, Do, Check, and Act’ to track our performance improvement,” notes Catherine Kay, Operations director at Aesica. “We are also looking to implement measures for ‘Mean Time to Repair (MTTR’), which is the average time that it takes to repair equipment after a failure.”

Programs used at Vetter include OEE, Six Sigma, lean manufacturing, and the internal “Vetter Optimization System,” which includes a Production Excellence (PRODEX) initiative. PRODEX is de-
signed to track all aspects of production, including people, material, machines, customers, and processes, explains Ger-
ald Buerkle, vice-president Pharmaceutical Production, Vetter-Pharma-Fertigung. The program has helped improve quality and yield, increase flexibility and capac-
ity, and improve personnel management, among other benefits.

The main benefit to any of these pro-
grams is having a structured approach

Operational excellence at Baxter BioPharma Solutions

The Baxter BioPharma Solutions (BPS) Oncology manufacturing expansion project at its Halle, Germany location was the winner of the Operational Excel-

ence category of the 2016 International Society of Pharmaceutical Engineering (ISPE) Facility of the Year Awards (1). The company applied lean manufacturing principles in designing the expanded facility. The flexible design with adapt-

cable equipment gave the company the ability to have rapid changeover to manufacture a wide variety of liquid formulations. Pharmaceutical Technology spoke with Frank Generotzky, plant manager for Baxter BioPharma Solutions’ Halle, Germany facility, about operational excellence at the site.

Keys to success

PharmTech: How would you define manufacturing excellence or operational excellence for the pharma industry, and what are the keys to achieving it?

Generotzky (Baxter): The pursuit of operational excellence is an ongo-
ing goal driving improvement. Operational excellence leads to continuous im-
provement to increase efficiency as well as capacity while maintaining high
quality and client satisfaction. Some examples of methods include:

- An innovative facility layout optimized using a ‘form follows function’ concept, designed and planned utilizing visualization tools for pro-
cesses and parameters
- Optimal equipment design defined by using simulation models for critical process steps (e.g., mock-ups, computational fluid dynamics, 3-D simulation models)
- An experienced project team that accompanies all phases from design and validation through routine operation.

PharmTech: What programs have you found to be successful?

Generotzky (Baxter): It is important to implement programs where all employees are involved (from operator to manager) to enhance success. Cre-
ating an uplifting experience for the employees by implementing programs internally such as SS and process visualization helps to pave the way for the implementation of more complex systems such as operational equipment effec-
tiveness or SixSigma. At the end of the day, success is dependent on having the necessary tools (e.g., a value stream map being supported, for example, by

Table: Operational excellence at Baxter BioPharma Solutions

<table>
<thead>
<tr>
<th>The Baxter BioPharma Solutions (BPS) Oncology manufacturing expansion project at its Halle, Germany location was the winner of the Operational Excellence category of the 2016 International Society of Pharmaceutical Engineering (ISPE) Facility of the Year Awards (1). The company applied lean manufacturing principles in designing the expanded facility. The flexible design with adaptable equipment gave the company the ability to have rapid changeover to manufacture a wide variety of liquid formulations. Pharmaceutical Technology spoke with Frank Generotzky, plant manager for Baxter BioPharma Solutions’ Halle, Germany facility, about operational excellence at the site.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keys to success</td>
</tr>
<tr>
<td>PharmTech: How would you define manufacturing excellence or operational excellence for the pharma industry, and what are the keys to achieving it?</td>
</tr>
<tr>
<td>Generotzky (Baxter): The pursuit of operational excellence is an ongoing goal driving improvement. Operational excellence leads to continuous improvement to increase efficiency as well as capacity while maintaining high quality and client satisfaction. Some examples of methods include:</td>
</tr>
<tr>
<td>- An innovative facility layout optimized using a ‘form follows function’ concept, designed and planned utilizing visualization tools for processes and parameters</td>
</tr>
<tr>
<td>- Optimal equipment design defined by using simulation models for critical process steps (e.g., mock-ups, computational fluid dynamics, 3-D simulation models)</td>
</tr>
<tr>
<td>- An experienced project team that accompanies all phases from design and validation through routine operation.</td>
</tr>
<tr>
<td>PharmTech: What programs have you found to be successful?</td>
</tr>
</tbody>
</table>
| Generotzky (Baxter): It is important to implement programs where all employees are involved (from operator to manager) to enhance success. Creating an uplifting experience for the employees by implementing programs internally such as SS and process visualization helps to pave the way for the implementation of more complex systems such as operational equipment effectiveness or SixSigma. At the end of the day, success is dependent on having the necessary tools (e.g., a value stream map being supported, for example, by failure mode and effects analyses, fishbone diagrams, and standard control charts). Additionally, statistical tools should be leveraged in order to determine variation signals early in the process so that countermeasures can be imple-
mented in a timely manner. |
| PharmTech: What aspects in particular of lean manufacturing have been most beneficial? |
| Generotzky (Baxter): Applying 5S in manufacturing areas and increasing the time that managers are on the floor (‘Gemba Time’) can help ensure a high degree of standardization and discipline. Continuous measurement of process parameters with standard control charts and statistical evaluation leads to continuous improvement of yield and reduction of process deviations. |
| Standardization and flexible design |
| PharmTech: What is the importance of process standardization? |
| Generotzky (Baxter): A high degree of standardization ensures low variability between batches, reduces stock and work in progress, and helps to enhance planning security. Standardization leads to stable and predict-
able processes, which are the basis for true efficiency enhancements. |
| PharmTech: What is flexible design and how does this lead to operational excellence? |
| Generotzky (Baxter): Today’s products have become more complex to manufacture (e.g., nanotech products) and smaller from a volume perspec-
tive, and additionally there is the demand to simplify the handling infrastructure to be as efficient as possible. In many cases, the same manufacturing rooms are used for different process set-ups. The result is that manufacturing departments need to change process design between manufacturing of batches quickly and efficiently. Standardized modular equipment and process design is important to minimize set-up and turnover times to manufacture efficiently and remain cost competitive. Therefore, we define flexible design as one important component in our operational excellence program. |
| Reference |
to determining what needs to be done to improve operations, and a viable course of action to implement the improvements, says Schniepp.

“We’ve found that a structured process makes it easier to train personnel and provides tools and techniques to solve problems,” says Bonner. “It also provides consistency and continuity to the problem-solving process, which helps streamline rapidly solved or similar problems and improves persistence and perseverance to systematically address larger or more complex issues.” Whatever approaches are used must fit in a company’s culture.

**Culture of excellence**

“Culture” might seem an ambiguous term, but experts say it is crucial for achieving excellence in anything, including manufacturing. “Manufacturing excellence is an entire philosophy, and, to become sustainable, it must be deeply ingrained in the structure and the culture of the company,” says Friedli. He notes that “one-dimensional efforts only aimed at cost cutting, short-term initiatives, and no visible top management commitment,” among other problems, are signs that initiatives will not be sustainable.

“All levels of the organization must be involved and invested, from the line operator and maintenance personnel to the general manager,” adds Schniepp. “Having a consistent culture can be particularly challenging when multiple sites or companies are involved, such as CMOs. The CMOs need to have a manufacturing excellence culture, as well as their clients.”

People tend to resist change, notes Van Trieste, but “an effective leader must create the case for change, tie the case for change to the mission of the organization, and be specific about what has to change and who it will impact.” Leaders must also overcome the fact that organizations in pharma still tend to work in silos (e.g., R&D, Quality Control, or Operations), rather than crossfunctionally.

They must gain and maintain alignment of goals and priorities across the silos in their organization so that all the stakeholders are engaged, says Van Trieste.

Quality and continuous improvement must be more than the names of departments in the company—they must become what everyone is trying to achieve. Ideally, if the concepts and tools of continuous improvement were to truly become “part of the way things get done, part of the first step, and not the last consideration, then I believe that manufacturing excellence would be something that more pharma organizations could achieve with ease,” predicts Rosenthal.

**References**

Oral delivery of drugs is the preferred route of administration by both patients and manufacturers. Ease and convenience are the greatest requirements for patients, which leads to higher medicine adherence. Production costs for oral dosage forms also tend to be lower than for other options and offer the greatest versatility with respect to optimization of drug delivery.

For biopharmaceuticals, however, oral administration has been limited to a few relatively smaller molecules, including peptide products such as desmopressin and cyclosporine for systemic treatment, and a number of other products for local treatment. Many attempts have been made to develop oral insulin and other treatments for diabetes, but none have yet been successfully commercialized. Novo Nordisk, for example, halted development of its oral insulin product in October 2016.

The difficulty lies in the physical and chemical properties of large biomolecules and the physiology of the gastrointestinal (GI) tract. Overcoming these fundamental characteristics is challenging. “Numerous approaches have been explored to enable the oral delivery of biologic APIs. These range from using permeation enhancers to support permeation through the tight junctions of the epithelium, to nanocarriers to force active transport while protecting the biologic API from the gut, to making pro-drugs of the biologic APIs to enhance passive permeation,” observes David Lyon, director of research at Capsugel’s Bend, OR facility. He notes that each of these approaches has had modest success in animal models, but has yet to develop into a commercial product.

The nature of things

The greatest challenge to the oral delivery of biologic APIs is absorption across the GI tract, according to Ronak Savla, scientific affairs manager, Catalent Pharma Solutions. Most oral drugs are absorbed in the small intestine, which has the highest permeability compared to the large intestine and stomach. Characteristics of the GI tract that influence absorption include the surface area and mucosa permeability of the particular segment; the pH; the presence of food, bile, enzymes, and bacteria; and the number of structures such as Peyer’s patches and lacteal ducts.

For biomolecules, however, their large size and polar surface make it difficult for them to diffuse across the epithelial layer. “Molecules with molecular weights of less than 700 Daltons are relatively easily absorbed, which does include peptidomimetics; while those above 1000 Daltons, regardless of size, are not typically absorbed to any extent,” Savla says. In addition, most biologic molecules, including peptides, violate Lipinski’s Rule of Five, which is used to determine if a drug molecule has physicochemical properties that will allow it to be therapeutically active when orally administered. “Drug lipophilicity has the strongest correlation with oral bioavailability; there appears to be a minimum degree of lipophilicity required for oral absorption,” Savla adds.

A second important issue for biologic APIs is their susceptibility to enzymatic and chemical degradation in the GI tract. “Specifically, the physicochemical delivery challenges include hydrolytic sensitivities of the molecules to the acidic media in the gut, as well as the enzymatic activity of the intestine,” explains Lyon. Once the active is absorbed, there are additional opportunities for degradation inside both intestinal epithelial and liver cells, which in the latter is referred to as the hepatic first-pass effect.

The main consequence of the poor absorbance and degradation of biologic APIs administered orally is low bioavailability. In some cases, this issue can be overcome by using higher doses, but doing so raises concerns about both potential side effects and excessive costs.

Drug formulation efforts focus on overcoming the various physicochemical challenges to increase bioavailability. Permeation enhancers

Cynthia A. Challener is a contributing editor to Pharmaceutical Technology.
“Off-the-shelf solutions? No thank you. After all, our customers are something special.”

Daniel Drossel
Mechanical Engineering Technician
(Design department)

Each customer has its very own special requirements. That’s why we, at Optima, manufacture filling lines that are fine-tuned to our clients’ particular needs while offering the benefits of an integrated and complete line: The complete machine package including high-precision functionalities, backed by consistent documentation and supported by an optimized and tailored software solution – in addition to a central point of contact who is passionate about your every concern… We are experts in special solutions, after all.

INTERPHEX New York | March 21 - 23, 2017 | Booth # 3103
and enzyme inhibitors are commonly used. Encapsulation and/or the use of protective (enteric) coatings can help prevent chemical and enzymatic degradation. Modification of the biologic API structure through either covalent or non-covalent bonding with lipophilic substances is another approach.

The stability of biologic drug substances must also be considered when developing formulations. For instance, some techniques used for the production of small molecules—such as those that introduce heat or organic solvents—may not be suitable for biologic products. In addition, according to Savla, the prevention of aggregation upon storage can be a challenge, particularly for biologic products in solution. “Temperature, pH, and—in some cases—light can have an important impact on protein structure during manufacturing, which can lead to a delicate balance between the formulation, process conditions, and stability of the biologic API,” Lyon comments.

**The role of functional excipients**

A common theme across current approaches is the use of functional excipients such as permeation enhancers. “The larger size and hydrophilicity of biologic molecules hinders their passage across cells. Permeation enhancers are typically used to increase the space between epithelial cells in the GI tract lining,” Savla explains. Common enhancers include bile salts, fatty acids, surfactants, salicylates, chelators, chitosans, and zonula occludens toxin (1).

Use of these excipients does, however, have the potential to cause damage to the mucosa and to allow absorption of other substances, such as other prescribed APIs in patients taking multiple drugs or even gut bacteria and their toxins.

Enzyme inhibitors are also used to prevent degradation of biologic APIs by enzymes in various parts of the GI tract, according to Savla. Examples include sodium glycocholate, bacitracin, and soybean trypsin inhibitor (1).

**Structural modification approaches**

In addition to the use of functional excipients as formulation solutions, common approaches to increasing the oral bioavailability of biologic APIs include modifying the drug molecule and/or the biological system.

**The greatest delivery challenge is absorption across the GI tract.**

A range of technologies have been explored for modifying the structure of biomolecules, including the use of polymers, the formation of nanoparticles, and their inclusion in lipid systems. In many cases, all three approaches are employed. “Each technology has its pros and cons and may be more suitable for certain molecules or applications over others. Lipid systems are interesting because there have been a lot of studies completed with small molecules and they can both increase the permeability of biologic molecules and protect them against hydrolysis and enzymatic degradation,” says Savla. Examples of lipid systems include liposomes, archaesomes, and emulsions.

Encapsulated biologics often exist as nanoparticles. Encapsulation protects the active against degradation, while the size of nanoparticles allows for better penetration through the stomach lining, according to Savla. In addition, tailored receptors that target the GI tract lining for enhanced absorption can also be attached to encapsulated proteins. Polymers used for the preparation of such nanoparticulate formulations include chitosan and chitosan derivatives and other polymers commonly used for the preparation of small-molecule drugs (1).

More exotic solutions include “robotic” pills, such as those being developed by Rani Therapeutics. Tiny needles comprised of a permeation enhancer, which are pushed by self-inflating balloons that function under specific conditions in the intestine, deliver the biologic active through the intestinal wall.

Actual modification of the protein structure through conjugation with lipophilic compounds (fatty acids) or oligomers such as polyethylene glycol (PEG) has also been investigated. Crystallization of proteins can improve oral delivery, but typically is quite difficult for most biologics (1).

“Manipulation of the structure of biologic drug substances using any of these approaches must be pursued with caution, however, given the fact these structures are not only complex but crucial to the efficacy and safety of the drug product,” Savla asserts.

**Manipulating biochemistry**

In addition to modifying the structure of the biologic API, some approaches focus on manipulation of bacteria that are commonly found in the intestine. Many of these bacteria are designed to tightly bind to the intestinal mucosa. Through genetic engineering it is possible to create versions of these bacteria that can produce and secrete protein APIs and deliver a high concentration to the absorption mucosa, avoiding the possibility of degradation, according to Savla. In addition, these bacteria can deliver the biomolecules throughout their lifetimes in the intestine. This technology can be combined with modification of protein structures to increase lipophilicity and resistance to degradation.

There are also promising oral technologies being developed by companies such as Applied Molecular Transport (AMT) that use poorly immunogenic transporter proteins covalently linked to biologic APIs to actively transport them across the epithelium, according to Lyon. AMT’s Transit platform provides targeted delivery of peptides and proteins to cells in the GI tract or liver using the non-toxic portion of the protein cholix toxin, which delivers a toxic compound produced by *Vibrio cholera* across the gut epithelium. The
Contract Aseptic Manufacturing

- Aseptic Fill/Finish
- Lyophilization Services
- Clinical & Commercial
- Formulation Development
- Analytical Services
- Product Storage & Distribution

Quality • Performance • Integrity

www.pyramidlabs.com
714-435-9800
carrier protein is covalently bound to the biologic API for delivery to the GI tract, while a linker inserted between the two allows delivery to the liver following enzyme cleavage.

“These types of approaches are elegant at delivering peptides and proteins, but still require protection of the construct from the stomach and intestinal environments,” Lyon says. He notes that the combination of such a transporter technology and Capsugel’s intrinsically enteric capsule technology, or enTRinsic drug delivery technology, may prove effective for providing both physicochemical protection and permeation. “Our enTRinsic drug delivery technology, which uses an enteric polymer in the capsule shell thereby avoiding the need for enteric coating and the high temperatures associated with coating processes, provides acid-, water-, and enzyme-impermeable capsule characteristics that allow the cargo to be delivered intact to the site of absorption while protecting the active molecules,” Lyon explains.

**Continued efforts**

Despite the high level of interest in formulating biologic drugs for oral delivery, it remains uncertain when commercial products will eventually be available. “Several programs have reached and failed in Phase III. While there are a few current programs in Phase II and III clinical trials, it is difficult to predict whether these trials will be successful. Most of these programs face competition from injectable formulations—a high bar to match or surpass,” Savla observes.

Lyon is more hopeful when it comes to biologic APIs that treat local gut disease states, such as Crohn’s diseases and irritable bowel syndrome, and expects that oral delivery for these drug substances will be fairly common within the next five years. Although he notes that great progress continues to be made translating “IV drugs to oral,” he says that significant breakthroughs have yet to be made if currently marketed biologic APIs are to be converted without covalent modification from IV delivery to drug products delivered orally.

To tackle this challenge, Catalent is taking a parallel screening approach. “We understand that there is no one-size-fits-all solution and it is difficult to predict oral bioavailability a priori. We first assess a molecule’s permeation through the oral and sublingual/buccal routes using the permeation enhancer sodium caprate. If the molecule demonstrates potential for one of these routes, we work on developing formulation candidates,” Savla explains.

**Oral delivery of biologic APIs has been a “holy grail” for several decades.**

The Catalent Applied Drug Delivery Institute’s Non-invasive Macromolecule Delivery Consortium also brings together academic and industry experts from a variety of disciplines to discuss and develop possible ways to address challenges faced by everyone in the area, according to Savla. The Institute organized a conference focused on routes of non-invasive macromolecule delivery in February 2017 in San Diego. The conference was designed to bring together leading experts from academia and industry to discuss challenges, share results, and pave the path for the next steps in the field.

“As a specialized contract service provider with a focus on product design,” says Lyon. “Capsugel has invested in technologies that solve some of the challenges associated with the non-invasive delivery of biologic APIs, including oral solutions.” As mentioned above, the company’s enTRinsic drug delivery technology overcomes the need to protect biologic APIs from the GI tract environment. “The enTRinsic technology can be used in conjunction with standard biologic APIs and pro-drugs for either systemic or local gut delivery, and we have ongoing development and clinical programs with a number of pharmaceutical and biopharmaceutical partners,” Lyon notes.

**Exciting and active area**

The oral delivery of biologic APIs—mainly peptides and proteins—has been a “holy grail” of pharmaceutical drug delivery for the past several decades, according to Lyon. “Oral delivery remains the preferred route for delivery of medicines. Biologic APIs are growing faster as a class of molecules than traditional small molecules and have enjoyed shorter development times and approval times over the past decade. While the driving factor is improved therapies, biotherapeutics also provide innovative companies with increased differentiation in their product lifecycle strategies. It is reasonable to expect that the interface of these two areas will remain an exciting and active area of research and investment in the coming years,” he states.

One potentially exciting direction of research for Savla is the intentional design of orally administered biologic APIs. “Given that most biologic drugs are injected, there is no guidance or rules of thumb for oral delivery. To date the focus has been converting existing biologic APIs initially developed specifically for parenteral administration to alternative oral delivery formulations. It is certainly possible that better success with oral delivery can be achieved if the biologic APIs are designed from the start to function effectively within the intestinal tract. Of course, there are significant risks in taking this approach given the numerous issues with the absorption and degradation of large biomolecules in the GI tract. It may in fact take initial successes with modified existing APIs before someone is willing to develop and orally administered biologic drug from scratch,” he concludes.

**Reference**

Any help with your manufacturing?

Rovi CM
Contract Manufacturing Services

Above all, your partner

Tel.: +34 91 375 62 45 / Madrid SPAIN / clopezdehierro@rovi.es / www.ovicm.es
Key Considerations in Capsule Filling

Q&A by Adeline Siew

Capsule filling is a complex process, and the product to be encapsulated must be well developed to ensure mass uniformity.

Hník Bueno, formulation and manufacturing manager at Idifarma, and Rob Harris, chief technical officer at Juniper Pharma Services, share insights on the challenges of capsule filling.

PharmTech: What type of formulations are filled in a capsule? What formulations are not suitable for capsule filling?

Bueno (Idifarma): In principle, any type of formulation may be dosed into hard capsules, from blends or granules, to coated pellets, to other oral dosage forms such as tablets, micro-tablets, smaller capsules, including various combinations of any of the mentioned forms. It is also possible to fill liquids, provided that the material of the capsule (generally gelatin, although there are other alternatives) is not soluble in the solvent used in the formulation.

Due to the need for a plasticizer in the capsule shell formulation, conventional hard gelatin capsules have a high water content (13–16%). For this reason, hygroscopic products can absorb moisture from the capsule, causing the capsules to become brittle, which can break under mechanical stress. On the other hand, such transfer of moisture to the contents of the capsule could generate problems of physical stability (crystalline form) or chemical stability of the API.

To solve these problems, capsules with a low moisture content can be developed, either by using plasticizers other than water or other polymers, such as hydroxypropyl methylcellulose (HPMC), which is the most widespread alternative.

Finally, mixtures with materials containing reactive aldehydes are not suitable for capsule filling, as they favor the “crosslinking” effect experienced by the gelatin, reducing the capsule’s solubility.

Harris (Juniper): It is possible to fill powders, granules, non-aqueous liquids, non-aqueous gels, and thermo-setting formulations into capsules. For solids, powders with poor flow properties can be problematic because of poor fill weight control. Liquids with very low viscosity can leak from two-piece shells soon after filling. Hygroscopic liquids can cause embrittlement in capsule shells.

“The choice of capsule size and fill weight is dictated by the unit dose requirements and the formulation used.”

—Harris, Juniper

Capsule size and fill weight

PharmTech: How do you decide on capsule size and fill weight per capsule?

Harris (Juniper): The choice of capsule size and fill weight is dictated by the unit dose requirements and the formulation to be used.

Bueno (Idifarma): Once the formula of the contents of the capsule is developed and the weight to be dosed is known, it is easy to define the most appropriate capsule size. The body of each size of capsule has a defined volume; and by knowing the density of the mixture to fill, we can establish the volume that will occupy the weight that must be filled in each capsule. In the case of mixtures (powder or granulate), knowing the tapped density makes it possible to determine the most suitable capsule size. For pellets or micro-tablets, where there is no possibility of compaction, it is necessary to use bulk density instead. All capsule suppliers provide capsule size tables that facilitate the choice of capsule size.

Clinical vs. commercial production

PharmTech: How is capsule filling for clinical studies different from that for commercial production?
IF YOU NEED ASEPTIC PACKAGING, BLOW-FILL-SEAL IS THE SOLUTION.

Would you like to process your liquid or semisolid formulation in a more reliable, more economical, and more user-friendly way than is possible with conventional packaging methods? Then it’s time for blow-fill-seal technology from Rommelag. Our bottelpack systems enable aseptic filling in application-optimized, tamper evident, break-proof polymer containers, which are directly produced, filled, and sealed by the system. This allows cost-effective manufacturing by avoiding container handling including empty container transport and storage, washing, and sterilization. The BFS process enables unique container designs and even insert of additional components such as valves, applicators or adapters; fill-volumes range from 0,04 ml to more than 1000 ml. More information on blow-fill-seal technology and your personal contact partner can be found on our website.

www.rommelag.com

Rommelag at INTERPHEX
New York
March 21 – 23, 2017
Stand 3516
Bueno (Idifarma): Capsule filling provides great potential for clinical trials, whether it’s filling just the API for first preclinical or clinical trials to filling other dosage forms in capsules (tablets or smaller-sized capsules, for instance) for blind or double-blind clinical trials. Capsules intended for clinical trials often have different geometries or dimensions.

Overcoming the Challenges of Capsule Filling in Preclinical and Clinical Studies

Capsule filling is common in preclinical and clinical studies. Companies are increasingly developing cytotoxic and potent compounds; containment of these substances is, therefore, a primary safety concern for laboratory managers. As the API dosed into capsules are typically not fully characterized at this stage, they must be treated as high-potency to protect the researchers handling them, because any spillage or exposure presents a potential safety risk.

Often, only a limited quantity of the drug substance is available. When working with a new chemical entity, where the synthesis program may run concurrently with the early dosing studies, early batches may be of the order of several grams, with perhaps a gram or less available for development work. At this phase, the drug is expensive and precious, so it is important to avoid wasting any.

Depending on the nature of the drug and test subject, new pharmaceuticals are often administered in gelatin capsules. The fill weight of each capsule must be accurately calculated and prepared according to the test subject’s weight. This preparation involves manually weighing highly potent, hazardous substances precisely with a spatula. Manual capsule filling, however, is tricky and challenging, especially with small capsules.

Manual filling is usually performed manually when the sample series are too small for filling machines or different amounts are required per capsule, which is not easy to automate. Manual filling can be slow and tedious, especially if tens, hundreds, or even thousands of capsules have to be prepared each day.

Alternatives to manual capsule filling

There are various solutions to overcome the manual filling challenges:

- Low-cost capsule boards are an extremely fast method of filling capsules, but have some drawbacks. Capsules cannot be filled with pure API because it would deliver too much API per capsule; hence, an excipient must be used. As segregation of powders cannot be controlled, homogeneous-proof samples are required and different formulations per capsule are not possible. Filling is achieved by volume, which is not highly reproducible, and capsule weights cannot be checked afterwards.

- Automated filling machines are a higher-throughput approach, but typically come at a high investment. Usually requiring at least a kilogram scale of material to run a batch, they are not flexible enough to fill different amounts per capsule. Additionally, these systems require time-consuming commitments of maintenance and cleaning between batches to prevent cross-contamination and ensure safety.

- Semi-automated capsule filling solutions bridge the gap between the manual and high-throughput machines. These flexible systems are usually compact and affordable, ideally suited for small batch capsule filling and accurately dosing different target amounts to each capsule gravimetrically (e.g., Quantos, Mettler Toledo GmbH).

Reduce time and enhance safety using automation

Reduce labor time. In a GMP lab, a validated filling system provides reduced labor time compared to manual filling. A technician may be capable of manually preparing 85–125 capsules per day at 3 mg target weights (technician dependent), whereas a semi-automated system produces 60 capsules per hour. Although the manual estimate depends on the standard operating procedure (SOP), a manual fill in a GMP lab would also require the eyes of two technicians: one to handle the balance, fill the capsule, and record the final fill weight; and the other present to verify each of these steps. Whereas, using a validated filling system requires only one operator to perform the task. Additionally, the tare and fill weights can be captured electronically and stored and/or printed automatically, which reduces the labor time associated with data recording/transcription.

Reduce development time. By using neat API in capsule, formulation development time can be reduced by simply evaluating the compatibility between the capsule shell and the API, instead of investigating excipient compatibility and fully formulating a dosage form. Analytical method development time can also be reduced because no specificity needs to be qualified, as no interfering excipients are present. Thus, the analytical method for the drug substance can suffice for the drug product.

Typically, release testing is performed on all incoming materials and final dosage forms before release to the clinical side. Using neat API in capsule, the initial release determines the purity and potency of the API, which minimizes the release testing and allows substances to get to the clinic faster.

Minimize cleaning and cross contamination. In setting up a typical fully automated encapsulation machine, there are a number of product contact parts that have to be cleaned and verified by swabbing after dosing to determine residual API left on the instrument. However, semi-automated filling systems are much simpler to clean, because no substance comes into contact with any other part of the system other than the dosing head and the sample changer, which is easily detached for cleaning. The rest of the system is considered non-product contact and thus needs no additional cleaning verification. Cross-contamination risk is eliminated, as separate dosing heads are used for each substance.

Enhance safety and reduce wastage. With high-potency substances, semi-automated capsule filling offers significant safety benefits. Potential exposure is reduced using a self-contained dosing unit. The drug substance is stored in a standard jar or vial with a dispensing head screwed on top, protecting the analyst from the drug, and the substance from the environment. At this phase, when working with new chemical entities that can cost thousands of dollars per gram, it is important to avoid any substance wastage. Weighing small quantities such as 1–5 mg, manually with a spatula, can result in significant loss or spillage. Having a system that accurately dispenses exactly the required amount, without wasting anything, is therefore, beneficial.

—Matthew Greene, CoreRx, Inc., and Joanne Ratcliff, Mettler-Toledo GmbH
More than hand made.
MADE IN IMA

We could explain that everything we create has a unique tone.

We could tell you that we use all our skills in every single detail, or that each project is tuned to your needs.

But maybe all you need to know is that the technology you use is made by IMA.

Visit us at
Interphex 2017
March 21-23, 2017 - New York, USA
Booth # 2545

www.ima.it
from the capsules used in production, and therefore, might require specific machine formats. Typically, the batch sizes for clinical trials are smaller than for commercial production, so in many cases, it is possible to fill capsules manually.

**Harris (Juniper):** For small numbers of capsules for clinical studies, it may be feasible to hand-fill capsules, either with neat drug or with a simple powder blend, or use a precision powder dispenser, such as the Xcelodose (Capsugel). Another approach for relatively small numbers of capsules is to ‘flush-fill,’ which involves holding an array of opened capsule bodies in a perspex frame and adding/spreading out the drug or formulation across the capsule shells to fill them all to the brim, followed by adding the caps and closing the capsules. Difficult to handle powders (e.g., micronized drug, poor flow powders) can be filled into capsules either by hand-filling or by flush-filling (although due consideration should be given to the quantities of capsules required).

For larger clinical trials, automation becomes important. For a batch size greater than a few thousand capsules, an automated filling approach is required, which demands the use of a suitable, free-flowing powder blend or granular formulation.

For commercial production of capsule products, speed and ease of manufacture is important and, therefore, automated capsule filling machines are used. There are two types of automated capsule filling machine—the dosator-type and the dosing disc type.

**Challenges in capsule filling**

**PharmTech:** What are the challenges of capsule filling for liquid and powder formulations?

**Bueno (Idifarma):** The main challenge when filling liquids in hard gelatin capsules is to find the right solvent (i.e., one that does not interact with the capsule material).

—Bueno, Idifarma

**Harris (Juniper):** For liquid formulations, very low viscosity liquids should be avoided due to the potential for leakage. For powder formulations, good flow properties are important to ensure satisfactory fill weight control.

**Things that can go wrong**

**PharmTech:** What are the common things that can go wrong in capsule filling that manufacturers should be aware of?

**Harris (Juniper):** When powder filling, the main challenge is poor capsule fill weight control. When filling liquid or semi-solid formulations, splashing of the liquid during the capsule filling can occur, making it necessary to reduce machine output speed or increase time for the pump stroke. In addition, ‘tailing’ during filling stroke for gels and semi-solids can lead to variable fill weights and contamination of capsules, making it necessary to adjust the speed of the pump stroke and/or increase the temperature of the formulation during filling.

**Bueno (Idifarma):** Capsule filling is a complex process, so there may be numerous challenges. It is important that the product to be encapsulated is well developed, with an acceptable flow and a reproducible batch-to-batch density to avoid problems of mass uniformity.

In addition, an automatic encapsulating machine is a complex equipment. Each capsule form is composed of numerous pieces, which must be perfectly aligned and adjusted to avoid the opening or breaking of capsules. When capsules are broken, they can release their contents, staining the entire batch produced.

Finally, hard gelatin capsules eventually undergo a cross-linking reaction that renders the gelatin less soluble and may affect the release of the capsule contents.
At Weiler Engineering, Inc. our ASEP-TECH® Blow/Fill/Seal machines produce shatterproof plastic, aseptically packaged products in a closed environment—a better alternative to conventional filling of glass vials for parenteral, ophthalmic, biologics, vaccines and respiratory products.

ADVANCED ASEPTIC TECHNOLOGY ADVANTAGES:

- Increased safety for both the patient and healthcare provider
- Lower product to market cost with streamlined packaging process
- Improved product quality with no aluminum leaching issues
- Less material handling reduces risk of product contamination

To see our hands-free, sterile manufacturing process in action, visit www.ASEP-TECH.com/ptus or call 847-697-4900.
An Investigation of the Anomeric Stability of Lactose Powder Stored Under High Stress Conditions

Mohamad J. Altamimi, Kim Wolff, Gary P. Martin, and Paul G. Royall

Lactose has two anomic forms: \(\alpha\) - and \(\beta\) -lactose. This study investigated the stability of solid lactose stored under high temperature and humidity conditions. Commercially available samples of \(\alpha\)-lactose monohydrate (98% w/w \(\alpha\); 2% w/w \(\beta\)) and \(\beta\)-lactose (84 % w/w \(\beta\); 16 % w/w \(\alpha\)) were stored at 40 °C and 93 ± 3% relative humidity (RH) for up to one week and analyzed using proton nuclear magnetic resonance. The data show that the storage conditions can change the anomeric content and potentially affect the functionality of lactose as a pharmaceutical excipient.

Mohamad J. Altamimi is a forensic analyst, Department of Forensic Evidence and Criminology, UAE, Dubai, Dubai Police HQ, Al Tawar 1. Kim Wolff is professor of addiction science; Gary P. Martin is professor (emeritus) of formulation science; and *Paul G. Royall is lecturer in pharmaceutics, Tel.: +44 (0) 20 748 4369, Paul.Royall@kcl.ac.uk, all at the Institute of Pharmaceutical Science, King’s College London, London SE1 9NH, United Kingdom.

* To whom all correspondence should be addressed.

Submitted: Dec. 9, 2015. Accepted: June 14, 2016.
A NEW GENERATION OF SOLID DOSAGE IS COMING

COMES SEE THE UNVEILING AT INTERPHEX 2017

Booth: 3153

Location: Javits Convention Center, New York, New York
Show Dates: March 21st-23rd

Specialty Measurements Inc.
RT 22 E, Lebanon NJ, 08833
Call Us: (908) 534-1500
Web: www.smitmc.com
This approach was carried out to investigate the extreme conditions that could affect the stability of the anomeric content in the lactose samples. Such conditions may occur during the bulk transport of the excipient across the world even if the final drug product is used and stored according to manufacturer's specification. Differential scanning calorimetry (DSC) was employed to determine the hydrate form of the resultant lactose samples after the incubation period.

**Materials and methods**

**H$^1$ NMR analysis.** Dimethyl sulphoxide (DMSO) -d6 99.9At% + 0.05% tetramethyl saline (TMS) (%v/v) was acquired from Goss Scientific Instruments and used as the solvent for the NMR samples. Aliquots were transferred to a 400 MHz Wilmad NMR tube (Sigma). DMSO solution (0.7 mL) was added to the sample and the lactose dissolved approximately 10 min prior to analysis using a 400 MHz NMR (Bruker Avance); the experiment was completed within 10 min. The NMR analysis was conducted using a Quatro nucleus probe (QNP) including 16 scans and a zg30 sequence, where a 30° pulse was applied prior to acquisition. TMS (appears at 0 ppm) in the DMSO was used as a reference to compare the chemical shifts. The method and the analysis of the resulting spectra from each NMR experiment were based on those outlined in previous studies (1). The anomeric composition was obtained by comparing the ratio of the integrated $\alpha$ and $\beta$ peaks using the Bruker Topspin software for NMR spectral data analysis (1, 15).

**Calibration.** The available lactose powders were mixed in different ratios and analyzed by NMR to create a calibration graph showing the correlation between the changes in anomeric ratio of lactose and the different mixtures of $\alpha$-lactose monohydrate and $\beta$-lactose. Mixtures of 1:4, 1:3, 1:1, 3:1, and 4:1 of $\alpha$-lactose monohydrate:$\beta$-lactose were used in this experiment. The amounts of lactose powders corresponding to these mixture ratios were weighed directly into NMR tubes and, after dissolution, analyzed by the above method.

**Stability study.** An environmental temperature of 40 °C and 93% RH was established in a temperature-controlled incubator (Gallenkamp, Wiess Technik). The humidity was maintained by introducing an open reservoir containing an excess of purified water into the incubator. Conditions within the incubator were monitored continuously using a thermometer/hygrometer (TraceAble, Fischer Scientific).

After equilibration of the environmental conditions, approximately 300 mg samples of commercial $\alpha$-lactose monohydrate (Sigma) and $\beta$-lactose (ACROS organic) were placed in aluminium weighing boats (QBI Consumables) within the incubator (middle shelf). Aliquots of lactose powder (3–4 mg) were removed from each sample, immediately prior to the start of the experiment, and these were designated the time-zero samples. On days 1, 2, 3, 4, 5, and 7, further aliquots were removed from each weighing boat for analysis by NMR. Care was taken to ensure that the removed portions comprised powder representative of the entire powder bed.

**Differential scanning calorimetry (DSC).** An automated DSC (TA instruments, Elstree) was used to analyze the lactose samples, as received and then after the incubation period.
Trying to keep your drug moving forward through development can be a painful experience. That’s why Mikart is the Contract Development and Manufacturing Organization (CDMO) that gives you the services you need, plus the speed and responsiveness you want.

**Relieves (Development) Headaches.**

Don’t put up with inflexible procedures and unreturned calls. At Mikart, we’re quick to respond with customized solutions that get your projects completed faster and to your individual specifications.

In addition to Formulation Development, Mikart also provides Clinical Trial Supplies, Regulatory Filing Support, plus Manufacturing and Packaging solutions.

You’ll find Mikart has everything you’re looking for in a pharma partner: innovative technology and equipment, highly skilled people and 41 years of solid CDMO experience.

To experience just how responsive we can be, contact us at 1-800-4MIKART or send us an email to info@mikart.com.
Three to four milligrams of β-lactose was weighed into a hermetic DSC pan using a Sartorious balance and covered with a DSC lid with a pinhole. The pans were then sealed and placed in the automator prior to the start of the experiment. In brief, the run program involved: equilibration at 25 °C, ramp up to 160 °C at 10 °C/min, equilibration at 160 °C and a hold phase for 1 min, followed by a ramp down to 25 °C at 10 °C/min, and re-equilibration at 25 °C.

Results

H1 NMR analysis and calibration. Figure 2 is an example of an NMR spectrum of α-lactose monohydrate powder, containing an insert of the region of interest 6–7 ppm where the α and β proton peaks occur, on a larger scale. The α and β protons are the most deshielded atoms in the lactose molecule because of their position with respect to a neighboring electronegative oxygen atom. The distance between the α proton and the oxygen atom is also greater than the distance between the β proton and oxygen atom. Therefore, the respective protons exist in slightly different chemical environments, which also accounts for the α and β protons of the α-lactose monohydrate sample appearing as two separate peaks found in the farthest region (6.2–6.7 ppm) (1).

Because of the nature of the NMR experiment, the α and β peaks appear split depending on the number of adjacent hydrogen atoms (referred to as n). Peaks are split by n + 1; therefore, in this case, both peaks are split into doublets as a consequence of the adjacency of one hydrogen atom. The relative intensities of the integrated α- and β-proton peaks were calculated and the anomeric content was determined for α-lactose monohydrate and β lactose at day zero (n=5). The purchased sample of α-lactose monohydrate was found to contain 98% ± 0.16% w/w α-lactose and 2% ± 0.16% w/w β-lactose. In contrast, the sample of β-lactose powder contained 16% w/w α-lactose and 84% w/w β-lactose, with the standard deviation being 0.29%.

Different mixtures of lactose powders (α-lactose monohydrate and β-lactose) were analyzed by NMR to generate the calibration graph shown in Figure 3. Five percent of the weight of α-lactose is water and approximately 20% w/w of the β-lactose powder is known to be α-lactose (11); thus, the calculated value for the percentage of the α anomer was determined using the Equation 1:

\[
\frac{(W_{\alpha\text{-lactose}} - W_{\text{water present in } \alpha\text{-lactose}}) + (W_{\alpha\text{ anomer present in } \beta\text{-lactose}})}{W_{\alpha\text{-lactose}}'\text{ and } \beta\text{-lactose}'} \times 100
\]

[Eq. 1]

where, W= weight; ’α-lactose’ and ’β-lactose’ powders as received.

The weight of the water present in lactose was determined using thermogravimetric analysis (TGA). The weight loss corresponding to the water loss detected by TGA was 4.97 ± 0.34% w/w (n=3). The α anomer content present in the β-lactose was found to be 16.3 ± 0.22% w/w by NMR. Using these data, the calculated α anomer composition was determined and used as the independent (x) axis. The NMR data derived from the mixtures of lactose samples were plotted as the abscissa values. As shown in Figure 3, the R² value (0.992) is strongly indicative of the linearity of the NMR analysis.

Stability study. Constant temperature and relative humidity were maintained during the seven-day experiment (Figure 4): the values upon daily monitoring being 40.0 ± 0.5 °C and 93 ± 0.7% RH (with an instrument accuracy of ± 3%). The β-lactose sample changed markedly in composition as a function of time. The original sample, which contained 16% w/w α-lactose and 84% w/w β-lactose was
Who We Are
Chemic Laboratories, Inc. is a full service cGMP/GLP contract analytical chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: Extractables/Leachables analysis, CMC Method Development & Validation, Quality Control analysis, Release testing, Raw Materials analysis, Compendial testing, Organic Synthesis/Formulation Development & ICH Stability testing. Chemic continually strives to exceed the requirements and expectations of our sponsors. We are committed to providing quality services to our clients in support of their product development needs.

Major Markets
Chemic Laboratories, Inc. is located in Canton, Massachusetts and provides cost-effective outsourcing solutions to a broad spectrum of global clients in the pharmaceutical, medical device and biopharmaceutical industries. We are committed to developing long term strategic alliances with our clients. Chemic offers the ideal blend of expertise and experience that is critical to our clients’ success.

480 Neponset Street,
Building 7, Canton, MA 02021
Tel. 781-821-5600
Fax 781-821-5651
www.chemiclabs.com

Services Offered
Chemic Laboratories, Inc. offers a wide array of cGMP/GLP contract testing services including:

- Quality Control Testing of raw materials, API’s and finished products
- Monograph Testing (USP, EP, BP and JP)
- CMC Method Development & Validation
- Degradate Quantitation
- Extractables and Leachables Analysis
- Container Closure Assessment
- ICH Storage and Accelerated Stability Studies
- GMP/GLP Method Development and Validation
- Organic Synthesis and Formulation Development
transformed and after seven-day storage, was found to comprise 48.5% w/w α-lactose and 51.5% w/w β-lactose (Figures 5 and 6). The increase in α-lactose content was found to be a (R² = 0.97) linear function of time (slope 4.7%/day).

In contrast, the composition of the α-lactose monohydrate sample did not change throughout the seven-day storage period (Figure 5). The mean α-lactose anomer content during storage of the sample was 98.4 ± 0.15%. The R² value was 0.53 indicating that the data points were randomly distributed around the mean, suggesting a small variation due to the NMR experimental procedure.

**DSC.** The thermogram in Figure 7 comprises an overlap of representative curves for α-lactose monohydrate, β-lactose, and β-lactose after storage at high temperature and RH conditions. α-lactose monohydrate exhibits a peak that corresponds to water loss at 140–160 °C, and this peak is represented by the blue trace in Figure 7. β-lactose did not exhibit any peaks in this region as expected because of the absence of the hydrate present in α-lactose monohydrate. The incubated β-lactose sample presented a peak that overlaps with the α-lactose monohydrate water-loss peak at 140–160 °C. The weight of α-lactose monohydrate (n=6), β-lactose (n=6), and β-lactose after incubation at high temperature and RH conditions (n=6) over seven days was measured before and after the DSC experiments and the weight loss was calculated to be 5 ± 0.4% w/w, 0.1% ± 0.1% w/w, and 3.6 ± 0.4% w/w, respectively.

**Discussion**

It is well known that amorphous lactose is an unstable form of lactose that changes into the more stable crystalline lactose, and some of the conditions that affect this process have been identified (17). In previous studies, however, there have been misidentified changes in the anomic composition of specific samples of lactose that have been incorrectly described as polymorphic changes (18, 19). In addition, the monitoring of the anonic interconversion of lactose and the presence of different forms during compression have also been neglected; issues with caking could be minimized if such aspects were investigated (19).

The aim of this study was to investigate the effects of high temperature and humidity conditions on the anomic composition of lactose powders, using H¹ NMR. This method requires the solid lactose samples to be dissolved in solutions of DMSO prior to analysis. It is important to establish that mutarotation within these solutions is minimized for the length of the NMR experiment (1, 7, 20). Previous work by the authors has shown that mutarotation of lactose is inhibited for up to 20 min in DMSO due to the aprotic characteristics of the solvent (1). Accordingly, all spectra were derived within this timeframe. The analysis carried out has allowed the unambiguous determination of the anomic content of lactose samples before and after storage under high stress conditions (21).

In this study, the anomic content of α-lactose has been shown to be stable even when stored under such extreme ambient conditions, when water sorption might be expected to occur (12). It has been reported previously that, in solution, the anomic content of lactose equilibrates at approximately 37% α-lactose : 63% β-lactose (1, 7). Moreover, a study by Lefort et al. using non-crystalline lactose suggested that the anomic ratio equilibrium in solid state is different from the equilibrium that occurs in solution, for example, when heated (up to
160 °C) samples of solid amorphous lactose were found to undergo mutarotation and equilibrate at 50% α-lactose : 50% β-lactose (22). In the same study, crystalline lactose was shown not to display mutarotation (22), but these experiments were conducted under low and uncontrolled humidity conditions.

The current study established that the α-lactose sample maintained its original anomic content under the predetermined extreme conditions, whereas the β-lactose did not. Initially, it was assumed that there would be no change in composition of either sample, as lactose powders have been previously considered chemically stable (11). The hypothesis to account for the transformation that occurred in β-lactose is that the water vapor in the immediate surroundings of the lactose sample condensed and pooled on the surface of the powder mass, thereby creating a saturated solution, which resides on the particles’ surface. In this saturated solution, the anomic composition would be expected to approach the equilibrium state observed in aqueous solution.

The proposed mechanism is that β-lactose present in the saturated solution is converted to α-lactose, which in turn recrystallizes into the α-lactose monohydrate form. The removal of the α-lactose from the solution present in the surface “pools” induces more β-lactose conversion within this solution to the α-lactose form to approach and
maintain the equilibrium. This mechanism, catalyzed by the storage conditions, might be expected to continue until an equilibrium between the two anomers is established, which is representative of the ratio found in solution.

The data show, interestingly, that β-lactose content reached a %w/w of ~50%, which is significantly lower than the β-lactose content at equilibrium in solution at 40 °C that was reported by Jawad et al. to be approximately 63% (1, 7). The aqueous solubility of α-lactose monohydrate is significantly less than the β-lactose form, and hence more β-lactose would be expected to dissolve and convert to α-lactose than the opposite, resulting in a powder with a higher solid-state concentration of the α-lactose anomer.

DSC analyses of lactose samples were carried out in support of this hypothesis. The thermogram of α-lactose monohydrate was found to exhibit a water-loss peak at approximately 140 °C, as reported previously in literature (23). This characteristic peak was used to determine whether β-lactose converts to α-lactose monohydrate or anhydrous α-lactose. According to the DSC analysis, the incubated β-lactose sample produced an endothermic peak that is indicative of water loss from α-lactose monohydrate. The peak shape was also not as sharp as that obtained from the α-lactose monohydrate, but this observation might have been attributable to the differences in the packing of the powder within the DSC pans. This non-uniform packing might have been expected to induce water loss in a less uniform fashion than for the α-lactose monohydrate sample. Additionally, the calculated % weight loss in the incubated β-lactose is indicative of water loss from that proportion of the β-anomer that has been converted to α-lactose monohydrate. Therefore, these findings appear to support the original hypothesis that β-lactose is converted to the α anomer, which in turn interacts with the surrounding humidity to form more crystalline α-lactose monohydrate.

Such results concur with those reported previously, where semi amorphous mixtures containing both α-lactose and β-lactose showed an increase in the formation of α-lactose monohydrate with increasing RH (24).

The consequence of such a hypothesis is that, at the point when equilibrium might have been expected to have been established in solution (i.e., at 63% β anomer : 37% α anomer), some of the α anomer in solution may have been converted to the crystalline (solid) hydrate. This conversion might hinder the equilibration process and result in the situation where the β anomer continues to undergo mutarotation, resulting in a higher α content than expected (see Equations 2 and 3). Alternatively, the interaction of lactose with water resulted in a saturated solution where the β lactose content, which was changing to α-lactose, remained constant through the dissolution of more β lactose. The reaction would, therefore, appear to follow a pseudo zero-order mechanism (Equation 3), despite zero-order models being applicable to solutions only. The mechanisms are summarized in the equations below:

Proposed mechanism of lactose reaction.

\[
\beta_{\text{B,cry}} \leftrightarrow \beta_{\text{B,aq,sat}} \leftrightarrow \alpha_{\text{aq,sat}} + \text{H}_2\text{O} \rightarrow \alpha\text{H}_2\text{O} (s) \tag{[Eq. 2]}\]

The integrated form of the zero order linear equation.

\[
[\beta] = -kt + [\beta]_0 \tag{[Eq. 3]}\]

In the pseudo zero-order rate equation (Equation 3), k is the rate constant, t is time, and [β]₀ is the initial concentration of β lactose. Using Equation 3 on the data displayed in Figure 6, the rate constant is 4.7% β-lactose per day and the half-life is 9.1 days. It should be appreciated that equilibrium has not been observed in this study, and thus the kinetics of the reaction may appear to be of zero order before the reaction starts to approach equilibrium. Therefore, the reaction should be referred to “pseudo” zero-order; the half-life quoted is based on the assumption that the reaction follows the proposed mechanism.

### Conclusion

The effect of the storage conditions on the anemic stability of crystalline lactose was investigated by NMR to determine unambiguously the anemic ratio of two different lactose powders. No significant change in the anemic content of the α-lactose monohydrate powder was detected. In contrast, samples with a high β-lactose content showed a significant increase in α-lactose content at high-stress conditions. The kinetics of the change in the anemic content of β-lactose, where β-lactose was converted to the α anomer, resembles a “pseudo” zero-order kinetic model with a half-life (t½) of 9.1 days. In addition, the results from DSC experiments supported the hypothesis that the β-lactose is converted into the monohydrate form of α-lactose, because the thermograms of the β-lactose-containing samples exhibited a sharp water loss peak at a temperature corresponding to that obtained from α-lactose monohydrate powder samples.
It was demonstrated that the conditions under which lactose is stored can greatly change the anomeric ratio that, in turn, might alter the efficiency of its use in the pharmaceutical industry (1, 3, 9, 25). Excipients that are shipped internationally in bulk, may experience exposure to spikes in relative humidity and temperature in transit. Long-term storage of medicines in unsuitable environments (e.g., bathroom cabinets) by the patient may expose lactose-containing products (e.g., dry powder inhalers, capsule, and tablets), which might affect not only the API, but also the lactose used as an excipient. The reproducibility and long-term efficacy of lactose-containing medicines is reliant on maintaining the anomeric content of the lactose therein at a constant ratio (3, 9). Therefore, it is recommended that the anomer composition of lactose should be monitored as a function of time to assess the potential impact on the overall stability of medicinal products.

Future studies will draw upon the practices of the pharmaceutical market/industry and investigate the conditions at which lactose is stored and handled throughout its production and subsequent integration into medicines. Further work and future publications will support and build on the findings reported here, by investigating the epimerization kinetics of lactose over a range of humidities and temperatures.

References
As the pharmaceutical industry begins to automate manufacturing processes, many companies are looking to the Industrial Internet of Things (IIoT) to provide a way to more efficiently transfer information. While the IIoT provides a viable method for automating the flow of data, the concept of and security risks associated with cloud-based data storage is still new to many in the industry. *Pharmaceutical Technology* sat down with Ben Blanchette, director of Strategy and Business Development for IIoT, and Torsten Winkler, lead of the Life Sciences Center of Excellence in EMEA, both at Honeywell Process Solutions; Dave Sharpe, global industry director, and Tony Baker, security lead, both at Rockwell Automation; and Lee Sullivan, regional manager, COPA-DATA UK Ltd to discuss IIoT and its impact on pharmaceutical manufacturing.

**Blanchette (Honeywell):** In terms of IIoT technology improving the flow, I don’t know if there is any major improvement in our ability to move data, and flow information up and down the supply chain. I think what’s different with respect to IIoT, the IIoT philosophy, and a fully capable IIoT infrastructure and network, is that it becomes easier to move that information. Because of the way we’re collecting and storing the data and because the applications we’re using to support IIoT are typically cloud native, it [improves] collaboration across separate enterprises and up and down the supply chain [because] data can be transmitted more easily. That’s what is different about IIoT versus technology we’ve had for 20 years. We’ve had the ability to connect systems together, but it was typically customized integrations that required a lot of up front effort and large switching costs if you were to switch from one supplier to another up and down the supply chain. Going to cloud native IIoT infrastructure framework simplifies all of that and improves flexibility. I think that’s probably the biggest opportunity there, the ease and flexibility with which data can move up and down the supply chain to allow collaboration. Everybody’s seeing the same data in the same way.

**Winkler (Honeywell):** Especially for the pharmaceutical industry there is an increasing demand for documented evidence and documented data for the production [of drugs]. One initiative, for example, from the [regulatory] authorities is serialization. Serialization is a requirement by the [regulatory] authorities that you have a proven record from where the final drug was produced, and you need to document this. Of course, if you have one supplier and proprietary interfaces, you can achieve the same thing, but the industry is moving away from these monolithic systems to more modular systems because they want to have the capability to exchange information in an easier way. If you build special interfaces between the different modular systems to achieve for example serial-

---

**Integrating Industrial Internet of Things and Pharmaceutical Manufacturing Processes**

Caroline Hroncich

Industry experts discuss IIoT and its impact on pharmaceutical manufacturing.

**Improving the flow of information**

**PharmTech:** How does IIoT technology improve the flow of information?

**Sullivan (COPA-DATA):** IIoT can provide you with data; lots of data. IIoT’s real potential comes from the ability to monitor and connect. For example, Zenon [a human machine interface/ supervisory control data acquisition system and communication platform from COPA-DATA] has more than 300 communication protocols, in real-time; therefore, hardware devices and business enterprise (SAP enterprise resource planning) systems can be linked to obtain data—and historical data—on demand. Furthermore, mobile technology and instant reporting capabilities allow for increased efficiency across a manufacturing site, as an IIoT-enabled system can pinpoint who, what, when, where, and how errors have and will occur.
Who sees opportunity at a molecular level?

We are passionate, tenacious solvers who thrive on developing practical, innovative, and elegant solutions to complex problems in pharmaceutical, always pushing the boundaries of what’s possible, and advancing the competitiveness of our customers across diverse industries.

ashland.com/pt2
Process Control and Automation

ization, this requires dedicated interfaces, dedicated software, and in terms of GMP compliance, these interfaces are a different class. There is a tremendous effort to achieve fully validated systems with these customized interfaces. The Internet of Things and the collaboration between all the different components allows the customer to achieve a better modularity and reduce the validation cost with standardized interfaces and standardized data flow.

Enhancing process controls?
PharmTech: How does the IIoT impact or enhance process controls?
Winkler (Honeywell): The intention of IIoT is not to increase the position of a process analytical technology (PAT) controller, or real regulatory control, but the IIoT gives you the infrastructure in a validated environment that reduces cost for validation to achieve the initiative, for example FDA’s PAT initiative. This means you can collect manual data more easily, do something with this [data], and the result is available for control. That means you can set up in a better or easier way multi-variable modeling, for example, or you can do indirect measurements. In a biopharmaceutical plant, it is relatively impossible to measure the quality of the products, but you can indirectly measure this information. That way you make this information and results more easily available for real control. The umbrella is the infrastructure to fulfill the PAT initiative.

Sullivan (COPA-DATA): At an IIoT-enabled facility, all process values can be accessed at any stage, including temperature, pressure, weight, flow, pH, dissolved oxygen, humidity, and energy. IIoT makes it possible to visualize the process, understand the science, and see where the edge of failure lies. Additionally, engineers can parameterize processes and monitor with increased resolution to create a control strategy and alerting mechanism that prevents the equipment from ever reaching, or getting close to, their predetermined limits. When we talk about process, we are referring to every small process loop or discrete control in the plant. This is a science, to advance with an accurate vision. And it is in this vision that you can find the paradigm shift for improvement.

Blanchette (Honeywell): I don’t think that going to an IIoT framework or infrastructure directly impacts process controls. I think we’re pretty good at that within a plant—we’re pretty good at controlling the process. Where the impact will probably be felt is in the fact that those process controls will probably be more consistent. You will probably have better repeatability and better reliability of those control systems so they will be functioning at peak efficiency all the time. I think what IIoT really enables is the ability of external experts and the right person to solve the current problem … the ability to look at the data, analyze the data, and provide some recommendations about how to improve the control of process. [The impact is] on the collaboration side and the optimization of the controls we already have, and the assurance that all those controls are performing as efficiently as possible. It’s maybe a level above the process controls. It’s that level of automation, watching how they perform, and providing some tools to enable experts to fine tune and refine those process controls and maybe even some automatic analytical-based enhancement to those controls from the cloud. I think that’s where we’ll see the impact on performance of process controls.

Looking to the future
PharmTech: How do you think the IIoT will impact pharmaceutical manufacturing in the near future?
Sharpe (Rockwell): Pharmaceutical manufacturers can look forward to the next generation of quality, productivity, and efficiency gains thanks to improvements in workflow standardization and scalable analytics. These capabilities are increasingly made possible because of IIoT technology that connects and contextualizes disparate data from production and enterprise IT systems. Workflow standardization is replacing time-consuming and error-prone manual operations like following recipe instructions and tracking work performed. Key to providing process guidance and enforcement are manufacturing execution systems (MES). This technology offers operator instructions while collecting product data as it moves across the facility and noting nonconformance issues. Easy-to-access information can then be electronically stored for however long the pharmaceutical manufacturer needs it, helping with serialization and track-and-trace efforts.

Scalable analytics have provided pharmaceutical manufacturers the ability to leverage actionable information when and where it is needed. Exact analytics capabilities vary based on the users’ need, but the technology is helping to pull and analyze data as close to the source as possible. On the plant floor, a maintenance engineer can connect directly to a device in order to access near-instantaneous incident data. At the enterprise level, information collected across a number of plants can integrate with business systems to evaluate production trends. From plant floor to distribution, information for individual users’ needs helps make enterprise-wide improvements.

Winkler (Honeywell): From a pharmaceutical market point of view, [IIoT] is the infrastructure; it will allow for completely paperless production. The digitization of the company’s procedures, production, supply chain—that is how it will impact the industry. Digitization is the key word here.

Sullivan (COPA-DATA): The pharmaceutical manufacturing facilities of the future will go well beyond current standard methods of operations and development. The IIoT will add orders of magnitude to quality by design (QbD), with six sigma performance made possible on all quality parameters. The IIoT vision is one of highly automated production with high levels of visibility in all processes. Equipment will be highly precise, process controls will be well understood and constantly refined. As a result, in the IIoT-driven
Fast Forward

The Eppendorf epMotion® Series: Enjoy easy-to-use and flexible automation

The new Eppendorf epMotion liquid handling workstations are the right choice for your highly reproducible and accurate pipetting results. Discover new features, more speed and worktable positions and the new intuitive software assistant concept.

Available as ThermoMixer®, vacuum manifold or magnetic separation options
> User guided, touchable software assistants for easy application programming
> UV light decontamination and HEPA air filter option

www.eppendorf.com/automation • 800-645-3050
Process Control and Automation

plant, products remain cost-effective long after patent expiration.

Addressing security concerns
PharmTech: What are some best practices to prevent unauthorized intrusions, or cyberattacks, on pharma IT systems?

Baker (Rockwell): A number of prevention best practices are available to avoid unauthorized intrusions and attacks. Pharmaceutical manufactures can determine what is the best fit for them based on system design, sustainability, and cost sensitivity. Good infrastructure design, for instance, is a recommended first tactic, including segmentation through industrial demilitarized zones, firewalls, virtual local area networks, and access control lists.

Today, a pharmaceutical manufacturer needs to look beyond prevention, focusing on investments to detect, remedy, and recover from intrusions. A number of tools are available that can inspect and monitor industrial automation control systems. Best security practices also go beyond the network by taking advantage of capabilities within applications that manage who is allowed to access the system and what extent.

Another best practice is to sufficiently harden operating systems in order to prevent malicious applications from spreading. Devices and computers should be physically hardened and locked up to keep unauthorized individuals from modifying or accessing the system. In addition, authorized personnel need to be trained on how to work with the security controls, such as being prepared for USB devices with malicious applications, phishing emails, and a number of other threats.

Blanchette (Honeywell): There’s a perception that hosting your data in a private cloud that is maintained is safer, but we’re starting to hear the argument that a publically hosted cloud with thousands of users and thousands of different and unique security requirements is much more secure just because you have so many more users of that public cloud space. The reason it’s more secure is the hosting companies have to meet the requirements of all of those users. Because of that, and the way that the deployments are built out today, if I meet the security units of one of those users on the public cloud, all of those users get to benefit from that security measure. We’re starting to get to the point in the market where the ability of large cloud hosting markets to secure their cloud environment is starting to get so far ahead of what any private entity can provide. I think ultimately you’ll see that public hosting will be a quantum leap better than anything you can develop in private. I think there’s some truth to that, and [there’s] starting to be some acceptance of that. That’s probably one of the single biggest ones. If you host it privately, you have to build all the security yourself. You have to develop it all, and there’s no way one entity can keep up with the giants out there that do this for a living. Those companies have tens of thousands of times more eyes on the security of those public clouds than any one business can build internally. I think that’s going to be important, that’s probably the most secure way to do it. The other thing we’re seeing a lot of, instead of just trying to be proactive, is the ability of companies to have people monitoring and reactively providing an intruding defense. You’ll have people fighting off those intrusion attempts. That proactive and reactive defense of the system is probably what we’re going to have as a standard across the space in the future. The first step is recognizing that no matter what you do you’re never going to be 100% secure. Don’t ever rest on thinking that you have a secure system in place. You have to be vigilant and consistently trying to improve proactively, and reactively respond to attempts to attack the systems. PT
Eliminate the ups and downs of continually replacing and retraining temps by retaining our scientists at your site. Hired, trained and managed by us, our award-winning Professional Scientific Services® (PSS):

- Eliminates headcount, co-employment and project management worries
- Avoids Temp turnover rate with managed insourcing
- Costs you less than your own full-time employees
- Delivers a 50-year history of regulatory compliant technical expertise in your lab
- Holds numerous client awards as the top insourcing service provider for the past 10 years

Choose the PSS Insourcing solution® that enables us to keep staff grounded.
A survey on risk-based predictive stability tools reveals how pharma companies are leveraging advanced stability approaches throughout the drug development process.

The science of stability has significantly evolved since the advent of International Council for Harmonization (ICH) Q1A (1). This guideline has been in effect for more than a decade and offers the benefit of global harmonization. However, divergent local regulatory expectations in accordance with this guideline have frequently increased both time and cost required for developing new molecular entities and can ultimately delay bringing new medicines to patients. Nevertheless, improved modeling tools coupled with the appropriate protocols have enabled similar or better stability predictions within accelerated timeframes when compared to a more traditional ICH approach (2–4). These tools provide increased understanding of the attributes that influence drug substance and product stability instead of following the traditional ICH approach that simply demonstrates stability in an empirical manner. These modern tools and approaches are well aligned with the science- and risk-based approaches detailed in ICH Q8–Q11 (5–8) and have been termed risk-based predictive stability (RBPS). Companies are using these RBPS tools to enable development (9). The perception, however, is that the application of these tools has been inconsistent across the industry. Additionally, there is no acknowledgement of these RBPS tools within regulatory guidance documents.

In 2015, the International Consortium for Innovation and Quality in Pharmaceutical Development consortium (IQ) launched a working group to focus on the use of RBPS tools to optimize pharmaceutical development. The working group has approximately 50 members from 18 companies across the pharmaceutical industry. During the initial conversations within the group, it became clear that there is considerable variability in the implementation of these tools and their use (and success) in regulatory applications. This realization led to the conclusion that the industry was not aligned in how to leverage the knowledge these RBPS tools provide, which prompted the working group to conduct a survey to understand sponsor companies’ experiences using RBPS tools. The survey, consisting of 56 questions, was conducted during 2016. The focus was on RBPS tools and excluded concepts associated with lean stability as discussed in the literature (10).

**Authors’ note:** This article was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader research and development community.
Custom Formulation Development

At Coating Place, the coating formulation is customized to each unique situation. Our highly skilled scientists consider all formulation alternatives to ensure an optimal product. Coating experiments are conducted to study the release characteristics that can be achieved.

Oradel® Platform

Each of our Oradel® oral delivery techniques offers a unique formula individually or in combination. Our Wurster coating capabilities allow us to add numerous coating layers to a core with the highest quality and uniform release distribution.
Quality: Risk-Based Predictive Stability

Table I: International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) member companies that responded to the IQ consortium Survey on Risk-Based Predictive Stability.

<table>
<thead>
<tr>
<th>AbbVie</th>
<th>Agios Pharmaceuticals</th>
<th>Alkermes</th>
<th>Amgen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>Bayer</td>
<td>Bayer Healthcare</td>
<td>Blueprint Medicines</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Daiichi Sankyo</td>
<td>Eli Lilly and Company</td>
<td>EMD Serono</td>
</tr>
<tr>
<td>Endo Pharmaceuticals</td>
<td>GlaxoSmithKline</td>
<td>Janssen Pharmaceutica NV</td>
<td>Merck</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Teva Pharmaceuticals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Survey responses to question: Which attributes are being modeled?

Results
Of the 18 companies that responded to the survey, 16 indicated they use RBPS. Responses from 18 companies represent approximately 58% of the IQ Consortium Analytical Leadership Group (11). Respondents represented a cross section of the pharmaceutical industry including large and small molecules as well as generic drug products. The list of respondents is provided in Table I.

How are RBPS tools being used? Ten of the companies who responded reported using ‘typical’ accelerated stability assessment program (ASAP) studies to evaluate/model chemical degradation, as published by Ken Waterman et al. (2,3,12–15). The survey responses and literature review show that some companies are using in-house predictive stability approaches (16, 17). The packaging moisture vapor transmission rate (MVTR) was used in the predictions by 12 of the responders, with the source of the MVTR data split fairly even between experimentally derived data, default values in software, and supplier information. Most responders utilized RBPS approaches to model assay/potency or impurities and moisture, as shown in Figure 1. Physical attributes such as dissolution, disintegration, hardness, color, and form changes were also modeled by a small number of respondents. Only two companies, however, reported performing specific stressed stability studies to monitor for physical changes when a shelf life claim is based on predicted chemical stability data. One responder reported focusing on chemical degradation early in development and then performing full ICH stability testing later in development, including physical testing.

How are companies using RBPS? The responders indicated that RBPS approaches have mainly been used on immediate-release solid oral dosage forms, and have also been applied across a wide range of formulated products including parenterals, oral solutions, modified- and extended-release formulations, as well as drug-product intermediates, drug substances, starting materials, and drug-substance intermediates. The survey responses indicated that while RBPS studies have primarily been used for formulation screening and shelf-life predictions/use period assignment, they have also been used across a range of applications including packaging selection, demonstrating equivalence, site-specific stability, and support of post-approval changes, as shown in Figure 2. Certain applications not specified in the survey questions were also reported, including inherent stability understanding, salt/polyform selection, mass balance assessments, supplier screening, specification setting, process evaluation for drug product, and device compatibility.

How are companies utilizing results to support regulatory strategies? Ten companies using RBPS approaches also reported filing the predictions in regulatory submissions. The majority of these reported having used RBPS in clinical submissions with only five companies using these approaches in marketing submissions and two in post-approval changes. In total, RBPS approaches have been used in excess of 100 submissions.

Clinical submissions containing RBPS approaches have been successfully approved in more than 23 countries. Countries that did not accept specific submissions from one responder were identified as Spain, Czech Republic, France, and Italy. In each of these cases, the respective health authorities requested additional real-time, long-term stability data before accepting the proposed clinical use period/retest period.
Pfizer has previously published a summary of their experiences of regulatory acceptance of RBPS approaches, where Freed et al. (9) discussed the regulatory responses to a number of submissions. Pfizer presented using ASAP data only to support an initial shelf life of not more than 12 months for drug product in numerous early clinical submissions in the United States, Canada, European Union, and emerging markets. They received queries from South Korea, Czech Republic, and Ukraine. While the queries from Ukraine were successfully answered, South Korea required at least three months’ data at the long-term storage condition and Czech Republic adhered to the ICH guidance. More recent submissions to South Korea with ASAP data only have been successful when a commitment protocol with ICH time points is also included. In another similar example in a Phase IIa submission, 12 countries accepted the filings with no questions, while two countries (Serbia and Romania) requested additional stability information. For stable systems when shelf-life predictions cannot be achieved from a RBPS approach (due to a lack of degradation), three companies reported claiming a 12-month clinical use period while others defaulted to ICH-based use period assignments in this case.

Most of the companies surveyed with RBPS approaches in clinical submissions were using the predictions...
to set an initial clinical-use period or as supportive stability data. Other applications reported were to demonstrate equivalence, packaging selection, specification justification, and device compatibility. In the majority of cases for clinical submissions, long-term stability testing was also performed and presented in the submissions as shown in Figure 3, although some companies report using reduced protocols (time point and conditions). Two companies reported only holding samples in long-term contingency storage.

Three companies provided further details of how RBPS approaches were used in marketing applications. In all three instances, successful applications were reported in major markets. Regulatory questions on the RBPS approaches in marketing applications were received from the US, EU, South Korea, Australia, Switzerland, Singapore, Israel, and Malaysia but all reportedly answered satisfactorily. One responder commented that the predictive stability approaches have been accepted by the vast majority of health agencies without questions. The predictions were used by the three responders for a range of purposes in marketing submissions including: as supportive stability data, to set initial shelf-life/retest period, for packaging selection, for excipient compatibility, for specification justification, and to demonstrate equivalence. The data were typically presented alongside full ICH stability testing.

Two companies reported using RBPS approaches to support post-approval changes but only one company gave further details, specifically that RBPS was used to support a packaging change in the US.

Nearly 85% of the responders agree that the industry would benefit from standardized templates for reporting risk-based predicted stability data in regulatory submissions, with approximately half of the responders already using internal templates. A standardized approach for presenting and leveraging RBPS data in regulatory submissions may increase worldwide approval of RBPS. The highest benefit area for standardized templates would be the clinical space, where companies use RBPS tools to set initial retest periods and clinical-use periods without long-term data available.

Opportunities

The results of this survey indicate that use of RBPS strategies in clinical submissions has been largely accepted by regulatory agencies around the world. Survey respondents noted that Spain, Czech Republic, France, and Italy did not accept their RBPS strategies. Other respondents, however, successfully reached a resolution with the reviewers in these countries.

In the clinical space, all respondents that used RBPS to support clinical applications indicated that the tools are used to set the initial shelflife of the clinical supplies. Most of the respondents also indicated that a commitment to run an ICH-like long-term stability program was added to the regulatory submission. Several respondents indicated, however, that RBPS is filed in conjunction with a lean long-term protocol. As highlighted in the results section, companies have successfully committed to protocols containing reduced time points and reduced storage conditions. One respondent indicated that a protocol with reduced storage time was filed to confirm the model predictions, rather than confirm shelf-life. There appears to be a significant opportunity for companies to strategically define their long-term stability programs based on RBPS conclusions. Sharing of case studies and specific regulatory successes and challenges may encourage additional companies to progress these strategies and further drive regulatory acceptance.

Although the survey results indicate that RBPS is primarily being used in clinical submissions, a few respondents indicated that RBPS strategies have been used in marketing applications or to support post-approval changes. Those who have used RBPS to support marketing authorizations indicated that it was accepted and worked for its intended purpose. One respondent indicated it was utilized globally with success. In the post-approval space, use is even lower, but has been successful as well. One respondent successfully used RBPS in a US submission to support a packaging change in conjunction with an annual lot testing commitment. Although the number of companies using these approaches for initial marketing applications and post-approval changes is low, results indicate a high success rate and a significant potential growth area for other companies. Knowledge of stability performance is greatest for a marketed product, making RBPS approaches a logical strategy.
The survey results imply that companies would like to progress these strategies further and that development of industry positions will help move these stability approaches towards broader applicability. Eighty-five percent of respondents agreed that developing standardized templates for presenting RBPS data and conclusions to support specific strategies would be valuable and 90% of respondents would be willing to help develop these templates. Most respondents (approximately 80%) are also willing to share specific case studies and learnings that could be published through the IQ RBPS Working Group. Pursuing harmonized regulatory submission strategies and learning about specific successes and challenges will undoubtedly provide a large opportunity to grow regulatory acceptance of RBPS.

**Conclusion**

This survey of industry was extremely informative in learning about the use of RBPS tools across the industry. A key learning from this exercise is that several companies are successfully leveraging these advanced stability approaches in their development paradigm. The information gathered can be used to continue the discussion around the broader utilization of these tools in accelerating drug development and advancing stability performance understanding.

**References**

1. ICH, Q1A(R2) Stability Testing of New Drug Substances and Products, Step 4 version (ICH, 2003).
5. ICH, Q8(R2) Pharmaceutical Development, Step 4 version (ICH, 2009).
6. ICH, Q9 Quality Risk Management, Step 4 version (ICH, 2005).
7. ICH, Q10 Pharmaceutical Quality System, Step 4 version (ICH, 2008).
8. ICH, Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities), Step 4 version (ICH, 2012).
11. https://iqconsortium.org/initiatives/leadership-groups/analytical/
A robust quality agreement and good communication scheme can help avoid and alleviate regulatory concerns.

Managing the relationships between clients and contract manufacturing organizations (CMOs) can be difficult as the pharmaceutical landscape and its related supply chains become more global and complex. One of the best tools to achieving a good working relationship between a client and their CMO is the use of a well-drafted, clear and concise quality agreement. To accomplish this, it is important to understand the different types of clients as well as the types of CMO models existing in today’s environment.

In May 2013, FDA published draft guidance on quality agreements, which was finalized in November 2016 (1). Although written quality agreements are not explicitly required under existing CGMP regulations, they are required by the European regulations. Chapter 7, Outsourced Facilities, in EudraLex Volume 4 states, “There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party” (2). The FDA final guidance is titled Contract Manufacturing Arrangements for Drugs: Quality Agreements and, like all final guidances, represents FDA’s current thinking on the topic. The need for quality agreements is underscored by 21 Code of Federal Regulations (CFR) 200.10, Contract Facilities that states, “Section 704(a) of the Federal Food, Drug, and Cosmetic Act specifically authorizes inspection of consulting laboratories as well as any factory, warehouse, or establishment in which prescription drugs are manufactured, processed, packed, or held” (3). This section of the regulations goes on to state, “The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer’s own facility.” And finally, 21 CFR 211.22, Responsibilities of the Quality Control Unit, states, “The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company” (4).

The emergence of CMOs and virtual companies has been at the forefront of some of the challenges the industry is experiencing. With the finalization of the FDA guidance, it is an opportune time to revisit the concepts and ideas regarding quality agreements.

**Comprehensive quality agreements**

Quality agreements should not be limited to what is meant by traditional manufacturing but should be expanded to include the support activities necessary to producing a final product. It is important to put into context what is meant by “manufacturing”. For the purposes of this article, “manufacturing” will be considered anything to do with the manufacturing, testing, processing, packaging, or holding of the product including the procurement of the active ingredient, excipients, and packaging materials, including labeling, used to assemble the product.

Another important issue to understand is the different client and CMO business models existing in the industry today. The various outsourcing models range from a single outsourced activity to the full range of activities to produce the product. Partners in the contract-manufacturing niche also include the full spectrum from small to large and from early development to late-stage generic drug companies. The complexity of the business models emphasizes the need of the industry to employ a meaningful quality agreement that focuses on defining who is responsible for what in the relationship and what the communication scheme will be between the organization(s).

Often the major issues include the actual logistics of the agreement itself. While there is obviously no one model for format and content, each party usually

Susan J. Schniepp is distinguished fellow at Regulatory Compliance Associates and a member of PharmTech’s Editorial Advisory Board.
FULL-SERVICE CDMO FOR A GLOBAL MARKET

Through our network of technology platforms and cGMP facilities for the manufacture of APIs, Drug Products and pharmaceutical Packaging, CordenPharma experts translate your complex ideas at any stage of development into high-value products.

www.cordenpharma.com

TECHNOLOGY PLATFORMS

- PEPTIDES, OLIGONUCLEOTIDES, LIPIDS & CARBOHYDRATES
- HIGHLY POTENT & ONCOLOGY
- INJECTABLES
- SMALL MOLECULES
- ANTIBIOTICS

VISIT US AT

DCAT Week ’17
March 20–23 – NYC, NY USA

Oligo & Peptide Therapeutics > Booth 10
March 27–28 – Boston, MA USA

CPhI Japan > Booth S-18
April 19–21 – Tokyo, Japan

OutsourcedPharma Boston > Booth 121
April 26–27 – Boston, MA USA
would like their own format for consistency. The real issue, however, is to agree on the scope and level of detail.

**Clients should look for a robust quality system and an open and communicative culture when choosing a contract organization.**

Looking at the situation from both sides might help in understanding the complexity of the issue. A CMO will have multiple clients. Each client will have different information they want highlighted in their quality agreements and will want to use their own quality agreement template. Keeping track of numerous commitments can cause regulatory risk for the CMO, particularly if one client wants to have a different approach to an issue than another client. CMOs should look for clients who understand the regulations and can evaluate the CMO’s systems against those regulations rather than demanding the CMO conform to their way of doing things. Clients should look for a robust quality system and an open and communicative culture when choosing a contract organization to perform work for them.

**A case study in quality agreements**

Let’s look at an example where robust quality agreements and a good communication scheme would have helped avoid and alleviate a regulatory concern. Keep in mind that the contracted parties involved in this scenario are unaware of the multiple contracts negotiated by the client, none of the contracts specify which party is responsible for investigations, and there is no mention in the quality agreement about how the parties will communicate in the event of an issue.

The CMO was manufacturing clinical-trial materials for a client. The CMO was scheduled to perform the sixth manufacturing run of the clinical material when they noticed a different physical appearance to the API during incoming inspection. The Certificate of Analysis accompanying the API indicated the material met the necessary specifications. The CMO was only capable of performing an incoming identity test because the client had contracted for the API release testing to be performed by a contract test laboratory (CTO).

The CMO contacted the client and expressed their concerns with the appearance of the incoming API. The client said that they were not concerned with the physical appearance of the API and told the CMO to manufacture the clinical-trial material. Once the manu-

---

**The importance of quality agreements**

*Pharmaceutical Technology* asked Siegfried Schmitt, principal consultant at PAREXEL, about the importance of quality agreements in the sponsor/contractor relationship.

**PharmTech:** Which parts of FDA’s quality agreements guidance, which was published in November 2016, should manufacturers pay close attention to? Are there similar guidelines in Europe?

**Schmitt:** Although the entire FDA guidance should be paid close attention to, one particular aspect of interest to manufacturers relates to ‘Approving or Rejecting Changes that Affect Product Quality and cGMP Compliance’ (Case 5 of the guidance). Change management can be challenging when a sponsor and contract acceptor disagree. When this occurs, the FDA’s guidance provides clarity around each party’s role and responsibilities which allows the two groups to better overcome these challenges. In Europe, written quality agreements/contracts are mandated within existing regulations, namely EudraLex Volume 4, Part I, Chapter 7 Outsourced Activities; Part II Paragraph 16 Contract Manufacturers (including Laboratories); and Part III Pharmaceutical Quality System (International Council for Harmonization Q10) Paragraph 2.7. Management of outsourced activities and purchased materials.

**PharmTech:** How can quality agreements enhance the sponsor/contractor relationship?

**Schmitt:** While many sponsors and contractors may share a close commercial relationship, quality agreements add a compliance component. This helps to build more of a common understanding of each side’s needs, building additional trust. Possessing a written framework that guides the relationship on both an operational and compliance basis allows for issues to be addressed at a level that is likely more amenable to cooperation and often eliminates legal team involvement.

---

**PharmTech:** How do quality agreements enhance the overall quality of pharmaceutical products?

**Schmitt:** Although the sponsor outsources certain activities, it maintains full responsibility for everything that the contract acceptor does when interacting with regulatory authorities. Thus, the responsibility for manufacturing safe products of a high quality remains with the sponsor. Therefore, the sponsor has great interest in writing quality agreements that assure the maintenance of high quality and compliance levels by the contractor.

**PharmTech:** How should quality agreements be designed?

**Schmitt:** Quality agreements should include clarity in terminology, unambiguously defined roles and responsibilities, and a precisely defined scope of the agreement. These documents are designed for project managers, operational staff, and quality experts. With these users in mind, the language of agreement should be appropriate for that audience and not be written like a legal document. Quality agreements should also be written as separate documents from commercial contracts to retain the flexibility to update and change these as needed.

**PharmTech:** What are some of the mistakes pharma companies make when developing quality agreements?

**Schmitt:** Issues are more likely to arise when both parties involved are not properly aligned, which may lead to a misunderstanding on expectations. Additionally, gaps may surface in specific areas where the sponsor and contractor have varying levels of expertise, such as information technology. To avoid potential gaps or conflicting details within an agreement, the contractor and sponsor should maintain a close relationship with clear objectives and a mutual understanding of the quality agreement.

—Susan Haigney
Manufacturing run was completed, the CMO, per the quality agreement, sent the final product to a different CTO. The product failed final product release testing, and the CTO opened an out-of-specification investigation.

The CTO found no error attributable to the laboratory and contacted the client that they thought there was a problem with the manufacturing run. The client contacted the CMO and told them to investigate the incident at their facility only. During the investigation, the CMO documented that they felt the failure of the product to pass the final product testing was due to the unusual appearance of the API and requested permission from the client to talk with the API manufacturer. The client denied the request; the clinical trial batch was placed on hold by the CMO; and the investigation was never closed out.

During a regulatory inspection, the inspector wanted to know what the outcome of the investigation was. The CMO had to tell the inspector that they could not complete the overdue investigation because they were unable to talk to the API manufacturer and the client had told them that they investigated the API manufacture and could find nothing wrong with the API. The CMO said the investigation was still open because the most probable root cause identified was the API, but it could not be verified. The result was that the CMO, the client, and the API manufacture were all issued FDA 483s and the product approval was delayed until the issue could be resolved.

How could a more robust quality agreement and a communication plan have helped resolve the situation? There are a couple of recommendations to be made. The first is when there are multiple quality agreements involved, the client should make sure each of the parties are aware of each other through their quality agreement. The client should also define that they will facilitate any communications between the various parties involved in the manufacturing including the testing laboratories, packagers, etc. In addition, the quality agreements should state who is responsible for the various activities including the facilitation and resolution of investigations.

There is no right or wrong in crafting quality agreements. A good quality agreement will take into consideration the needs of the CMO, the client, adherence to compliance, and regulatory commitments of both parties. If both parties keep these principles in mind, they will have a great working relationship despite the quality agreement.

References
2. EudraLex, Volume 4, Chapter 7, Outsourced Activities.
4. 21 CFR 211.22, Responsibilities of the quality control unit. PT

---

**ILC Dover**

creati ng what’s next

**Dover Pac**

containment solutions

**EZ BioPac® a Novel Single-use Powder Transfer System**

- Faster fill and dispense
- Minimize product waste
- Reduce exposure to powder
- Easy sealing
- Powder friendly film

Visit [http://www.ilcdover.com/ez-pac](http://www.ilcdover.com/ez-pac) for whitepaper, videos, and more
Data Integrity

Harnessing Advances in Informatics to Ensure Data Integrity

Darren Barrington-Light

Although best practices are key, advances in integrated informatics platforms and automation can make it easier to ensure data integrity and improve overall lab efficiency.

Data shape every decision in the pharmaceutical value chain, from production line optimization to quality control (QC) and quality assurance (QA), batch release, and supply chain logistics. Pharmaceutical manufacturers collect, analyze, and interpret raw data, transforming them into the information that they need to make better decisions.

As competition drives pharmaceutical companies to integrate diverse functions (e.g., research and development with manufacturing, or quality control with supply chain operations), there are prerequisites to ensuring data integrity in lab operations, including those that involve chromatography. And to connect with outside partners (e.g., university laboratories or contract research and manufacturing organizations [CROs and CMOs]), complete and reliable data are essential, both for business efficiency and regulatory compliance.

To ensure safety and efficacy, any data associated with a pharmaceutical product must be “attributable, legitimate, contemporaneous, original, and accurate,” as FDA has noted (1), using the mnemonic, “ALCOA.” Meeting these requirements for chromatography and laboratory has challenged some manufacturers, and even driven a few out of business, in the past.

In 2004, for example, FDA inspectors accused the pharmaceutical manufacturer Able Labs of fraud (2,3). Inspectors found differences between paper and electronic chromatography data, and learned that some of the company’s staffers had been copying chromatograms from records for passing batches and pasting them onto records for failing ones, reintegrating chromatograms, and adjusting measured weights and calculations to ensure passing quality test results for problematic batches (4).

The company had been using both paper and electronic data systems, and the software’s audit trails ultimately showed who had doctored the data. They were charged with criminal fraud and the company went out of business soon thereafter.

But data integrity continues to challenge pharmaceutical manufacturers around the world. Between 2011 and 2014, FDA issued more than 30 warning letters and form 483s citing problems with data integrity (1). From June 1, 2015 through June 1, 2016, the agency’s inspectors issued 25 warning letters and 483s, according to Douglas Farquhar, principal with the Washington, DC-based law firm, Hyman Phelps & McNamara (5).

Regulatory bodies are demanding the highest standards of consistent data robustness. In 2015, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom and the World Health Organization (WHO) both issued new guidance on data integrity (6, 7). In the United States, FDA updated its draft guidance on data integrity in April 2016 (8,9). These latest efforts aim to safeguard data quality throughout the pharmaceutical development process—from testing, manufacturing and packaging medicines, through to distribution and end-user monitoring.

There are prerequisites to ensuring data integrity in lab operations, including those that involve chromatography. First, any and all data must be saved and stored properly and in their original form. Technicians should not enter data into a computerized system, then copy the data on paper, unless systems are in place to verify and store all of that.

Darren Barrington-Light is marketing specialist for informatics and chromatography software at Thermo Fisher Scientific.
THINK UPGRADE

Optimize your capability

Taking your processing capabilities to the next level is a strategy for success; one that often demands upgrading equipment to meet new production goals and future requirements. For immediate access to the best technologies at the right price while maximizing returns from surplus idle equipment, Federal Equipment Company is ready to help you optimize operations while recovering equipment value through accurate appraisals, strategic liquidations and full logistical support.

Find us at Interphex Booth #3110

When you think equipment, think Federal Equipment

1.877.536.1538  >  www.fedequip.com
Data Integrity

data properly. Any data that have been entered manually must be checked and verified by another person. In addition, access to software and passwords should be available to one person at a time, and not issued to groups of technicians. Another important point is to ensure that the right level of data access is given to people on staff, so that nobody can change results that have already been recorded.

Robert McDowall, a consultant in the UK, has analyzed recent FDA warning letters and European regulatory agency citations to highlight the errors that pharmaceutical labs most often make that involve lab and chromatography data (4). These errors tend to fall into the following categories (see Figure 1):

- Laboratory control issues (e.g., unofficial product testing)
- Automation and equipment issues (data that were not backed up or archived properly, use of shared passwords for access to databases and platforms, no standard operating procedures [SOPs] for data management)
- Laboratory record issues (e.g., no reviewer signatures recorded, deletion or falsification of data, data not entered at the point of record).

However, advances in data management, and specifically the move to integrated informatics systems, have made it easier for companies to ensure the integrity of their data. For example, not only chromatography equipment, but laboratory equipment such as scales can be connected directly into a laboratory information management system (LIMS) to ensure that the correct data are recorded and cannot be tampered with (10).

In addition, there is a need to move beyond ALCOA, to ensure that data are also consistent, complete, enduring, and available. LIMS and chromatography data systems (CDS) can help by having relational databases to record complete data, automatically and consistently, and store them for the long-term, while maintaining the user’s ability to retrieve that data easily.

This article looks at how improvements in LIMS and CDS can help ensure the integrity of data and improve overall laboratory efficiency. These improvements have been driven by user demand for more automation to ensure compliance and data integrity while delivering better usability. As computer systems have evolved, the ability to add more intelligent functionality to laboratory software has increased, enabling the support of smart functions that provide more assurance of data integrity.

The right decision at the right time

For anyone working for a pharmaceutical manufacturing company, making the right decision requires timely access to data that can be trusted. With the evolution of smarter laboratory software, the ability to control and reduce sources of potential data-integrity issues is now in the hands of laboratory managers. Even in a QC lab that uses the most robust chromatographic methods, it can be challenging for technicians to adhere to SOPs every time they run a specific procedure to ensure that routine analyses generate reliable data every time.

When out-of-specification (OOS) results are identified, discovering the root cause of the problem is often a time-consuming, manual process that can only take place after errors have been spotted. Once an error has been identified, troubleshooting a specific chromatographic method can lead to workflow delays, pushing back project deadlines and squeezing budgets.

The latest CDS use intelligent control features such as system suitability testing and run control to allow the results of analytical runs to be recorded more efficiently. By taking automated, in-run pass or fail actions based on real-time chromatographic results, these tools can reduce the number of OOS tests required to determine root cause and help minimize post-run analysis time.
Are you ready for the next wave of bio/pharmaceutical manufacturing?

Biosimilars are gaining increased attention – be sure you have all the knowledge you need about this rapidly expanding area!

Attend the 2017 PDA Biosimilars Conference where industry and regulatory experts will discuss the latest advancements and strategies intended to successfully bring biosimilars to market.

Through presentations, case studies and practical examples, Conference sessions will address:

- Current Agency Expectations for Approval for Biosimilars
- Strategies for Reverse Engineering
- Expectations and Practical Considerations for Analytical Similarity
- CMC Considerations for Global Regulations
- Post-Marketing Change Management
- Control Strategy for Biosimilars
- Product Specifications for Biosimilars
- Data Quality Expectations in Biosimilar Development

Attendees will also have the opportunity to share their questions and concerns with the experts during the Conference.

Learn more and register at pda.org/2017bio
**Data Integrity**

The most up-to-date LIMS can help laboratories not only to identify when runs fail, but to predict when they will fail. Left unchecked, errors that mask small performance problems can grow into much larger quality issues that require costly remediation. Real-time monitoring using statistical algorithms is extending the power of chromatography run-control software. Some integrated systems have been designed with statistical quality control capability built in. Such technology allows real-time process monitoring and trending, and can track nonconformance before it reaches pre-defined thresholds, allowing the overall process to be optimized automatically while the root-cause investigation is still going on.

Unscheduled maintenance in a QC laboratory can cause costly delays to the release of an entire product batch. These delays are often caused by a gradual decline in instrument performance, which, unless detected and trended, can easily be ignored. Integrated informatics systems that control SOPs and capture data from all lab instrumentation and equipment can become a crucial component in increasing laboratory productivity by managing instrument maintenance schedules and reducing downtime.

**Monitoring instrument performance**

Once trended and analyzed, data such as area counts, baseline conductivity, and retention time provide valuable information on the general health of an instrument. Both CDS and LIMS offer capabilities that allow users to monitor instrument performance so that equipment downtime can be carefully planned as part of a regular maintenance schedule. This way, users can be notified, and workflows can be planned around this schedule.

Another example of how real-time data analysis can streamline workflows and boost operating efficiency is in inventory management. The flow of commonly used disposable labware such as gas chromatography and high-pressure liquid chromatography vials is essential for smooth lab operations. While the cost of an individual vial may be low, the repercussions from poorly managed inventory can be significant. For example, if an inventory for a QC laboratory is depleted, it can have a downstream impact on other workflows, affecting productivity. Such shortfalls can result in the need for expedited delivery, usually at increased expense—which could have been avoided had the shortfall been identified earlier.

Managing the inventory of a single lab running routine tests should be predictable. However, tracking what has been used, when, and by whom is a critical but commonly overlooked step. Using spreadsheets to track consumables cannot support live updates, but LIMS can record and trend usage automatically to ensure vital workflows.

**Garbage in, garbage out**

Of course, the quality of data depends on how the data are collected. It’s difficult to overstate the importance of developing and documenting SOPs for laboratory workflows. Many laboratories devote considerable time and resources into developing SOPs. Inconsistencies in QC or QA testing protocols, however, can result in costly delays due to compromised regulatory audits. The result puts consumer safety and commercial reputation at risk.

Every company and laboratory has its own approach to creating, distributing, and monitoring SOPs. Many labs still rely on paper-based systems, which suffer from a number of practical limitations. It is time-consuming for analysts to input data manually, when configuring instrumentation. Paper systems are also more prone to human error—especially if analysts are not familiar with the intricacies of a particular system or test. And when changes must be made across a portfolio of workflows to bring them in line with the latest guidelines, it can require significant time and resources to ensure that each individual SOP has been completely updated.

Electronic SOPs (ESOPs) help eliminate some of these problems. With ESOPs defined in a LIMS, for instance, analysts have access to all of the relevant protocol information, ensuring that they adhere to protocols and providing confidence in the robustness of workflows and validity of test results.

Some platforms feature built-in lab execution systems (LES) that allow the LIMS platform to interface with the laboratory’s CDS to download method parameters required for a particular SOP and initiate the analytical sequence. This approach ensures that each analysis is performed correctly, and that the data obtained meet the necessary SOP requirements.

**Safeguarding data integrity**

With QC and QA laboratories responsible for hundreds of tests every week, and each test involving multiple component parts, preparing reports and defending data can involve time-consuming steps to retrieve details of analytical conditions, reagent compositions, and instrument calibration tests. Many of these details are often so deeply embedded in laboratory workflows that it can be extremely difficult to isolate them. In fact, research has shown that pharmaceutical laboratory analysts spend around 15% of their time collecting the data they need to defend a result (11).

The time and productivity lost hunting for these data can be reduced by using integrated information management solutions. Laboratory CDS software automatically records all chromatographic run data and conditions as well as a detailed audit trail of user actions. The latest LIMS can integrate seamlessly with CDS platforms to retrieve all of this information, along with instrument calibration history and colleagues’ laboratory notebooks, giving users access to who did what, when, and why in one location.

FDA recommends that all audit trails capturing changes to critical data be reviewed for every record and before each record’s final approval (8). Audit trails subject to regular review should
We are Patheon, and we bring to bear 40 years of experience and expertise, from development to manufacturing. We also bring global reach. An industry reputation for being right on time, the first time. Supply chain solutions designed to simplify complexity and speed up the process. And a passionate belief that together we can make the world a healthier place.
include any changes to sample run sequences, sample identification, and critical process parameters. To make these checks a matter of course, the most efficient laboratories are using a combination of LIMS and CDS software to review an instrument’s daily audit trails, search and filter for events, and add audits to reports for review.

**When data are generated from multiple instruments or systems that use older versions of software, the potential for data incompatibility increases.**

Integrated informatics platforms such as the latest LIMS offer built-in scientific data management system (SDMS) functionality for this purpose. These systems offer easily configured paperless review and approval procedures and include advanced search and data mining tools to review chromatography and mass spectrometry data, showing when processes are drifting towards nonconformance, giving labs a complete overview of performance based on analyst, instrument, or test.

Given the sensitive nature of commercial or consumer sample data, it is essential to ensure that any changes to records are made only by authorized personnel. Recent advances in LIMS and CDS design have given laboratory managers the ability to control what users can do with data and how they can access it, helping laboratories meet FDA recommendations. Integrated CDS, for instance, track and generate audit trails in real-time by capturing all changes made to data within the software. Modifications can only be permitted by the system administrator, and even then, the software retains details for all versions, allowing users to view all changes, deletions, and additions. Such features help maintain transparency and safeguard data integrity at every stage.

**Archiving and storing data**

Securing and archiving an ever-increasing amount of data, the lab’s mass spectra and chromatograms documented at the time of analysis, is also a challenge today. It is also a requirement in case of a regulatory question or audit. Modern CDS software will place acquired chromatographic data immediately into a secure database that supports long-term storage. The latest LIMS systems also capture data from non-chromatographic instruments, recording reagent weights and pH meter readings, for example, alongside chromatographic method details, audit trails, report formats, and electronic notes and files, making it easier for all relevant information to be recalled for audit purposes.

When data are generated from multiple instruments or system that use older versions of software, the potential for data incompatibility increases. The latest solutions utilize vendor-neutral formats so that handling data is easier when collaborating with other labs or when integrating QC testing workflows with a manufacturing plant to make decisions on batch release.

Integrated CDS and LIMS solutions are not only helping laboratories and manufacturing facilities comply with the latest current good manufacturing practices, but allowing them to analyze trends in real-time to predict problems before they escalate. These advances in data management can help the industry reach the highest levels of data integrity while bringing safe, effective therapeutic treatments to market more efficiently and affordably.

**References**

8. FDA, FDA Guidance for Industry Data Integrity and Compliance with cGMP, fda.gov, (CDER April 2016), www.fda.gov/downloads/drugs/guidancemcompliance/ucm061813.htm
Global Reach With A Breadth of Services

The Aenova Group’s services cover the entire value chain for the development and production of all the main dosage forms and product groups in pharmaceuticals and dietary supplements. With more than 4,000 employees and over 21 sites, Aenova is one of the leading companies in the pharmaceutical and healthcare industries...and the right choice for your next project.

Members of the Aenova Group

C.P.M. • Dragenopharm • EVP • Haupt Pharma • Swiss Caps • SwissCo • Temmier

www.aenova-group.com » (862) 881-4439 » info.us@aenova-group.com
Facility modernization can be a complex and difficult process even under the best of circumstances, but when one factors in the global regulatory hurdles in pharmaceutical manufacturing, the challenges are significantly greater. However, the reality of aging facilities that must be maintained in a state that is reliable, efficient, and compliant with current good manufacturing practice cannot be avoided. Successful implementation of change must be executed with a good understanding of the challenges associated with introducing new technology and an execution strategy that proactively achieves strategic outcomes.

Obstacles to new technology implementation
In an industry-wide survey of the life-sciences sector conducted by DME in partnership with INTERPHEX, DME Facility Focus (1), industry insiders—those in engineering and operations roles—were asked what they believed was the biggest obstacle to the adoption of new technologies for facility modernization. As shown in Figure 1, the majority (62% of respondents) indicated that regulatory challenges (process validation or regulatory acceptance) were their biggest concerns. The remaining survey participants cited the biggest obstacle as process development requirements (18%), lack of industry standards (12%), and insecure vendor supply chain (5%). Those with “other” responses (4%) most frequently indicated their belief that general industry conservatism is the biggest obstacle.

This finding is consistent with a recent survey by the Parenteral Drug Association (PDA), which reportedly suggested, among other things, “that product-related post-approval changes (PACs), and the time and investment that they require, are stifling conversion to new technologies or methods” (2). In response, PDA established a task force (PAC iAM) to seek comprehensive post-approval change reform, focusing on the global regulatory challenges. As group members noted in an op-ed published in the August 2016 edition of PDA Letter, these challenges “create a disincentive—albeit unintentional—for manufacturers to integrate growing product and process knowledge, continually improve, or innovate technologies” (3). In their public call to action, the taskforce went on to link the current post-approval change environment to drug shortages and deferred process improvement, writing, “In order to avoid the burden of implementing changes in such a complex environment, many [manufacturers] find it easier to postpone improvements to facilities, processes, and analytics, or simply refrain from planning advancements at all.”

Industry insights
While PDA focuses on systemic change through a global forum and their regulatory harmonization efforts, manufacturers still need to deal with aging facilities in the here and now. The DME Facility Focus survey provided further insights into how manufacturers are coping with these challenges.

When asked what new technologies they have introduced as part of a facility modernization project, ranked from most common to least common technology, participants responded as follows:
- Process automation
- Single-use/disposables
- Clean-in-place (CIP) improvement
- Continuous manufacturing
- Modular construction.

As shown in Figure 2, these trends generally held true even when broken down by industry cohort. The lone exception is single-use technology, which is far more commonly implemented in biologics manufacturing than chemical synthesis.

The most common technologies implemented likely correspond to post-

David M. Marks, P.E. is the president of DME, an engineering design and consulting firm that specializes in solutions for advanced technology facilities in the life-sciences industry, www.DMEforLife.com.

The DME Facility Focus survey revealed best practices for coping with the challenges of aging facilities.
Grand River Aseptic Manufacturing (GRAM) is a full-service, contract parenteral manufacturer located in Grand Rapids, Michigan. We are committed to superior regulatory performance and it is our mission to deliver quality products and services. As a result of our commitment to excellence, our last FDA inspection resulted in no Form 483 issued. This is reflective of the level of quality standards with which GRAM has successfully manufactured and launched numerous clinical and commercial products. At GRAM, we treat every client project as if it were our own.

Services Offered:
- Pharmaceutical Development
- Clinical and Commercial Parenteral Manufacturing
- Lyophilization
- DEA Controlled Substances (CSIII-V)
- Biologics Manufacturing

Meet with GRAM in 2017:
- DCAT Week 2017
- Interphex Booth #1543
- PDA Booth #216

www.grandriverasepticmfg.com  bd@grandriverasepticmfg.com
approval changes that yield the greatest advantage and are easiest to implement. There is a strong case to be made that the most frequent type of change, process automation upgrades, will improve product quality, particularly when the operations being automated were originally manual. In many instances, it’s relatively easy to demonstrate that process automation changes will not adversely affect the manufacturing process. In addition, the DME survey found that aging automation drives 11% of equipment obsolescence issues in legacy equipment (1). Automation can also be a key component in the corrective action addressing manufacturing deviations.

The second most common technology, single-use, has garnered a lot of attention in recent years as manufacturers explore the potential for bioprocessing with a completely disposable wetted path. Such facilities could potentially do away with expensive utility systems associated with cleaning, and they promise less reliance on cleanroom environments for process segregation. These initiatives, however, require a purpose-built facility and a significant commitment to process development within the single-use framework and are, therefore, more useful as a platform for new products in the pipeline. The prevalence of single-use technology in facility modernization projects is most likely limited to the replacement of specific unit operations and procedures within traditional facilities with predominately stainless-steel equipment. The replacement of a sampling system on a stainless-steel process vessel with a disposable sample assembly is a good example of the kind of process change that can yield a significant improvement with a reasonable post-approval change effort. Similarly, manufacturers have adopted single-use bag systems for supporting operations such as buffer preparation and hold vessels without disrupting the primary unit operations that are processing product.

The survey findings suggest that manufacturers choose to selectively introduce new technology in aging facilities where the potential benefits significantly outweigh the pain points (e.g., total cost and risk due to many aspects of implementing a change). In legacy facilities, a new technology is strategically adopted in areas that yield the greatest benefit and where it is relatively easy to demonstrate that the change will not adversely affect product quality.

Drivers for renovation
Considering the PAC iAM task group’s conclusion that the complexity of post-
approval changes discourages facility improvements, it is instructive to examine the most common drivers for the introduction of new technology within legacy pharmaceutical facilities. When asked to rank the frequency of risk-based drivers for GMP facility renovations, respondents clearly identified product quality and regulatory compliance as dominant concerns. The survey also found that internal assessments of facility and equipment compliance are most frequently triggered by manufacturing deviations (58%) (1). These responses suggest that a reactive approach to modernization is typical in the pharmaceutical industry. The ensuing corrective action and preventive action (CAPA) process after manufacturing deviations requires the implementation of corrective action, which presumably mandates facility improvements in some circumstances. CAPA is clearly the worst possible driver for facility improvement because changes are forced irrespective of the disruption to scheduled manufacturing, and a failure to follow through in a timely manner can result in regulatory action.

The second most common driver for GMP assessments is opportunistic (55%), executed as part of planning for a GMP renovation driven by other factors, which suggests a path forward to a more proactive approach to facility improvements. Given the high pain threshold required to implement post-approval changes, there are many factors that must accumulate before improvements can be justified. These include both risk-based factors (e.g., compliance, safety, obsolescence, reliability) and opportunity-based factors (e.g., new products, increasing throughput, improved flexibility, reduced costs, better sustainability). When product quality and patient safety are at stake, manufacturers are required to take action immediately. But manufacturers can introduce new technology in a more controlled and comprehensive way if they piggyback risk-reduction and GMP improvements on projects that are primarily driven by opportunity-based factors.

Figure 2: New technologies used in facility modernization. Results from the DME Facility Focus survey (1).

<table>
<thead>
<tr>
<th>New Technology</th>
<th>Consultant</th>
<th>Biologics manufacturer</th>
<th>Small molecule manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process automation</td>
<td>56%</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>Single-use / disposables</td>
<td>68%</td>
<td>49%</td>
<td>19%</td>
</tr>
<tr>
<td>Continuous manufacturing</td>
<td>19%</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>Clean-in-place improvement</td>
<td>30%</td>
<td>48%</td>
<td>30%</td>
</tr>
<tr>
<td>Modular construction</td>
<td>30%</td>
<td>34%</td>
<td>19%</td>
</tr>
</tbody>
</table>

References
2. A. Shanley, Pharm. Tech., Quality Throughout the Supply Chain ebook, pp. 27-32 (2016).
Serialization and traceability have been discussed for so long in the pharmaceutical industry that it’s easy to forget the fact that the concepts have been with us for 15 years now. In the early 2000s, efforts to secure the supply chain in Florida first brought the term “e-Pedigree” into pharma’s everyday vocabulary.

So far, more than 40 countries around the world have set standards and deadlines for item-level pharmaceutical serialization and traceability, and two to three countries join this list each year. By November 2017, the US Drug Supply Chain Safety Act (DSCSA) requires that all pharmaceutical manufacturers serialize products down to the item level, including a product identifier on labels and cases, as well as information on product transactions as the product makes its way through the supply chain. Most larger pharmaceutical companies are well-prepared for the deadline, and successful pilot programs (see Sidebar, p. 76) have shown that manufacturers and distributors can synchronize operations and exchange the data required to make traceability possible.

Not all companies are ready, however. In December 2016, a survey of more than 331 industry professionals sponsored by TraceLink and designed to be a snapshot of industry’s efforts (see Sidebar, p. 78) found that 19% of pharma companies, 11% of distributors, and 9% of dispensers still haven’t begun to address requirements, while only 24% of pharmaceutical manufacturers say that their contract manufacturing organizations (CMOs) will be ready for the deadline (1).

This lagging response is likely due to a combination of factors. Most of the companies that aren’t prepared are small to mid-sized companies, says Bruce Bleiman, Systech International’s global senior vice-president of sales, and many of them were not exposed to serialization concepts in the earliest stages of the industry’s efforts.

Misunderstanding serialization
Even if these companies did have some understanding of the concepts involved, many viewed serialization as a limited, packaging project rather than the far-ranging multifunctional effort it is, notes Paul DuPont, vice-president of marketing with Ropack Pharma Solutions, a contract development and manufacturing organization (CDMO) based in Montreal, Canada. In addition, compliance deadlines for past serialization programs (notably California’s) were extended and some companies may have questioned why they should invest in something that, in the end, might not be required, says Shabbir Dahod, CEO of TraceLink, which offers Life Sciences Cloud, a cloud-based solution for pharmaceutical serialization.

Even companies that have invested heavily in serialization have been surprised by the level of commitment required. First, there are capital costs, which tend to run approximately $200,000 to $300,000 per packaging line. But beyond that is the complexity of data integration, notes Dahod, especially with CMOs and customers, and the networking and data exchange aspects of serialization.

Dealing with complexity
Complexity already defines the pharmaceutical supply chain and the relationships within it, he says. This was clear in the TraceLink survey results: Pharmaceutical manufacturers may say that they do most of their business

As the November 2017 deadline nears, a surprising number of companies still don’t have a serialization plan in place. New programs aim to get them compliant in time.
TruCLEAN Mopping Systems effectively capture and isolate contaminants from cleaning and disinfecting agents. The TruCLEAN Pro XL is our most well-equipped mopping system, featuring an extended stainless steel trolley with heavy-duty casters and the largest material capacity of all TruCLEAN systems. Handle-mounted carrying basket provides ample storage for extra supplies. TruCLEAN systems are designed to be simple and efficient while delivering superior cleaning results.

Compatible with gamma, ETO and autoclave sterilization.

Customer Service:
1-800-848-8483
with the “Big Three” pharmaceutical distributors (McKesson, AmerisourceBergen, and Cardinal Health), says Dahod, but, in reality, they have more customers and different relationships, and use different delivery models (e.g., drop ships or special orders) with each one. Pharmaceutical company professionals who responded to the survey said that more than 40% of their business transactions are with customers other than the Big Three; 25% of pharmaceutical manufacturers had more than 10,000 customers, while 31% had between 500 and 10,000. In addition, 29% sell directly to hospitals and pharmacies.

Not only must companies deal with individual product transaction histories, says Dahod, but, as they bring CMOs and internal packaging lines on board, the number of business and operational processes they must integrate with, both internally and externally, increases dramatically. “Ten to twenty thousand times the amount of information must now be exchanged, and floated forward to wholesalers and hospitals,” he says.

Companies that have made the effort, however, are seeing results. “Where, in the past, maybe less than 5% of their customers were integrated digitally, they are now connected with all of them. For some companies, that means tens of thousands of connections, promising more efficient information exchange, better systems integration and fewer errors,” says Dahod.

No short-term results
Making those connections puts companies in a position where they can see the potential for return on investment. “This effort requires end-to-end thinking, from packaging all the way through to our customers,” says Mike Rose, vice-president of supply chain visibility with Johnson & Johnson Supply Chain (JJSC). “The reward is improved visibility that will help ensure that our patients receive genuine product,” he says.

Some of TraceLink’s original customers are just beginning to see, and leverage, this potential (e.g., with Secure Chain, a product designed to provide closed loop end-to-end traceability for serialized product, within specific supply chain segments).

TraceLink has also been working with pharma companies to develop consumer-based authentication solutions, and software that would mine event data to better manage inventory. “In 2018, when large volumes of serialized product are out there, we expect to see more of these types of applications,” says Dahod.

But, in the meantime, how can unprepared companies be ready by November 2017? “The serialized mandate is approaching fast. Using the conventional approach, not everyone will be able to be ready in time,” says DuPont. “One of the harsh market realities is that there is a limited number of hardware providers out there to help companies who are just starting to put their serialization programs together.”

DuPont notes that some CMOs, even those who partner with large pharma companies that have advanced serialization programs in place, won’t be ready for the deadline. For pharmaceutical companies and CMOs, he notes, the highest hurdles are buying and installing the hardware, especially given demand for services as the deadline approaches. Others are internal testing (investing in and installing software and data management tools), and managing different requirements at each location.

Accelerated compliance
To help companies become compliant by the DSCSA deadline, a number of solutions providers are now offering accelerated compliance programs. In late January 2017, Systech International launched “Serialized by November,” a program involving its long-standing equipment partners, which include Omega, LSI by ID Technology, UPAK by Ultimate Solutions, Etipack, and Inno4Life. The program compresses the process into 90 business days, with the initial phase (kickoff discussion, data collection and software shipment) taking two weeks; the

---

**Testing GS1’s EPCIS Standards in the Real World**

In 2016, the pharmaceutical manufacturer Johnson & Johnson Supply Chain (JJSC) and the distributor AmerisourceBergen launched a four-week pilot program to test GS1’s EPCIS standards and to see how effectively data could be transferred between the two partners. JJSC has been working on serialization for some time, and began shipping serialized product back in 2012, so both companies were fully connected, in terms of their IT, and they could try this approach with serialized product. The test simulated the real-world supply chain.

A DataMatrix barcode was applied containing a serialized global trade item number (GTIN), batch and lot number, and expiration data for each sellable unit (whether bottle, vial, or blister), and the units were packed into cases and loaded onto pallets, while downstream vision systems and scanners read the barcode to capture all the information. EPCIS recorded events associated with the GTIN, so that AmerisourceBergen could confirm receipt of each item sent by JJSC, automatically.

Results showed not only the viability of this approach, but its potential power. “It’s like electronic data interchange (EDI) on steroids,” says Mike Rose, vice-president, supply chain visibility at JJSC. “Over time, supply chain partners will be able to exchange a lot of critical data for additional value,” he says. The pilot ensured that all processes, from plant to warehouse and distribution center to docks, were tracked. “It forced us to test all processes along with way. We got confirmation from our partner that everything fed back to them, from plant to distribution center, and that they were receiving relevant process data.” Rose expects to see return on investment in terms of improved inventory management and transparency in the future. “But for now, our focus remains on the patient first,” he says.
GEMÜ Quality Products...
GEMÜ Quality Service

4212 & 4242 Automation features:
- Class 1 DIV 2, UL & CSA
- Multiple control options: 24 VDC, AS-I, DeviceNet
- Super bright LEDs indicate valve position

Multiport Diaphragm Valve features:
- Thousands of block designs to solve process challenges
- Minimize dead leg and hold up volume for optimal process efficiency

Globe Valve features:
- High cycle life
- Variety of end connections, materials of construction and actuation

See us at Interphex Booth 2663
www.gemu.com
design phase (involving integration drawings, documentation, validation and hardware shipment) taking six weeks; implementation, including factory and site acceptance tests (FAT and SAT) and startup, requiring four weeks; and project closure taking two weeks.

**Fee-for-service approach**

In late November of 2016, Ropack and TraceLink, together with the equipment specialist Optel, first announced the formation of the International Serialization Hub, which they plan to launch formally in the Spring of 2017, to help pharma companies comply with DSCSA serialization requirements by November 2017 (2). With this program’s operating model, DuPont explains, companies send product to Ropack, which will take it and serialize at the unit of sale (whether item, carton, or pallet), and then send it on to its destination. It’s a simple, fee-for-service approach, he says, and can work with any data management platform. For companies that already use TraceLink’s solution, however, the costs will be much lower and the timeframes, shorter.

The service would be offered, but not limited to, Ropack’s existing client base. As DuPont explains, the idea for the program came from a large pharma client that had serialized, but still could not get one of its 50-year-old plants ready for DSCSA serialization.

For Ropack, investment in the program reflects the reality that serialization is no longer 'nice to have,' but a mandated regulatory compliance platform. “Serialization has become like validation was 15–20 years ago,” Of course, DSCSA mandates are only one facet of the global serialization requirements that pharma companies now face. Accelerated programs may not be a long-term solution, but at least they may help resource-strapped companies achieve basic compliance in time for the deadline.

**Speed Bumps on the Road**

In December 2016, TraceLink and the market research firm Actionable Research released results of the first *Global Drug Supply, Safety, and Traceability Report* (1). The study surveyed 331 professionals from pharmaceutical manufacturers, wholesalers, pharmacies, and hospital pharmacies, to better understand issues and compliance trends at the lot level to get a more realistic picture of gaps in readiness, and the challenges that face pharmaceutical companies, distributors, and dispensers of all sizes in realizing full product traceability.

Half of the pharmaceutical companies that responded to the survey expect to comply with electronic data transfer requirements within six months of the November 2017 deadline, and 54% describe themselves as well-prepared for serialization. However, 19% of companies say they have not begun to address requirement, and only 24% say that their contract manufacturing organization (CMO) partners will be ready.

Respondents from pharmaceutical companies said that they underestimated the complexity of implementation, the total cost of IT upgrades required, and the overall impact that implementation can have on business. Customers at the dispenser level complain that the documentation needed for compliance is often missing from products that they buy directly from manufacturers. In their dealings with drug distributors, dispensers fear that their electronic data, which are now accessible via distributor portals, may not be available if they change distributors.

The following highlights from the research emphasize the data integration challenges inherent in serialization:

- Roughly 37% of pharmaceutical companies bought a solution specifically designed to help with lot-level compliance, while 33% modified an existing third-party business system, 28% have implemented a manual process, and 20% have developed customized solutions.
- Twelve percent of T3s (data required for serialization, which include transaction statements and history as well as product information, e.g., lot number) are being handled via a portal, 30% on paper, and 58% electronically. Seventy-one percent say that customers cannot handle electronic transaction types, but 21% say that they are not prepared to handle them.
- In cases where pharmaceutical manufacturers sell directly to dispensers, 27% of respondents from retail pharmacies and 5% of respondents from hospitals say that they do not receive any compliance documentation when they purchase directly from the manufacturer.
- Eighty-three percent of pharma company respondents say they understand the Drug Supply Chain Security Act requirements, 70% say they can handle the scale and volume of data, and 67% say that responsibilities for serialization have been made clear within their companies.
- Where companies say they are not fully meeting requirements, 50% describe needing more dedicated resources, while 40% are concerned about customer connectivity.
- Fifty-four percent of pharmaceutical companies found that they had to modify systems to accommodate a customer request, but 16% reported being unable to make those changes.
- Twenty-six percent of pharmaceutical companies experienced an increase in bad or incorrect data exceptions as a result of the requirements. Clearly, serialization challenges remain, but at least more companies “know that they don’t know,” and are networking and learning from their peers from pilot tests and implementations to figure out what to do next.

**References**


Understanding Containment

Richard Denk

The new ISPE Containment Manual is a summary of the process involved in the manufacture of highly active or highly hazardous pharmaceutical substances.

The manufacture of highly active or highly hazardous pharmaceutical substances involves a complex interplay between the required threshold values, such as the permitted daily exposure (PDE), which is used to calculate the occupational exposure limit (OEL) and the maximum carry-over from one product to the next. In addition to these threshold values, a risk assessment of the overall process and the associated containment transfer systems, cleaning, and staff training are also important. An account of this complex interplay and how it can be successfully implemented has now been published in the first edition of the International Society for Pharmaceutical Engineering (ISPE) Containment Manual (1).

A group of experts came together in 2008 to establish an ISPE Community of Practice (CoP) in Germany, Switzerland, and Austria (DACH), which laid the foundation for a comprehensive document about containment. After almost six years of intensive collaboration, with numerous meetings, working group sessions, workshops, and reviews by industry, the Containment Manual was presented and distributed to participants at the ISPE Containment Workshop in Germany in November 2015.

The Containment Manual is the most comprehensive document to date on the topic of containment, and it comprises an introduction followed by 10 different chapters that cover the principles of containment, risk assessment, the lifecycles of containment solutions, process requirements from API manufacturing to the packaged tablet, technical systems such as isolators, secondary containment, filter systems, occupational hygiene validation, cleaning/waste treatment, and staff training. Selected chapters are outlined in the following discussion.

Principles of containment

How are OELs calculated? The chapter entitled “Fundamental Considerations” focuses on defining the relevant terms. From establishing the critical effect to establishing the no observed effect level (NOEL), which is then used to calculate the acceptable daily exposure (ADE) or, in accordance with the new EU GMP guideline for shared facilities (2), the PDE.

The relationship between the ADE/ PDE and the OEL can also be seen in the containment pyramid (see Figure 1). Along with the OEL, the ADE/PDE is used to calculate threshold values for cleaning residues and for product carry-over from one substance to the next. The threshold values calculated using the PDE also replace, in Europe, the 10 ppm and the 1/1000 of the daily dose criteria previously applied (2).

A further point relating to the principles of containment is the distinction between primary and secondary containment. Primary containment refers to all of those technologies that enclose the substance and prevent it from spreading. Examples of this include isolators and endless liner systems. Secondary containment, on the other hand, involves preventing any further spreading of the substance that could not be held back through primary containment.

Risk assessment

Every planning process begins with a risk assessment, which takes the overall manufacturing process into account, from delivery of the API to the finished and packaged pharmaceutical product. The procedure involves assessing the risks that may arise and the extent of the immediate hazard for users and the environment. In addition to the immediate hazard associated with product transfer systems, cleaning, maintenance, and repair should also be taken into account. During cleaning, for example, it must be noted that dust exposure is possible when opening containment or process systems at critical points. Maintenance work, for its part, involves the risk of visible product deposits being left on shaft seals when parts are disassembled, for example. As part of the risk assessment, all experienced individuals who are familiar with the manufacturing process should sit together with suppliers to discuss critical areas, risk reduction, and risk acceptance.

The lifecycle of containment solutions

The lifecycle of a containment installation does not end when it goes into operation—it is only just beginning. More precisely, the lifecycle starts with the planning process for manufacturing a highly active or highly hazard-
Protected.

Everyone wants to be protected. With Emergent BioSolutions, you can be sure you are. They have a proven track record as a world-class provider of contract manufacturing services, for both bulk drug substances and sterile injectable drug products. They are dedicated to one simple mission: to protect and enhance life.

See how Emergent protects lives.

ebsi.com/CMO
800-441-4225 | CMO@ebsi.com
ous pharmaceutical product, together with its specifications, and ends with decommissioning. There may be a significant period of time in between, during which the containment installation and its safety function will need to keep pace with the relevant requirements. One of the most significant factors for ensuring compliance is maintenance and repair. Consumables used in pharmaceutical manufacturing are subject to a constant process of wear, and this wear can vary according to process, frequency, and product. Based on these requirements, it can be necessary to shorten the inspection and maintenance intervals. Ideally, the OEL measured on the installation (referred to as the DEL, or “design exposure limit”) should be significantly close to the required OEL. It is, in any case, essential to note the point in time at which the first effect level is reached, or alternatively to ensure that this does not occur. The first effect level is reached when the DEL becomes very close to the required OEL. Maintenance plans and instructions help to secure the lifecycle of the containment.

**Process requirements**

As a rule, the processes involved in API manufacturing or pharmaceutical formulation are considered to be closed and hence safe. There are, however, several important points to take into account when it comes to planning functioning process containment. One of these is product residue, as shown in the following example.

A high shear mixer is a process device that is closed while the product being manufactured is processed. It must be noted, however, that this technology is not completely self-emptying. It may be necessary to open the system to remove (potentially expensive) product residues from surfaces and make them available for further processing. These systems also have shaft feedthroughs from the exterior to the interior, and these feedthroughs are subject to wear, even when equipped with the best seals and air flushing. In particular, when the product is abrasive and friction against the seal is intensified by the rotation of the mixing paddle, product may be carried over into the seal. Inerting with a noble gas can also result in residue. Flushing the gas with low pressure can result in air turbulence at the point where the gas enters into the process, making it possible for product dust to be deposited in the gas pipe against the direction of flow.

**Technical systems**

In addition to describing the functions of the individual process systems, the *Containment Manual* also lists the possible technical containment systems that can be used for this process together with the critical areas to be considered in each case. The term “containment” primarily refers to product transfer systems such as isolators. These technical systems are intended to ensure that highly active or highly hazardous substances do not escape. Further product transfer systems include double valve systems, film connection systems, endless liner systems, rapid transfer ports (RTPs), film isolators, and various others. All of these systems have their merits and are used in the pharmaceutical manufacturing of highly active or highly hazardous substances.

Isolators are undoubtedly the most frequently used form of containment system. They can be put to various different uses...
and can achieve a high level of containment down to the low nanogram range. Achieving this result in the low nanogram range, however, needs a significant amount of experience in isolator manufacture and design. Here, the glove port design and glass door seals also play an important role, in addition to hygienic design. Figure 2 shows an example of an isolator with high containment.

The filter technology used for inlet and outlet air is a further important factor. In many cases, bag in/bag out or push–push systems are used. With bag in/bag out systems, the low nanogram range cannot be reached due to technical limitations. While this is possible with push–push filters, they are a concern from a GMP perspective, as they involve pushing the contaminated filter cartridge into the cleaned isolator. However carefully this procedure is carried out, the risk of contamination within the isolator cannot be ruled out, nor can the risk of contaminating the new filter. Isolated filter cartridges called “FiPa” are the better option in this regard. The FiPa, shown in Figure 3, is constructed in a similar way to the isolator itself; it is completely sealed before use and is connected to the isolator in this state. Once the FiPa has been connected, the cover plate is opened from the outside into the isolator so that the contaminated air flows inwards and the dust is collected. Before the isolator is cleaned, the cover plate is closed to seal the highly active or highly hazardous substance within the filter housing. The FiPa is disconnected and disposed of once the cleaning process is complete. Sophisticated technical solutions are required to ensure that the low nanogram range can be reached in a secure installation.

**Personnel**

An essential factor in the success of a containment installation is the production team that operates the facility once it has been successfully commissioned. The production team should be selected at the early stages of planning and integrated into the decision-making process. Intensive and recurring training during commissioning and the initial stages of routine production is significant when it comes to complying with the required OEL.

**Conclusion**

The development and manufacture of highly active substances are becoming increasingly common. While in the past, these were primarily APIs and products in the pharmaceutical manufacturing of oral solid dosages, they are now also being used increasingly in biotech, such as in antibody drug conjugates. The Containment Manual will support those planning a new, high-potency API facility or modernizing an existing production facility.

**References**

1. ISPE Germany/Austria/Switzerland Affiliate, Containment Manual (ISPE, November 2015).
2. EMA, Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities (EMA, Nov. 20, 2014).
The bio/pharmaceutical industry is still buzzing about President Trump’s meeting with pharmaceutical executives on Jan. 31, 2017 (1). While promising the industry lower taxes and less regulation, the President emphasized that those benefits will come only if the industry lowers drug prices and moves more manufacturing back to the United States.

The President’s insistence that manufacturing move back to the US set off a wave of promises from the bio/pharmaceutical industry about the number of jobs that might be created, including a projection by the head of the industry trade association PhRMA that the industry would create 350,000 jobs during the next 10 years if the tax and regulatory changes were enacted. At the same time, it triggered some excitement about the opportunities that might await the contract manufacturing industry in the US if bio/pharma companies chose to outsource the manufacturing of products moved back from offshore sites.

Certain segments of the contract manufacturing organization (CMO) industry have in fact been very US-focused. PharmSource research has shown that of the 99 new drug applications (NDAs) and biologic license applications (BLAs) approved by FDA in 2016, the drug product for 40 (40%) was manufactured exclusively in a facility owned by the sponsor or the sponsor’s partner while 59 had the drug product manufactured by a CMO as either the primary or secondary source. Of the products manufactured at a CMO, 52% of the manufacturing sites were in the US, but only 20% of the captive sites were in the US (see Figure 1).

The picture for APIs was not quite as favorable for the CMOs. Of the 40 small-molecule NDA approvals that use an identifiable CMO to manufacture the API, only 9 (24%) are made at US manufacturing sites; European API manufacturers account for 70%, a reflection of the traditional dominance of European fine chemical manufacturers. Still, the nine made in the US is still three times the number made in sponsor-owned API manufacturing sites located in the US. Most in-house small molecule API manufacturing was also concentrated at European manufacturing sites. The three outsourced biologic APIs (out of 15 total approved biologics) in 2016 were all made in US facilities.

Moving pharma manufacturing is complicated

Leaving aside the fact that bio/pharmaceutical manufacturing has never really left the US, the realities of the current bio/pharmaceutical manufacturing environment make the prospects for wholesale movement of drug manufacturing a long-term proposition, for the following reasons:

- Capacity for manufacturing innovative drugs is tight across the industry, especially for APIs, both

---


---

**Figure 1: Dose manufacturing site for 2016 new drug application/biologic license application approvals.**
When it comes to delivering drug product, you need a CMO with longstanding commercial expertise to ensure fast time to market.
Outsourcing Outlook

small molecule and biologic, regardless of the location of that capacity. Capacity at CMOs is especially tight for anything but immediate release solid-dose products.

While global bio/pharma companies have spent more than $50 billion in just the past five years on new plant and equipment, much of that new capacity has been built in tax-favored locations such as Ireland and Singapore, and in emerging markets. Only about a quarter of the projects have been in the US. There just aren’t many US manufacturing facilities that products could be transferred into from offshore. The facilities that are for sale are old and ill-suited for modern products like biologics.

It takes nearly four years to design, build, and qualify a greenfield manufacturing facility. Large-scale biologics facilities can cost $1–2 billion. It will take time to make and implement the decisions to build the necessary new capacity.

Lead times for ordering/receiving key equipment such as filling lines for injectables are approximately 18 months these days. It takes at least another year to install and qualify it. So even expanding a current facility is likely to be a three-year proposition.

CMOs don’t have a lot of spare capacity and don’t have the cash to invest in massive capacity increases themselves. Patheon’s recent acquisition of Roche’s small-molecule API facility in Florence, SC, was attractive because it was inexpensive and because the facility had lots of unused capacity. Much of the ongoing capacity expansion in the CMO industry is customer-funded.

It can take up to two years to transfer a single product to a new manufacturing site (process transfer and scale-up, validation, stability protocols, regulatory filings, etc.). To move multiple products at one time will take armies of technical, quality, and regulatory staff. Even if enough people with the right skills were available, the time and cost of hiring all those people would be prohibitive.

Increasing the US share of bio/pharma manufacturing is not likely to yield the benefits that the administration might be hoping for.

Even if these challenges could be addressed in a timely and cost-effective way, increasing the US share of bio/pharma manufacturing is not likely to yield the benefits that the administration might be hoping for, especially if it is demanding lower drug prices at the same time. For one thing, any new capacity that is built will likely involve the latest, most efficient technologies, including continuous manufacturing, process analytical technology, and single-use contact parts, so fewer jobs would be created. Further, the new facilities would be designed to maximize the use of labor-saving automation and intelligent systems.

A global market

Finally, it should be remembered that many global bio/pharma companies are headquartered outside the US, notably in Europe and Japan, and will be under their own domestic pressure to keep manufacturing in-house. America-first manufacturing policies are likely to invite retaliation from other countries, which will blunt the job-creating impact.

Realistically, moving bio/pharma manufacturing back to the US in a meaningful way will be a 7–10-year process and is unlikely to deliver a big increase in manufacturing jobs. The bio/pharma industry may find it more expedient to just find ways to put some window dressing on the issue while waiting out the President’s term in office.

Reference

Unistick® single unit dose liquid stick packs are user-friendly, convenient, and affordable. They help patients take their medicine on-time and in the right amount, and can reduce the need for artificial preservatives.

Speak to Unither Pharmaceuticals today to differentiate your products and improve your patient’s experience without increasing costs.

Unither is a global development and manufacturing partner for pharmaceutical dosage forms, with facilities in Europe and North America.

Visit us at Interphex booth #1318  www.unither-pharma.com
Sanofi and Lonza Partner on mAb Cell Culture Facility in Switzerland

Sanofi and Lonza have entered into a strategic partnership to build and operate a large-scale mammalian cell culture facility for monoclonal antibody production in Visp, Switzerland. The initial investment will be approximately $290 million (€270 million), to be split equally between each company. The initial phase of the facility will commence construction in 2017, pending necessary regulatory approvals, and is expected to be fully operational by 2020. Lonza has previously built and licensed three similar facilities in the United States and Singapore.

The partnership provides both Sanofi and Lonza with flexibility. Each party will share the available capacity in line with their equity shareholding in the joint venture. Sanofi will have additional access to bio-manufacturing capacity to support increasing demands for their portfolio of biologic therapeutic products, should they require it. Lonza will be free to market their share of capacity, if not required by Sanofi, and will also market unused Sanofi capacity, where available. Lonza will construct the facility and will support the joint venture in its operations of the facility.

The strategic partnership enables Sanofi to react quickly to fluctuations in demand in a short timeframe, reinforcing their capability to launch biologic medicines and ensure consistent access for patients. It also provides Lonza with needed capacities to respond to growing manufacturing demands for large-scale mammalian cell culture-based therapeutic proteins. By adding flexibility in this way, this model will help to optimize biologics production capacity across the whole industry.

Catalent Completes Accucaps Acquisition

CDMO Catalent announced that it has completed the acquisition of Accucaps, the Canada-based developer and manufacturer of over-the-counter (OTC), high-potency and conventional pharmaceutical softgels. No financial details of the transaction were disclosed.

The acquisition complements Catalent’s global OTC and prescription pharmaceutical softgel capabilities and capacity, adding a portfolio of products supplied to pharmaceutical companies in North America, and two state-of-the-art facilities offering integrated softgel development, manufacturing, and packaging. Accucaps’ facilities house sizeable blistering, bottling, and other packaging capabilities, as well as high-potency prescription softgel development and manufacturing expertise that are complementary to Catalent’s. More than 500 employees at Accucaps at the facilities in Windsor and Strathroy, Ontario, have joined Catalent’s network of 11 softgel technologies facilities.

Symbiosis Announces Plans to Open US Office

Scottish CMO, Symbiosis Pharmaceutical Services, has announced plans to open an office in North America to meet increasing demand from US-based biotechnology companies for its vial-filling expertise. The new commercial site, which is set to be located in Cambridge, Boston, MA, will serve clients on both the East and West Coast. It will also be the base for reaching new customers in this territory. Symbiosis is currently on a recruitment drive to strengthen its US commercial team.

Increased demand for both liquid and lyophilized formulations in injectable dosage forms at Symbiosis has been driven mainly by biotech firms looking for an outsourcing partner with small-scale aseptic manufacturing capabilities to support clinical trials.

The CMO made the decision to strategically focus on the North American market after seeing a surge in funding for early stage biotech companies, which are the type of drug development companies that will seek Symbiosis’ manufacturing scale and specialist capabilities. According to MacKay, Cambridge is the epicentre of the global biotech community, and therefore, makes an ideal location for the company’s new US office.

Over the past 12 months, Symbiosis has seen a revenue growth of 40%. Recruitment has been ongoing, with a 30% increase in staff to meet demand for its aseptic fill/finish service.

PfizerCentreOne Expands Fill/Finish Services in Michigan

Pfizer CentreOne has expanded fill/finish services to its Kalamazoo, Michigan facility. Along with vial-filling of small molecules and biologics, the facility also provides vial-filling of sterile suspensions, expanding the company’s service portfolio. The Kalamazoo facility currently supplies drugs to more than 100 countries around the world.

Services at the Kalamazoo site now encompass small molecules and biologics, sterile suspensions, potent and controlled substances, aqueous and oil-based formulations, lyophilization, and vials 1-100mL; bulk formulation <1-1600 liters. The Kalamazoo facility also has dedicated, on-site technical, manufacturing science, regulatory affairs, and quality teams.

Quotient Clinical Expands US Operations

Quotient Clinical announced the acquisition of QS Pharma, a contract development and manufacturing organization based near Philadelphia, from Charles River Laboratories International, Inc. The acquisition increases Quotient’s presence in the US and will enable the company to replicate its Translational Pharmaceutics platform in America, according to a press statement. On Feb. 6, 2017, Quotient announced the acquisition of SeaView Research, a Florida-based clinical pharmacology business. Quotient’s Translational Pharmaceutics platform integrates clinical testing with formulation development and real-time GMP manufacturing; more than 100 pharmaceutical and biotech companies have chosen Translational Pharmaceutics to accelerate the development of their products, the company reports.
CHOOSE SERVIER CDMO

Servier CDMO’s comprehensive range of services includes drug substance manufacturing from lab to pilot batch through scale-up to commercial volumes. Servier brings 60 years of experience of process development, intermediates, advanced intermediates, APIs and High Potency APIs. Our full cGMP/FDA approved chemistry network includes R&D, production and supply chain expertise with full regulatory support. With 11 global manufacturing sites and a presence in 148 countries, we have launched 50 commercial products. Choose Servier CDMO to protect your molecule.

Contact us at cdm@servier.com to book an appointment during DCAT Week.

www.servier-cdmo.com
INTERPHEX 2017 EXHIBITOR GUIDE

Plan Your Visit to
INTERPHEX 2017
March 21–23
Javits Center–New York City

VISIT US AT INTERPHEX 2017

ACG Worldwide

ACG Worldwide is an integrated manufacturing, packaging, and R&D solutions provider for the global pharmaceutical industry. Backed by a R&D cell in India, ACG Worldwide offers empty hard capsules, fluid bed processors, capsule-filling machines, tablet presses, tablet tooling, tablet coaters, packaging films, blister packing & cartoning machines, and vision inspection systems.

ACG Worldwide • www.acg-world.com
INTERPHEX Booth #3253

Admix sanitary stainless steel mixers meet the strictest hygienic standards. With hundreds of global installations, we deliver clean-in-place, 3-A compliant designs, equipment for benchtop or volumes to 60,000 gallons, and full validation packages. Whatever your application, see how our technology helps bring your product to market faster.

Get a free pass to see our Rotosolver high shear mixer in action!

Admix • 144 Harvey Road, Londonderry NH 03053 • tel. 800.466.2369 • fax. 603.627.2019 • www.admix.com/pharma • admixsales@admix.com
INTERPHEX Booth #2171

AdvantaPure® manufactures highly validated Single-Use molded tubing manifolds, BioClosure® container closure assemblies used for batch sampling and storage applications, and AdvantaSil® high purity silicone tubing and hose for use in pharmaceutical and biopharmaceutical manufacturing and development.

AdvantaFlex® biopharmaceutical-grade TPE tubing is sterilizable, moldable, weldable, and sealable.

AdvantaPure • 145 James Way • Southampton, PA 18966 • www.advantapure.com • info@advantapure.com • Phone. 215.526.2151 • fax. 215.526.2167 • INTERPHEX Booth #3055

VISIT US AT INTERPHEX 2017

Allegheny Bradford Corporation

Allegheny Bradford Corporation manufacturers and fabricates the highest quality heat exchangers, filter housings, tanks, pressure vessels, process systems, and custom fabrication in stainless steel and high nickel alloys for end users and OEM.

Allegheny Bradford Corporation • P.O. Box 200, Bradford, PA 16701 • www.alleghenybradford.com • sales@alleghenybradford.com • tel. 814.362.2590 or 800.542.0650 • INTERPHEX Booth #2445

Ascendia is a specialty CDMO dedicated to developing enhanced formulations for poorly water-soluble molecules. Ascendia provides comprehensive services—analytical, pre-formulation, formulation development, and cGMP manufacture of clinical materials. Ascendia formulates products for injection, topical delivery, and for oral administration. Our formulation expertise includes nanoparticles, nano-emulsions, and amorphous solid dispersions.

Ascendia Pharmaceuticals • 675 US Highway One, North Brunswick, NJ 08902 • www.ascendiaPharma.com • tel. 732.640.0058
INTERPHEX Booth #1567

Capsugel designs, develops, and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health & nutrition industries. Our unique combination of science, engineering, formulation, and capsule expertise enables our customers to optimize the bioavailability, targeted delivery, and overall performance of their products. For more information, visit www.capsugel.com.

Capsugel • 412 Mt. Kemble Avenue, Morristown, NJ 07960 • tel. 800.845.6973 • www.capsugel.com • solutions@capsugel.com
INTERPHEX Booth #1452
If this pill could talk.

Discover how CMIC can take you from concept to commercialization.

From early development to commercial manufacturing, CMIC has the proven expertise to take you straight to success. We blend leading-edge processes and technology with experience and dedication. Our fully integrated pharmaceutical solutions include formulation, processing, testing and manufacturing. Plus, CMIC can provide customers with full analytical support throughout the lifecycle of their project. Providing outstanding service is our main goal.

If you’re looking for a trustworthy and knowledgeable partner for pharmaceutical development and manufacturing, contact Han Bang, Business Development, at 609-395-9700 or bd@cmiccmousa.com. Han and the CMIC team are welcome to discuss your requirements and show you around our expanding facility.

At CMIC, our work speaks for itself.

CMIC is a contract manufacturing organization that specializes in formulation development and commercial services for oral solid dose products.

CMIC CMO USA Corporation
3 Cedar Brook Drive
Cranbury NJ 08512
609-395-9700
www.cmiccmousa.com
VISIT US AT INTERPHEX 2017

Chemic Laboratories, Inc. is a full service cGMP/GLP contract analytical chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: Extractables/Leachables analysis, CMC Method Development & Validation, Quality Control analysis, Release testing, Raw Materials analysis, Compendial testing, Organic Synthesis/Formulaion Development &ICH Stability testing.

Chemic Laboratories, Inc., 480 Neponset St., Building 7, Canton, MA 02021 • www.chemiclabs.com • lcw@chemiclabs.com • tel: 781.821.5600 • fax: 781.821.5651

INTERPHEX Booth #1372

Visit Our Booth
CMIC CMO USA Corporation specializes in the formulation development and GMP commercial manufacturing of solid dosage products with expertise in sustained and controlled release. We will guide you towards regulatory approval and commercial launch while helping you reduce your development cycles and capital costs.

CMIC CMO USA Corporation, Cedar Brook Corporate Center, 3 Cedar Brook Drive, Cranbury, NJ 08512 • www.cmicmousoa.com • tel. 609.395.9700

INTERPHEX Booth #1304

Contec, Inc. is a leading manufacturer of contamination control products for mission-critical cleaning in manufacturing environments worldwide. Our extensive product line for cleanrooms and critical environments includes knitted, woven, and nonwoven wipes; presaturated wipes; sterile and non-sterile wipes; disinfectants; mops; wall washing systems; sponges; and swabs.

Contec, Inc. • 525 Locust Grove, Spartanburg, SC 29303 • tel. 864.503.8333 • www.contecinc.com • wipers@contecinc.com

INTERPHEX Booth #1133

Emergent provides contract manufacturing services for the aseptic fill/finish of vials and syringes: liquid and lyophilized products. Emergent’s manufacturing facility currently produces 20 commercial products and has contributed to the development of over 200 clinical products.

Emergent BioSolutions • www.ebsi.com/CMO • CMO@ebsi.com • tel. 800.441.4225

INTERPHEX Booth #1240

Eppendorf

Eppendorf is a leading life-science company that develops and sells instruments, consumables, and services for liquid-, sample-, and cell handling. Its portfolio includes pipettes and automated pipetting systems, mixers, spectrometers, and DNA amplification equipment, bioreactors, CO2 incubators, shakers, and cell manipulation systems. Consumables such as pipette tips, plates, and disposable bioreactor vessels complement the range of premium products.

Eppendorf, 102 Motor Parkway, Hauppauge, NY 11788 • www.eppendorf.com • custserv@eppendorf.com • tel. 800.645.3050

INTERPHEX Booth #3639

Eppendorf

Thinking about equipment? Federal Equipment Company delivers huge price and lead time savings when you are sourcing top-brand pharmaceutical processing and packaging equipment for your operations. Shop from our vast, on-hand inventory of equipment that covers all of your needs from R&D, scale-up, and commercial production to facility support and utility equipment. Do you have equipment to sell? Contact us! When you think equipment, think Federal Equipment.

Federal Equipment Company • 8200 Bessemer Avenue • Cleveland, OH 44127 • marketing@fedeqquip.com • fedeqquip.com • tel. 800.652.2466

INTERPHEX Booth #3110

GEMÜ Valves is a leading world-wide manufacturer of valves, measurement, and control systems for the Pharmaceutical, Microelectronics, and Semiconductor, and Food and Beverage industries, as well as the Chemical, Mining, and Metal Extraction, and Water/Waste Water Treatment industries. GEMÜ is committed to the pursuit of quality and excellence in the development, production, and manufacturing of engineered diaphragm valves.

GEMÜ Valves • 3800 Camp Creek Pkwy SW • Bldg 2600 Suite 120 • Atlanta, GA 30331 • www.gemu-group.com • info@gemu.com • tel. 678.553.3400 • fax. 404.344.9350

INTERPHEX Booth #2663

The FEC40 Capsule Filler can produce up to 400,000 capsules/hr—nearly twice the volume of any competitor. Its remarkably small footprint makes machine reconfiguration due to floor space issues unnecessary. Extraordinarily high performance-to-footprint ratio is made possible by Fette Compacting’s patented Duplex Concept, enabling FEC40 to feature a dual capsule filling process. The result is significant production savings (up to 30% per 1000 capsules).

Fette Compacting America • 400 Forge Way, Rockaway, NJ 07866 • www.fette-compacting-america.com • tel. 973.586.8722 • INTERPHEX Booth #2505C

Fluid Metering Inc. Dispensers & Pumps

Fluid Metering has 55+ years of experience meeting the demands of the medical, analytical, process, and industrial markets for ultra-precise fluid control from microliters to liters. Fluid Metering’s dependability has been demonstrated by more than 250,000 OEM pumps in service.

Fluid Metering Inc. • 5 Aerial Way #500 • Syosset, NY 11791 • www.fmipump.com • pumps@fmipump.com • tel. 800.223.3388 or 516.922.6050

INTERPHEX Booth #1468

GEMÜ Valves

Pharmaceutical Technology MARCH 2017 PharnTech.com
Holistic track & trace solution improving efficiencies of packaging lines, preventing counterfeiting and creating brand differentiation.

- Bottling Line
- Cartoning Line
VISIT US AT INTERPHEX 2017

**Genesis Packaging Technologies**

Genesis Packaging Technologies is a worldwide leader in the science and technology of parenteral vial sealing and residual seal force testing. We provide the best capping equipment in the world, and we offer both the global service and technical support to back it up. Offering our customers the tools and knowledge to consistently achieve container closure integrity remains our priority.

**Genesis Packaging Technologies**

435 Creamery Way, Suite 100, Exton, PA 19341 USA • tel. 800.552.9980 • www.gen-techno.com • info@gen-techno.com

INTERPEX Booth #330C

---

**Grand River Aseptic Manufacturing, Inc.**

GRAND RIVER ASEPTIC MANUFACTURING, INC. is an FDA-approved full-service parenteral contract manufacturer. For more than 5 years, GRAM has been serving the life-sciences industry by offering flexible solutions to our clients’ parental outsourcing needs. We offer product development through commercial manufacturing, with expertise in liquid and lyophilized vials and controlled substances (CSII-V).

**Grand River Aseptic Manufacturing**

• 140 Front Ave SW Suite 003 • Grand Rapids, MI 49504 • tel. 616.678.2400 • fax: 776.5584 • www.grandriverasepticfg.com • info@grandriverasepticfg.com

INTERPEX Booth #1543

---

**Halkey-Roberts Robertsite® Male Luer Valves**

Valves are designed to close off the male side of any IV set, or connection to the patient, IV bag, or irrigation/drainage line. The valves are high flow and incorporate proven technology that eliminates dripping and leakage when disconnected without the need for clamping.

**Halkey-Roberts Corporation**

• 2700 Halkey Roberts Place North • St. Petersburg, FL 33716 • Phone: 727-471-4200 • www.halkeyroberts.com • sales@halkeyroberts.com

INTERPEX Booth #3951

---

**ILC Dover**

**ILC Dover®—ILC Dover’s EZ BioPac® single-use systems allow faster powder transfer and higher recovery rates. Choosing EZ BioPac as your containment system can have a significant impact on plant productivity and profitability.**

**ILC Dover**

• One Moonwalkers Road, Frederica, DE 19946 • tel. 302.335.9111 • fax. 302.335.1320 • customer_service@ilcdover.com • www.ilcdover.com

INTERPEX Booth #2763

---

**IMA Sustain**

**IMA** is a world leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceutical products thanks to a high technological profile and the ability to offer tailor-made solutions to satisfy the most sophisticated requests of the market. Interphex 2017 will be a chance to discover what’s new in the IMA world for the pharmaceutical industry.

**IMA Life North America Inc.** • tel. +1.716.695.6354

**IMA North America Inc.** • tel. +1.978.537.8534

www ima.it • sales@imalife.com • sales imausa.net

INTERPEX Booth #2545

---

**Jubilant HollisterStier Contract Manufacturing**

Jubilant HollisterStier Contract Manufacturing is an integrated contract manufacturer, able to manufacture sterile injectable, ointment, cream, and liquid dosage forms. Our facilities across North America provide specialized manufacturing services for the pharmaceutical and biopharmaceutical industries. Fill/Finish; Lyophilization; Multiple Dosage Forms; Certified Project Managers.

**Jubilant HollisterStier Contract Manufacturing**

• A Jubilant Pharma Company • 3525 N. Regal St. • Spokane, WA 99207 • www.jubhs.com • info@jubhs.com • tel. 509.489.5656

INTERPEX Booth #1830

---

**Lighthouse**

Lighthouse is a leading global provider of laser-based, non-destructive headspace analysis systems for leak detection, moisture monitoring, and media fill inspection. Our laboratory instruments and automated systems monitor oxygen, moisture, pressure, and CO₂ in sealed parenteral containers. Our measurement services support product, package, and process development as well as testing in support of QC stability protocols.

**Lighthouse Instruments, LLC** • 2020 Avon Court Suite #2 • Charlottesville, VA 22902 • lighthouseinstruments.com • info@lighthouseinstruments.com • tel. 434.293.3081 • INTERPEX Booth #3305

---

**LSNE Contract Manufacturing**

LSNE Contract Manufacturing is a CMO with a proven regulatory history specializing in a wide range of services including formulation/lyophilization development, fill/finish, and lyophilization. Through the integration of three facilities, qualified staffing, and an extensive manufacturing history, LSNE is strategically positioned to provide uninterrupted material for clinical through commercial use.

**LSNE Contract Manufacturing** • 23 Commerce Dr., Bedford, NH 03110 • www.lyophilization.com • info@lyophilization.com • tel. 603.668.5763

INTERPEX Booth #1338

---

**The Extrafill Syringe Filling and Stopping machine** with incorporated de-lidding station has a production capacity of up to 10,000 syringes per hour. Capabilities include regular or vacuum stoppering and rotary piston or peristaltic pumps. Marchesini Group USA • 43 Fairfield Place, West Caldwell NJ 07006 • www.marchesini.com • sales m marchesiniusa.com

INTERPEX Booth #3125
Get Educated. Stay Innovative.

New in 2017: The Connect Conference Program

May 16-18, 2017
Pennsylvania Convention Center
Philadelphia, PA, USA

To strategically address the industry-driving changes within the fine & specialty chemical and pharmaceutical industries, CPhI North America has partnered with the American Chemical Society (ACS), the largest scientific association in the world, and the U.S. Pharmacopeial Convention to bring you a market-leading conference program.

The CPhI Connect Conference Program will have four tracks featuring sessions such as:

- Innovative Breakthrough Technologies for Drug Targets and Emerging Pathways
- Formulation Trends for Topical Dosage Forms
- Navigating GDUFA — Reduce Cost and Accelerate Delivery
- Packaging Innovation
- Pharmaceutical Impurities
- Legal and Policy Strategies for Drug Companies in Today's Global Market
- Accelerating Your Product's Development: Practical Considerations from Pre-Clinical through Commercial
- Determining the Value of Re-Shoring Drug Ingredient Manufacturing

...and more!

Go to schedule.cphinorthamerica.com to see the full lineup.

Save an extra 25% when you register by May 8!

Go to cphinorthamerica.com/register and use PROMO Code PHARMTECH to receive an additional 25% off your conference pass when you register before May 8, 2017.

Schedule is subject to change. Discount applicable to non-exhibiting badges only.
VISIT US AT INTERPHEX 2017

MG America is the US subsidiary of MG2 of Bologna, Italy and a leading supplier of processing and packaging equipment. The PLANETA 200 Capsule Filler is the latest evolution in a line of well-established continuous motion machines. The PLANETA 200 produces up to 200,000 capsules per hour, but its primary advantage is its premium flexibility: its modular design results in a highly configurable platform suitable for a wide array of production requirements, including an ability to fit several dosing units simultaneously, enabling one capsule to be filled with differing products.
MG America, 31 Kulick Road, Fairfield, NJ 07004 • www.mgamerica.com • tel. 973.808.8185 • INTERPHEX Booth #2221

Nemera

Nemera is a world leader in the design, development, and manufacturing of drug delivery devices for the pharmaceutical, biotechnology, and generics industries. Nemera’s services and products cover five key delivery routes: Ophthalmic, Nasal, Buccal, Auricular, Inhalation, Dermal/Transdermal, and Parenteral.
Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including off-the-shelf innovative systems, customized design development, and contract manufacturing.
Nemera • 20, Avenue de la Gare 38290 La Verpillière, France • information@nemera.net • www.nemera.net • tel. +33 4 74 94 06 54 INTERPHEX Booth #1636

Nipka Denso USA provides high speed online non-destructive pinhole inspection systems to detect pinholes, cracks, and defective seals in liquid-filled pharmaceutical packaging and containers using HVLD technology. Applications include pre-filled syringes, vials, ampoules, BFS containers, IV bags, and other containers made from glass, plastic, and poly laminates. Nipka Denso USA will also be exhibiting Nipka Research’s automated label and print inspection systems. Our 100% print inspection systems are widely used on pharmaceutical labels for rewinders, on press, and offline.
Nipka Denso USA, Inc. • 700 Corporate Cir Suite H • Golden, Colorado 80401 • tel. 303.202.6190 • fax. 303.202.6195 • INTERPHEX Booth #3305B

VISIT US AT INTERPHEX 2017

At INTERPHEX 2017, Optima Pharma will present visitors its latest MultiUse Filler series during a 3D cinema show at the booth. The systems can process all types of nested syringe, vial, and cartridge formats. Live at the show, Optima Pharma will present two types of glove integrity testers, among them the new wireless GTS-WL model from METALL+PLASTIC. More than 35 gloves can be tested simultaneously in just 15 minutes.
OPTIMA Pharma GmbH • Otto-Hahn-Str. 1 • 74523 Schwabach • www.optima-packaging.com/pharma • pharma@optima-packaging.com • tel. +49 791 9495 - 0 INTERPHEX Booth #3103

PTI is a global leader in package testing equipment. We manufacture non-destructive inspection technologies for package integrity testing, leak detection, container closure integrity, and seal integrity testing and seal analysis. PTI’s inspection technologies are deterministic, non-subjective test methods that produce reliable, quantitative test data. Applications include all parenteral products as well as blister packs and many other packaging formats.
PTI Inspection Systems • 145 Main Street Tuckahoe, NY 10707 USA • www.ptiusa.com • tel. 914.337.2005 INTERPHEX Booth #3305A

VISIT US AT INTERPHEX 2017

Connecting People, Science, and Regulation®
The Parenteral Drug Association (PDA) is the leading global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community. Founded in 1946 as a nonprofit organization, PDA is committed to developing scientifically sound, practical technical information and resources to advance bio/pharmaceutical science and regulation through the expertise of its more than 10,000 members worldwide, so members can better serve patients.
Parenteral Drug Association (PDA) • www.pda.org • INTERPHEX Booth #1653

SMI

Company Services
SMI, founded in 1982, brings over 30 years of engineering excellence to the industry. Initially, SMI pioneered instrumentation systems for pharmaceutical equipment. SMI introduced a tablet press of its own, the “Piccola”. The Piccola was the first bench-top tablet press designed for R&D. Today, SMI provides a complete line of solid dosage equipment ranging from the single station MiniPress to bench top rotary, to the 21 station pilot scale Nova, designed for mono and multi-layered tablets. Specialty Measurements Inc. (SMI), P.O. Box 356, 1309 US Highway 22 East, Lebanon, NJ 08833 • www.smimtc.com • tel. 908.534.1500 INTERPHEX Booth #3153

VISIT US AT INTERPHEX 2017

Bottapack Offers Disposable Filling Option
The Disposable Filling System (DFS) is an alternative dosing system for use with the bottapack®, which consists of pre-assembled disposable components in the product section. It is based on a peristaltic feed with a design for low-viscosity products. It is designed for in-line sterilization. Its simple installation makes it possible to cover various volume ranges quickly, with less refitting.
Rommelag USA, Inc. • 27905 Meadow Dr. Ste. #9, Evergreen, CO 80439 • www.rommelag.com • tel. 303.674.8333 INTERPHEX Booth #3516

ROVI CM

ROVI CM provides contract manufacturing services for injectable and solid forms at our FDA-approved and GMP-certified manufacturing plants. We offer manufacturing, testing, and packaging with an annual capacity of 250 million prefilled syringes, 60 million vials, and 3 billion tablets.
ROVI CM • Julián Camarillo, 35 28037 Madrid • clopeze@rovi.es INTERPHEX Booth #1125
May 16-18 2017
Pennsylvania Convention Center
Philadelphia, PA, USA

Get Educated. Stay Innovative.

New in 2017: The Connect Conference Program

To strategically address the industry-driving changes within the fine & specialty chemical and pharmaceutical industries, InformEx has partnered with the American Chemical Society (ACS), the largest scientific association in the world, and the U.S. Pharmacopeial Convention to bring you a market-leading conference program.

The Connect Conference Program will feature 44+ sessions covering topics such as:

- Regulatory Update on US Toxic Substances Control Act-Current Interpretations and the Impact on Business
- Discover the Latest Innovations in Green Chemistry
- How to Create a Start-Up Environment in a Traditional Company
- Plant Operations to Efficiently Meet Regulatory Requirements for Multiple Markets
- The Latest Developments in Chiral Chemistry
- The Future of the Chemistry Industry
- The Agriculture Chemicals Market
- Compliance Best Practices and Standardized Methods for Testing for Metals
- Regulatory Update on US Toxic Substances Control Act Reform
- ...and more!

Go to schedule.informex.com to view the full schedule.

Save an extra 25% when you register by May 8!

Go to informex.com/register and use PROMO Code PHARMTECH to receive an additional 20% off your conference pass when you register before May 8, 2017.
Unither Pharmaceuticals is a unique development and manufacturing partner for proprietary and generic dosage forms, and a global leader in single unit dose technologies such as sterile blow-fill-seal, and liquid and powder stick-packs. Unither’s focus is delivering medicines that are convenient, affordable, and easy-to-use. Unither technology benefits patients by offering improved dosing safety and compliance with pre-measured, correct dosing that reduces the risk of medication errors.

Unither Pharmaceuticals • 755 Jefferson Road • Rochester, NY 14623, USA • www.unither-pharma.com • anthony.neda@unither-pharma.com • tel. +1.585.475.9000 • fax. +1.585.272.3905 • INTERPHEX Booth #1318

VAI’s manufacturing and testing operations mirror current GMP/GLP standards. With over 35 years of contamination control experience, our products and services include a comprehensive line of disinfectants, sporicides, residue removers, process cleaners, quality water, saturated and dry wipes, disposable garments, cleanroom paper, documentation materials, printing systems, viable monitoring, cleanroom cart systems, cleaning equipment, consulting, and laboratory services.

VAI • Booth #2527

VISIT US AT INTERPHEX 2017

The ASEP-TECH™ Blow/Fill/Seal (BFS) system has been marketed by Weiler Engineering, Inc. for more than 55 years to the world’s leading pharmaceutical and healthcare companies. This advanced aseptic technology combines blow molding of plastic bottles, sterile filling of liquid products, and hermetic sealing on one compact machine frame in bottle sizes ranging from 0.2mL to 1000mL.

Weiler Engineering, Inc. • 1395 Gateway Drive • tel. 847.697.4900 • fax. 847.697.4915 • www.weilerengineering.com • solutions@weilerengineering.com • INTERPHEX Booth #1224

AbbVie’s Contract Manufacturing business has been serving its partners for over 35 years. Our contract/toll development and manufacturing capabilities span Fermentation, Drug Product, Potent, Hot Melt Extrusion, Prefilled Syringes, Biologics, and Bulk Active Pharmaceutical Ingredients (APIs) across 10 production facilities in North America and Europe.

AbbVie Contract Manufacturing • 1401 Sheridan Rd, North Chicago, IL 60064 • abbviecontractmg@abbvie.com • www.abbviecontractmg.com • tel. 1.847.938.8524

New Products and Services

Catalent has a comprehensive range of fill/finish services within its global network of facilities, including sterile services and advanced aseptic technologies. The company’s 265,000 sq ft Brussels facility has the capacity to produce more than 200 million pre-filled syringe units annually, and Catalent’s ADEASEPT™ blow-fill-seal technology is designed for the safe and efficient glass-free delivery of injectable medications.

Catalent Pharma Solutions • 14 Schoolhouse Road, Somerset, NJ 08873 • tel. +1 888 SOLUTION • www.catalent.com

Coating Place develops and manufactures modified release oral products. We are the leading provider of Wurster microencapsulation. Services include formulation development, technology transfer, scale-up, and commercial manufacturing. We process solvent and aqueous formulations. We offer capsule filling, tablet compression, pan coating, extrusion spherization, and particulate milling. Controlled substances schedule II-V.

Coating Place, Inc. • 200 Paoli Street, PO Box 930310, Verona, Wisconsin 53593 • info@coatingplace.com • www.coatingplace.com • tel. 608.845.9521 • Fax. 608.845.9526

CoredenPharma is your full-service Contract Development & Manufacturing (CDMO) partner for APIs, Drug Products, and Packaging Services. Through a network of cGMP facilities organized under five technology platforms—Peptides/Lipids/Carbohydrates/Oligonucleotides, Injectables, Highly Potent/Oncology, Small Molecules, Antibiotics—CoredenPharma experts translate complex ideas at any development stage into high-value products.

CoredenPharma • www.coredenpharma.com

New Products and Services

Watson-Marlow Fluid Technology Group (WMFTG) is the world leader in peristaltic pumps and associated fluid path technologies for the pharmaceutical market. Comprising eight established brands, each with their own area of expertise, but together offering our customers unrivaled solutions for their pumping and fluid transfer applications.

Watson-Marlow Fluid Technology Group • 37 Upton Drive, Wilmington, MA 01887 • www.wmftg.com • info@wmftg.com

INTERPHEX Booth #2833

Delivering pharmaceutical and nutraceutical performance, Ashland provides solutions for applications in tablet binding, film coating and disintegration, controlled-release formulation and drug solubilization. Ashland creates value for customers through bioavailability enhancement, applications knowledge, regulatory support and a powerful product portfolio. We’re proud to celebrate Klucel™ hydroxypropylcellulose (HPC), a compound so versatile it changed the way the pharmaceutical industry produced oral dosage forms.

Ashland Inc. • www.ashland.com

VISIT US AT INTERPHEX 2017

INTERPHEX 2017 EXHIBITOR GUIDE AND INDUSTRY PIPELINE

98 Pharmaceutical Technology MARCH 2017 PharmTech.com
2017 PDA Annual Meeting

Innovation in Manufacturing Science and Technology

April 3-5, 2017 | Anaheim, California
Anaheim Marriott

Exhibition: April 3-4 | 2017 Cell and Gene Therapy Workshop: April 5-6 | Courses: April 6-7
#PDAAnnual

Conference Theme: Manufacturing Innovation: The Next Wave of Sterile and Biopharmaceutical Science, Technologies and Processing

Attend PDA’s flagship Annual Meeting to gain the tools you need to address current pharmaceutical development and manufacturing challenges and strategies to effectively deliver future medicines and novel therapies.

Hear the latest thinking and best practices on:

- Future facility designs for flexible manufacturing
- Use of Big Data for process optimization
- Interfacing pharmaceutical delivery systems with mobile device applications
- Accelerated process and product development
- Applying phase-appropriate GMPs to novel therapeutics

Learn more and register at pda.org/2017Annual

Following the Meeting, on April 5-6, PDA will offer the 2017 PDA Cell and Gene Therapy Workshop to provide a more in-depth look at how these new therapies will impact the industry. Learn more and register at pda.org/2017CGT

On April 6-7, PDA Education will be hosting five courses as part of the 2017 PDA Annual Meeting Course Series to help you further advance your knowledge. Learn more and register at pda.org/2017AnnualCourses
NEW PRODUCTS AND SERVICES

Cautiously Quick Testing Services
Does your lab have comprehensive capacity and capabilities to proficiently advance projects of any size? Will your data withstand regulatory scrutiny? Do you have a trusted Lab partner helping you win the race for market approval? Eurofins Lancaster Laboratories delivers fast results with a methodical quality approach for your Biopharmaceutical Products. Contact us to get timely results without sacrificing quality.

Eurofins Lancaster Laboratories • www.EurofinsUS.com/BioPharmTour

NEW PRODUCTS AND SERVICES

The Leistritz LHLG series air quench pelletizer mates with an extruder and enables die face cutting of pellets in air for water soluble, highly filled and foamed formulations as typically used for pharmaceutical, nutraceutical, and specialty plastics products. The die is electrically heated and the flow geometry is matched with the formulation and throughput rate. The die, blades, and all contact areas are fabricated of hardened stainless, tool and carbide steels.

Leistritz • sales@leistritz-extrusion.com • www.leistritz-extrusion.com

Mikart specializes in the development, manufacturing, and packaging of solid-dose and liquid-oral dose products. The company’s services include formulation development; analytical, manufacturing, packaging, and regulatory services; and complete project management. Mikart offers clients more than 40 years of experience, a responsive working relationship, and the ability to take products from formulation development through full-scale commercial production.

Mikart, Inc. • www.mikart.com • tel. 404.351.4510

NEW PRODUCTS AND SERVICES

You deserve a strategic, responsive, and efficient partner for your early-stage drug development. MPI Research offers that and more. With an impressive breadth of discovery, preclinical, and clinical scientific knowledge and services, our team of highly trained scientists and world-class facilities offer the insights to see your project through. We do everything we can to make your vision a reality.

MPI Research • 54943 North Main Street, Mattawan, MI 49071 USA • www.mpiresearch.com • tel. +1.269.668.3336

NEW PRODUCTS AND SERVICES

Dispersers
Ross Bow Tie Dispersers, or High Viscosity Dispersers, are heavy-duty mixers designed for heavy pastes and viscous liquids up to several hundred thousand centipoise, with stainless steel 304 wetted parts. An explosion-proof inverter-duty motor helps the mixers incorporate solids into liquid vehicles in a consistent manner without running at high speeds.

Ross, Charles & Son Company • Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS

Company description
Widely recognized global supplier of two piece capsules, Suheung Capsule has solely focused on manufacturing the highest quality Capsules. Through ceaseless efforts in research and development, as well as technical investments to be the world’s quality leader of hard capsules, Suheung’s dedication to quality is seen in each and every element, and every process of capsule production.

Suheung Capsule • 428 E. Saturn St. Brea, CA 92821 • www.suheung.com • tel. 714.854.9887 • fax. 714.854.9896 • nasales@shcapsule.com

VAC-U-MAX Vacuum Conveyor for Gel Caps, Capsules, and Coated Tablets
VAC-U-MAX offers a full range of Vacuum Conveyors for conveying capsules, liquid-filled gel caps, and coated tablets. Unit conveys up to and over 2500 units per minute, gently delivering product to capsule filling machine or packaging lines. For more information, visit our website at www.vac-u-max.com/pneumatic or call 973.759.4600 or (800) VAC-U-MAX.

VAC-U-MAX • 69 William Street • Belleville, NJ 07109 • info@vac-u-max.com
IPEC Federation presents Excipient FEST Americas

Connecting Biotech and Pharma

April 24 - 26, 2017 | Rhode Island Convention Center | Providence, RI

Excipient Industry’s Best EXPO for Regulatory, Science and Supply Chain Education

Gold Sponsors

pharm-a-spheres®
JRS PHARMA LP
JRS The Excipient Family
Mutchler Inc.
Pharmaceutical Ingredients
Now part of IMCD

Silver Sponsors

Chemical Solutions Ltd.
DPL-US
A division of Dr. Paul Lahmann Inc.
ShinEtsu

Media Sponsors

Tablets & Capsules Review

Contact: T. 787-714-3000 F. 787-714-6000 marisol.perez@excipientfest.com

Pharmaceutical Technology

Principal Media Sponsor

BASF

USP

Solvay

NFE
Titration in Early Drug Discovery and Development

ON-DEMAND WEBCAST Originally aired March 16, 2017

Register for free at www.pharmtech.com/pt/titration

EVENT OVERVIEW:
Many assay methods described in the United States Pharmacopeia and European Pharmacopoeia rely on the accuracy and simplicity of titration. These methods however, usually require several hundred milligrams of the active ingredient, which is expensive and difficult to obtain during the discovery and development stages. This analytical challenge is addressed by microtitration technology so that sample waste is minimized and re-analysis is avoided. Attend this webcast to hear Andy Lever, Research Scientist at AstraZeneca, discuss his experience optimizing titration for research and development.

Further optimization can come from selecting the proper solvent, optimizing titration parameters, and using alternative techniques such as thermometric titration. Lori Spafford, Titration Product Manager at Metrohm USA, will discuss these elements of titration and offer practical insights for developing API microtitration methods.

Key Learning Objectives
- Learn how microtitration technology can be applied to early-stage pharmaceutical compounds
- Understand how optimizing titration parameters affects titration speeds, data resolution, and result accuracy
- Learn proper titration techniques specific to pharmaceutical assay titrations

Who Should Attend
- R&D Scientists and QA/QC managers from pharmaceuticals, biopharmaceuticals and nutraceutical industries
- Experts involved in method development for pharmaceutical products
- Anyone interested in learning about developments in potentiometric titration for applications in the pharmaceutical industry

For questions contact Ethan Castillo at ethan.castillo@ubm.com
EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

ALL OF THE SOLUTIONS YOU NEED TO COST EFFECTIVELY DEVELOP & MANUFACTURE PRODUCT

REGISTER TODAY FOR FREE

INTERPHEX
TUESDAY, MARCH 21 - THURSDAY, MARCH 23, 2017 | JAVITS CENTER, NYC

REGISTER FOR YOUR FREE TECHNICAL CONFERENCE & EXHIBIT HALL PASS AT: INTERPHEX.COM/REGISTER
Accelerate Bioprocess Development Using the Modular Automated Sampling Technology (MAST) Platform

ON-DEMAND WEBCAST  Aired Feb. 23, 2017

Register for free at www.pharmtech.com/pt/bioprocess

EVENT OVERVIEW:
In-process sampling and analysis is a vital function in biopharmaceutical manufacturing; however, transferring samples from bioreactors to analytical devices while maintaining process sterility is a challenge.

An aseptic bioreactor sampling system, Modular Automated Sampling Technology (MAST), allows for obtaining media, cell, and product information on development and commercial scales.

In this webinar, an expert will discuss the MAST technology and how it can be incorporated into aseptic processing application. Three case studies will be shared to demonstrate how a MAST system can accelerate a development process.

Participants will learn how to:
- Minimize non-value added work with automated sample collection, preparation, and processing in the Nova BioProfile FLEX
- Reduce experiments by using novel process development approaches
- Gain fundamental understanding of a product and process by implementing a Product Quality Attribute Control (PAC) strategy

Who Should Attend:
- Scientists and engineers who work in cell culture and microbial process development in both upstream and downstream applications
- CSOs from biopharma
- PAT implementation experts
- Technology evaluation scientists
- Pilot plant operators

Key Learning Objectives:
- Understand how the implementation of autosampling and auto-analysis can accelerate development
- Learn how the MAST modules work together to create a complete autosampling solution
- Hear about the exciting new MAST products that are in development

Presenter:
Clint Pepper, PhD
Director, MAST Technology
Capsugel

Moderator:
Rita Peters
Editorial Director
Pharmaceutical Technology

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

Sponsored by
Pharmaceutical Technology

Presented by
Pharmaceutical manufacturing company (Ewing, NJ) seeks QC Chemist to perform new analytical method development, method validation & method verification for pharmaceutical raw materials and finished products. Perform IQ, OQ & PQ for analytical instruments like HPLC, UPLC & UV-spectrophotometer. Review laboratory deviations such as LDN, OOPS & CAPA; create & review protocols for stability testing and method validation; write & review SOPs, reports for method validation & verification, and Stability testing protocols according to OGD recommendation.

MAIL RESUME TO: HR Dept., Navinta LLC, 1499 Lower Ferry Rd., Ewing, NJ 08618.
Covering Global Regulations in a Quality System

Siegfried Schmitt, PhD, Principal Consultant at PAREXEL, discusses how to mitigate risk in a global regulatory environment.

Q: During a recent inspection by the Chinese regulatory authority, we were informed that our quality system had not met all requirements of Chinese good manufacturing practices (GMP). We export to many countries around the world and regulatory compliance is of the utmost importance. Could you advise on how to mitigate future regulatory risk?

A: It is important to understand the nuances of each regulatory authority and take the appropriate steps to fully abide by each set of standards. Some agencies wish to see their regulations specifically stated in a company’s quality system, whereas others are satisfied with a generic statement (e.g., “we comply with all applicable laws and regulations in the markets we operate in”) about compliance.

It is necessary to maintain compliance with current regulations; any regulatory changes must be assessed for their impact on your QMS.

In addition to a generic statement, consider including a list of the regulations (e.g., 21 Code of Federal Regulations 210, 211, and 820; EudraLex volume 4 Part II) in your quality manual or similar high-level document. It’s unclear if the inspectors felt your company had not clarified within the quality management system (QMS) which regulations it knowingly complied with. Including a list of regulations will help ensure transparency.

It is also unclear whether your company assured compliance with all the country’s regulations and provided documented evidence. Inspectors often prefer organizations demonstrate compliance through established processes and documented evidence. All too often, companies list within their standard operating procedures (SOPs) a series of regulations pertinent to the subject of the SOP (e.g., International Council for Harmonization [ICH] Q9 in a risk management SOP). Merely listing a regulation, however, doesn’t demonstrate that you have read, understood, and implemented it into your QMS. You must have a process in which dedicated persons or teams assess regulations for their applicability to your operations, and then implement these into your QMS. Documenting this process provides the necessary proof of compliance.

In your particular case, employees fluent in the Chinese language should review the regulations, log which regulations they reviewed for documentation purposes, and then implement the new or changed requirements from these regulations within the QMS as necessary. For example, if the cleaning SOP would require an amendment, this amendment should be noted in the change section of the document.

It is necessary to maintain compliance with current regulations; any regulatory changes must be assessed for their impact on your QMS. This assessment may require a review of all documents in your QMS, unless you maintain a matrix (e.g., in a spreadsheet or relational database) that shows which regulation translates into which documents (e.g., SOPs) within your QMS. Such a correlation matrix has another important benefit: should you plan a change to a system, process, or document, you could easily verify if this is permissible under the regulations impacted by the change.

It is unlikely that such a matrix is 100% complete, covering all and every regulation from every country you operate in. However, taking a detail-oriented, risk-based approach helps ensure you cover the countries and regulations most critical to your operations.

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.
You Discover
We Deliver for Patients

Process Development | cGMP Manufacturing | Aseptic Vial Filling | Lyophilization

www.samsungbiologics.com
Your molecule has a soluble future.
Our passion is to help unlock it.

**OptiForm® Solution Suite.** An integrated solution designed to efficiently and rapidly help solve complex bioavailability and formulation challenges for early stage compounds. We match the best formulation technologies to your molecule, and utilize an accelerated parallel screening and development approach, to deliver a full testing report and animal PK study material, all in 12 weeks!

- **EASIER.** integrated solution with minimal material needed
- **SIMPLER.** optimal recommendations based on real data from a dedicated scientific advisor
- **FASTER.** parallel process with 4 formulation technologies