Volume 41 Number 1 PHARMACEUTICAL TECHNOLOGY JANUARY 2017 PharmTech.com

PLUS: Solid-Dosage Packaging : Single-Use Systems : Process Operations

JANUARY 2017 Volume 41 Number 1

Advancing Development & Manufacturing

Pharmaceutical Technology®

PharmTech.com

PHARMACEUTICAL TECHNOLOGY 40 Years 1977-2017

2017

Defining BioPharma's 2017 Agenda

Policy changes, R&D strategies, and drug approvals

PEER-REVIEWED

A Statistical Decision System for Out-of-Trend Evaluation

UBM

FORMULATION
Oligonucleotide Therapeutics

QUALITY AND REGULATIONS
Transition to Electronic Records

PROTEIN CHARACTERIZATION
Using Microcalorimetry

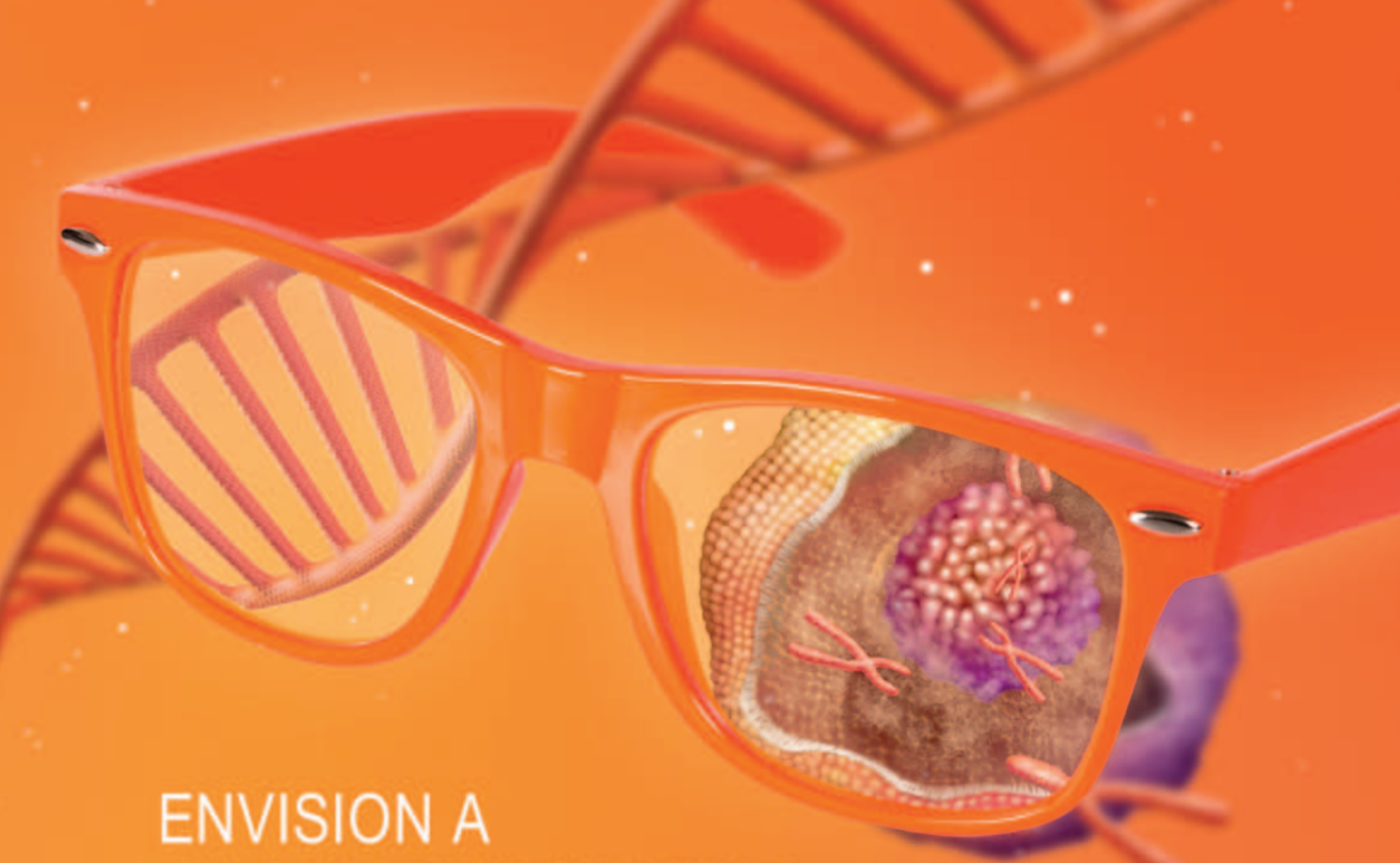
WWW.CAPSUGEL.COM

ENGINEERING MEDICINES TO LIFE

Capsugel®

RISING TO THE CHALLENGE

Tomorrow's complex medicines face challenges to overcome low bioavailability and optimize drug delivery. This calls for a partner with the credibility, ingenuity and flexibility to deliver both the product and process design required to make your compound a commercial reality. With a unique range of technology and integrated product development from design to commercial manufacturing, Capsugel is that partner.



ENVISION A PARTNER WITH MORE.

More Services. More Insights. More Support.

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, preclinical and clinical 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.

To take a closer look, visit www.mpiresearch.com.

- DRUG SAFETY
- DISCOVERY SCIENCES
- BIOANALYTICAL & ANALYTICAL
- SURGICAL SERVICES
- MEDICAL DEVICE EVALUATION
- TRANSLATIONAL IMAGING
- CLINICAL RESEARCH

MPI® RESEARCH

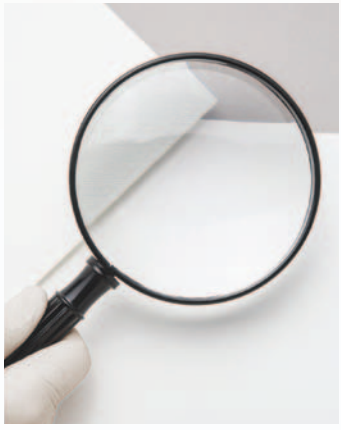
Pharmaceutical Technology®

EDITORIAL

Editorial Director **Rita Peters** rita.peters@ubm.com
Senior Editor **Agnes Shanley** agnes.m.shanley@ubm.com
Managing Editor **Susan Haigney** susan.haigney@ubm.com
Science Editor **Adeline Siew, PhD** adeline.siew@ubm.com
Manufacturing Editor **Jennifer Markarian** jennifer.markarian@ubm.com
Science Editor **Randi Hernandez** randi.hernandez@ubm.com
Community Manager **Caroline Hroncich** caroline.hroncich@ubm.com
Art Director **Dan Ward**
Contributing Editors **Jill Wechsler** jillwechsler7@gmail.com;
Jim Miller info@pharmsource.com; **Hallie Forcinio** editorhal@cs.com;
Susan J. Schniepp sue.schniepp@mac.com; **Eric Langer** info@bioplanassociates.com;
and **Cynthia A. Challener, PhD** challener@vtlink.net
Correspondent **Sean Milmo** (Europe, smilmo@btconnect.com)
485 Route One South, Building F, Second Floor, Iselin, NJ 08830, USA
Tel. 732.596.0276, Fax 732.647.1235, **PharmTech.com**

Pharmaceutical Technology's eNewsletter Team:
- *ePT*, Editor Caroline Hroncich, ptpress@ubm.com
- *Sourcing and Management*, Editor Rita Peters, rita.peters@ubm.com
- *Equipment & Processing Report*, Editor Jennifer Markarian, jennifer.markarian@ubm.com
- Send news and product releases to ptpress@ubm.com

ELIMINATE PARTICULATES & FIBERS IN THE CORE.



SYNTHETIC WRITING SUBSTRATE

CleanPrint 10

- Low particulate and non-shedding
- Exceptionally durable
- Abrasion and chemical resistant
- Easy to write on
- Double bagged packaged sterile

CUSTOM DOCUMENTATION

Core 2 Write

- Logbooks, ID tags, Forms and Labels
- Constructed using CLEANPRINT 10
- Customized specifically per customer
- Individual unique numbering and integrity features
- RFID Technology available

HEPA FILTERED PRINTING SYSTEM

Core 2 Print

- Print wirelessly into cleanrooms
- Use with pre-sterilized CLEANPRINT 10
- 316L Stainless Steel Construction, can be completely disinfected
- HEPA Filter cabinet
- Sheet fed, high speed digital printer using chemical resistant ink

vai
VELTEK ASSOCIATES, INC.

15 Lee Boulevard
Malvern, PA 19355-1234 USA
(610) 644-8335

www.sterile.com

Pharmaceutical Technology®

SALES

Publisher **Mike Tracey** mike.tracey@ubm.com
Mid-West Sales Manager **Irene Onesto** irene.onesto@ubm.com
East Coast Sales Manager **Joel Kern** joel.kern@ubm.com
European Sales Manager **Linda Hewitt** linda.hewitt@ubm.com
European Senior Sales Executive **Stephen Cleland** stephen.cleland@ubm.com
Executive Assistant **Barbara Sefchick** barbara.sefchick@ubm.com

ADDRESS

485 Route One South, Building F, Second Floor, Iselin, NJ 08830, USA
Tel. 732.596.0276, Fax 732.647.1235
PharmTech.com

Sr. Production Manager **Karen Lenzen**
International Licensing **Maureen Cannon** maureen.cannon@ubm.com,
tel. 440.891.2742 or toll-free 800.225.4569 ext 2742, fax. 440.756.5255
Audience Development Manager **Rochelle Ballou** rochelle.ballou@ubm.com

american business media
Alliance for Audited Media

NON-OEM PARTS HAVE EARNED A VERY SPECIAL PLACE IN THE TABLET PRESS MARKET.

TRUE STORIES…

Buying a non-OEM emergency stop switch saved a customer a couple of dollars up front, but ended up sparking thousands of dollars in damage, downtime and repair costs when it shorted out.

A warped, non-OEM baseplate caused metal contamination in the product, risking consumer safety and regulatory action.

A non-OEM turret had an improper weld on the lower punch retaining band, causing erratic product weights and expensive material loss.

We could go on and on, but you get the ugly picture. Why risk everything to save nothing? Put your trust in the superior precision and guaranteed performance of Genuine FETTE parts.

FETTE PRICE MATCH GUARANTEE

FETTE will meet or beat any legitimate price on major replacement parts **GUARANTEED.**
Call 973.586.8722

FETTE COMPACTING

FETTE COMPACTING AMERICA
400 Forge Way
Rockaway, NJ 07866
parts@fetteamerica.com

www.fette-compacting-america.com

January 2017 Volume 41 Number 1

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.

Pharmaceutical Technology
PharmTech.com

On the cover

COVER STORY

Cover Design/Illustration by Dan Ward

FEATURES

Continued on page 10

PEER-REVIEWED RESEARCH

PYRAMID
Laboratories, Inc.

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

Continued from page 8

FEATURES *continued*

NEWS & ANALYSIS

REGULATION & COMPLIANCE

DEPARTMENTS/ PRODUCTS

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
- DECHEMA
- 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.

PHARMACEUTICAL TECHNOLOGY (Print ISSN: 1543-2521, Digital ISSN: 2150-7376) is published monthly, except two issues in June, by UBM Americas 131 W. First St., Duluth MN 55802-2065. Subscription rates: US and possessions — 1 year (13 issues), $76; 2 years (26 issues), $133. Canada and Mexico — 1 year, $99; 2 years, $151. All other countries 1 year, $145; 2 years, $263. International price includes air-expedited service. Single-copies (prepaid only) — US, $15; Canada and Mexico, $16; outside the US, $19. Back issues (if available): US and possessions — $34; Canada and Mexico, $39; all other countries — $41. Include an additional $6.50 per order plus $2 per additional copy for US postage and handling. If shipping outside the US, include an additional $10 per order plus $3 per additional copy. Periodicals postage paid at Duluth, MN 55806 and additional mailing offices. POSTMASTER: Please send address changes to Pharmaceutical Technology, PO Box 6188, Duluth, MN 55806-6188. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

Tired of Your Temps Bouncing?

eurofins | Lancaster Laboratories PSS Insourcing Solutions

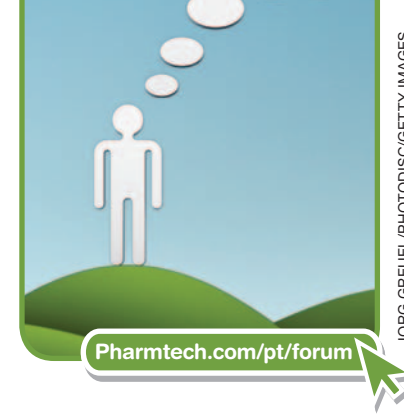
Partner and prosper with our award-winning PSS Insourcing Solution®

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.

www.EurofinsLancasterLabs.com



JORG GREUEL/PHOTODISC/GETTY IMAGES

Beyond Distractions, Pharma Moves On

Rita C. Peters

Translating campaign promises to predictions for bio/pharma is difficult, but optimism prevails.

In 1977, an unexpected presidential winner, Jimmy Carter, was sworn into office and the first *Star Wars* episode premiered in movie theaters. In that year, *Pharmaceutical Technology* also published its first issue. As 2017 begins, the United States will inaugurate another unexpected winner of the presidential race, and heroic rebels still battle an evil force in the latest installment of the movie series.

As we mark 40 years of publishing this year, it is easy to look back and assess factors that impacted the economy and pharma during the past decades. Predicting the next few months, yet alone the next few years, is far more difficult. Following the contentious 2016 presidential election, uncertainty was the prevailing sentiment as the Trump administration initiated the transition to the White House and federal agencies.

In general, big business had a positive outlook toward the new administration, as reflected in a post-election stock market surge. Other campaign promises, in particular the repeal of Obamacare, generated protests and unease for pharma companies, payers, and patients. In this issue, the editors look at some of the political, economic, and regulatory trends that may influence the business activities in 2017.

As the nation waited for more information about the leadership and policies of the new administration, the airwaves and social media were buzzing with opinions about politics, policies, the economy, and the future. Still, bio/pharma development moves on. Prior to the election, *Pharmaceutical Technology* sampled opinions from those who work in pharma about the industry's prospects.

Predicting the near future is far more difficult than reviewing the past 40 years.

More than 440 bio/pharma professionals from around the world participated in the 2016 *Pharmaceutical Technology/Pharmaceutical Technology Europe* annual employment survey (1). Respondents expressed opinions about job security, seeking new opportunities, salary levels, as well as trends in the industry, how changes impact their daily work, and future business prospects. The survey was conducted in September and October 2016.

Business continues to improve

Almost 44% of the respondents said business at their company increased in 2015, three percentage points higher than reported in 2015 (2). More than one-quarter of the respondents (28.8%) reported that their company had been through a merger or acquisition in the past two years, up slightly from the 2015 survey. Fewer respondents reported a company downsizing or restructuring.

Respondents were even more upbeat about the prospects of business improvements at their companies; 59.1% predicted that their company's business would improve in 2017, compared to 54.6% predicting improvements for 2016. Only 13% predicted business would decline.

Overall, respondents expressed a positive outlook for the bio/pharmaceutical industry as a whole for the next year; however, optimism slid a bit in recent years. Fewer respondents said business would improve (45.6% in 2016 compared with 47.8% in 2015 and 54.2% in 2014). In a reverse of sentiments in previous years, respondents based in North America (42.3%) were less optimistic that business would improve compared with respondents based in Europe (46.4%).

When looking at the next five years, nearly two-thirds of respondents (63.3%) predicted that business will improve; however, 15.2% of the US-based respondents expect business to improve overseas, but not domestically.

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rita.peters@ubm.com.

References

1. 2016 *Pharmaceutical Technology/Pharmaceutical Technology Europe* Annual Employment Survey.
2. 2015 *Pharmaceutical Technology/Pharmaceutical Technology Europe* Annual Employment Survey. **PT**

Fully Automated Capping Systems

The Thermo Scientific Decapper 500 and 550 series tube capping systems from Thermo Fisher Scientific and Hamilton Storage are fully automated capping systems for use in medium- to high-throughput biotech, pharmaceutical, and clinical laboratories doing compound storage, high-throughput screening, biobanking, and genomic storage. The systems allow users to cap and decap both Thermo Scientific Matrix and Nunc automation tubes without multiple pieces of equipment. The new decapper system features Quick Switch technology that allows users to transition between different tube and rack types. The systems can also cap and decap partial racks of tubes. The Decapper 550 provides additional functionality with its built-in barcode reader.

Thermo Fisher Scientific
www.thermofisher.com

Automatic Purge System for Control Panels

The Ross SysCon control panels from Ross, Charles & Son can now be supplied with a fully automatic Type X Purge System, which forces clean air through the enclosure until all hazardous gases are removed. The system then maintains a slight positive pressure within the panel. The Type X Purge System includes a 24-volt power supply. The UL-listed Operator Stations are designed for use with a remote PLC System to ensure full operational functionality of the equipment they control.

Ross, Charles & Son
www.mixers.com

Vials Reduce Risk of Drug Container Interactions

The DualFUSION vials from Wheaton for the storage of lyophilized materials are engineered using a plasma enhanced chemical vapor deposition technology to fuse an organosilicate protective layer with silica-like barrier layer, and then fuses that inner material to a cyclic olefin polymer outer shell. The inert silica-like barrier layer of the vial is impermeable to oxygen and other gases from the surrounding environment, and protects against delamination and leaching of contaminants, reducing the risk of drug-container interactions. The protection provided by the innovation composition and construction of DualFUSION vials minimizes caking that can occur in lyophilized drug products.

DualFUSION vials can withstand a temperature range of -196 °C to 121 °C without cracking. A unique 2D barcode laser etched onto the bottom of each DualFUSION vial facilitates sample identification and product lot traceability. The vials can be used in the manufacture of proteins, peptides, enzymes, DNA, and RNA—of complex formulations that may be sensitive to oxygen or metal ion exposure—and of highly potent and radioactive substances.

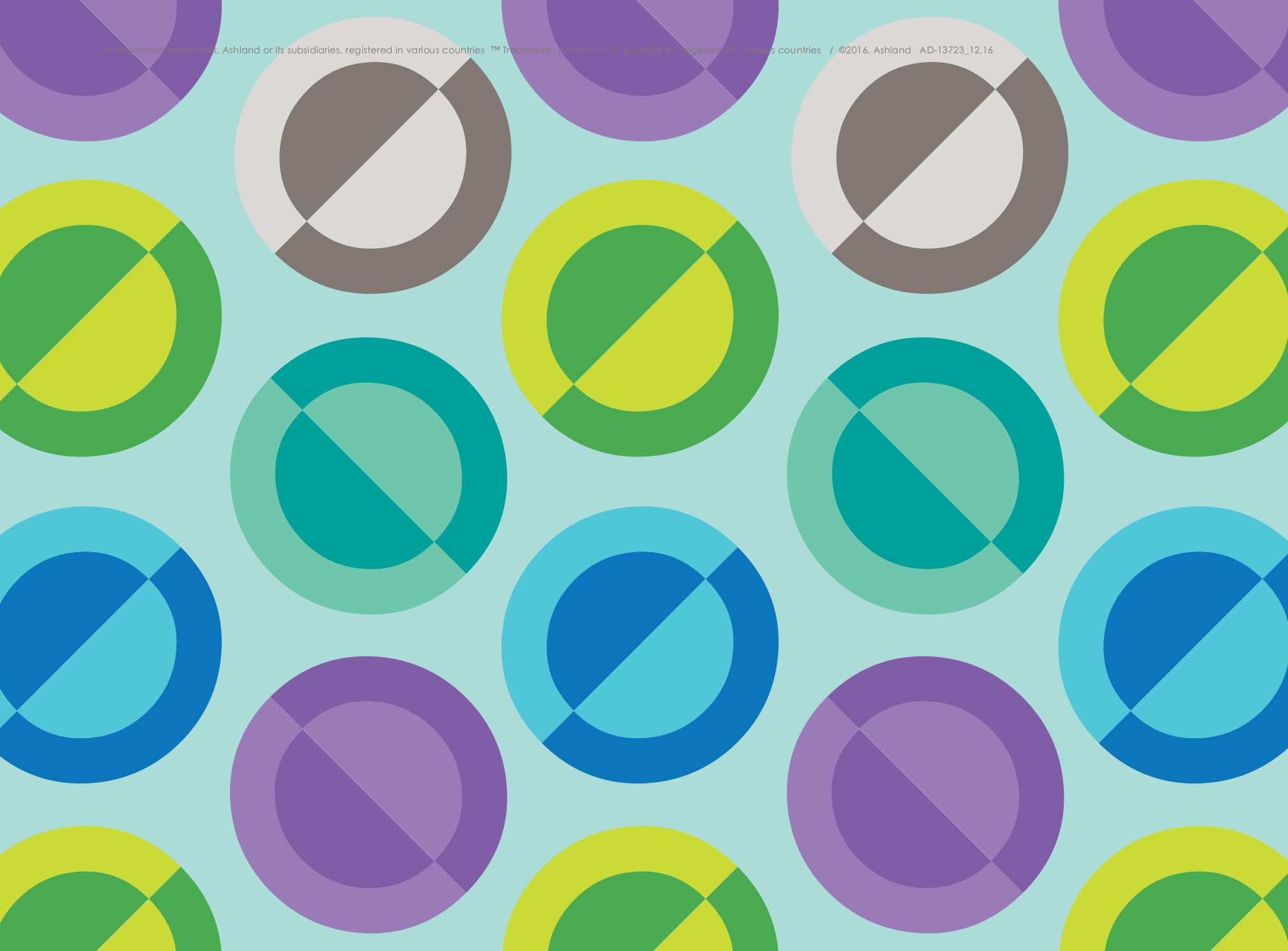
Wheaton
www.wheaton.com

Spray Dryer for Efficient Microencapsulation

The new patent-pending PolarDry Electrostatic Spray Dryer from Fluid Air, a division of Spraying Systems Co., uses electrostatic technology, rather than heated drying gas, for microencapsulation. This technology eliminates the intense heat of traditional spray drying and is more efficient at encapsulating the active ingredient. The system also allows agglomeration during the drying step, eliminating the need for secondary agglomeration operations. The spray dryer's electrostatic technology drives water to the shell and active to the core, lowering the evaporation temperature and eliminating active ingredient loss and degradation, thus creating a longer shelf life, and higher bulk density. Inlet drying temperatures remain low (from ambient to 80 °C).

The machines incorporate a patent-pending collection and particle-separation plenum that can be configured for batch or continuous processing. The systems are currently available in four scales: the feasibility scale (Model 001) with a once-through design for the laboratory, an R&D scale (Model 004), a pilot scale (Model 032), and a production scale (Model 050). The R&D scale is a semi-portable unit with a recirculating gas-handling system and a nominal evaporation rate of 4 kg/h; this unit uses the same nozzle as the larger-scale units for ease of scale-up. The pilot-scale unit has a nominal evaporation rate of 30 kg/h, and the largest unit has a rate of 50 kg/h.

Fluid Air
www.fluidairinc.com/spray_dryer_systems.html



Bio/Pharma's 2017 Agenda

Rita C. Peters

Healthcare policies, R&D investments, and drug approvals will test bio/pharma.

For an industry that relies on the stability of its products for patient safety and company success, the outlook for the bio/pharma industry itself—as well as the healthcare system, patient access to affordable medicines, speedy drug approvals, and global regulatory compliance—had a large dose of uncertainty as the calendar turned to 2017.

The election of populist candidate Donald Trump as president of the United States shocked many and created unease in the public and private sectors, but it also boosted the financial outlook for bio/pharma companies, at least in the short term. The investment community viewed the Trump administration as more pharma-friendly compared to the stated positions of the Clinton administration to rein in drug costs. Bio/pharma stocks rallied after Election Day. Analysts noted a "sunny" weather forecast for the pharma and biotech sector, but cautioned that while "many believe that the political wind in the world's biggest drug market is, for the time being, blowing in the right direction," ongoing concern about drug pricing, payer pressure, and economic questions still created uncertainty (1).

This volatility was illustrated when President-elect Trump, in a Dec. 7, 2016 interview with *Time* magazine, said he was going to lower drug prices, driving down biotech and pharma stocks (2). While patients, payers, bio/pharma companies, and the investment world await decisions about health insurance, drug prices and reimbursements, FDA leadership, and regulatory changes, instability may be the new norm for the foreseeable future.

Healthcare reform tops the list

Healthcare was a hot-button issue during the presidential campaign, with candidate Trump and the Republican Party promising to repeal and replace the Affordable Care Act (ACA) of 2010. Republican legislators have strategized that they could "repeal" parts of the ACA through a budget reconciliation process; replacement would require cooperation from both parties and could take months or years to accomplish.

Under ACA, bio/pharma companies benefited from the increased pool of patients seeking medicines, but also paid higher fees and made concessions on drug prices. Industry and patient groups are sure to be part of the negotiations for changes or a repeal/replacement of the legislation.

In a Dec. 20, 2016 letter, senators representing Democratic and Independent interests sent Trump a letter that outlined areas where the different sides could cooperate, including increased transparency and incentives for innovation. Debate on ACA reform, repeal, or replacement should dominate the conversation in 2017.

Financial and investment focus

Programs to fulfill the business-friendly campaign promises had not been revealed as 2016 ended. Still, analysts project that major bio/pharma companies can benefit from tax repatriation, which would bring more cash back to the US, and potentially leading to more R&D investment, acquisitions, or shareholder payouts (1).

When polled prior to the election, investors were optimistic for the US drug market for 2017, but with "less exuberance" than in previous years. The results of the election may have shifted that opinion already, Evaluate Pharma suggests. Through November 2016, mergers and acquisitions totaled about half what was spent in 2015. The number of deals were down. Companies waited for the election outcome, and the valuations of some targets remained high. The initial public offering market slid in 2016 following a rally in previous years. Analysts note that the venture capital market in 2016 was "respectable" and with new funds being raised, the trend is expected to continue in 2017 (1).

ILLUSTRATION BY DAN WARD

Drug industry performance

If the performance of the bio/pharma industry is measured by the number of new drug approvals, 2016 did not live up to expectations. As of mid-December 2016, only 20 new drugs received FDA approval, compared to 41 in 2014 and 45 in 2015. Fewer submissions and more complete response letters were a few reasons for the lower number of approvals, FDA noted. The number of applications received by FDA through Dec. 9, 2016, however, surpassed the average number of new molecular entity filings for the past decade (3).

All but one of the novel drugs approved in 2016 through Dec. 9, 2016 met the Prescription Drug User Fee Act (PDUFA) goal dates for the approval review cycle; and all but one were approved on the first cycle. Approximately two-thirds of the 2016 new drug approvals were approved under Priority Review. The number of breakthrough-designated development programs held steady compared to the past two years (4).

R&D roadblocks

Amid the clamor about controlling drug prices, drug company executives are examining R&D methods and declining returns. The cost to bring a drug to market, as estimated by the Deloitte Centre for Health Solutions (5), declined slightly from $1.576 billion in 2015 to $1.539 billion in 2016, perhaps due to shorter cycle times for breakthrough designations. The study also concluded that companies with less volatility in the therapy-area focus of their late-stage development programs outperform those that continually change the focus of their drug development efforts. Company size is also a factor. The study of 12 leading biopharma companies revealed a negative correlation between company size and predicted returns, and indicated that scale is a barrier to creating value in an R&D organization.

Companies have demonstrated greater efficiency in drug development through "nimble decision-making, empowering key decision-makers, accepting greater risk, making quick kills, and embedding a rigorous but dynamic process for funding projects," the study authors reported (5).

One anticipated source of gaining efficiencies—extensive outsourcing—has not delivered on expectations, the study authors report. Sub-optimal partner management by drug companies and operating models that hinder externalization contribute to less-than-expected results from outsourcing arrangements (5).

Drug company executives are examining R&D methods and declining returns.

Reducing regulations?

Another campaign theme—reducing the number of federal regulations perceived as roadblocks to business—may impact FDA and its efforts to expedite the approval of innovator and generic drugs. While a new president and administration may bring some differences in philosophies at FDA's Center for Drug Evaluation and Research (CDER), "the work of the Center goes on," said Janet Woodcock in a Dec. 14, 2016 interview (6).

The number of warning letters issued by FDA for adulterated APIs or drug products nearly doubled from 2015 to 2016 (7), with many letters addressing data integrity issues and citations at overseas operations. Data integrity is an ongoing initiative at FDA; in 2016, the agency issued a draft guidance document on data integrity and compliance with cGMPs (8). Its efforts to encourage drug manufacturers to self-monitor quality and manufacturing practices also continued with a revised draft guidance for technical conformance guidelines for quality metrics (9). Expect more discussion in 2017.

FDA reported progress in advancing a mutual reliance agreement for GMP inspections with regulatory authorities in Europe and beyond, part of negotiations for the Transatlantic Trade and Investment Partnership. Under the initiative, investigators and inspectors from FDA and other regulatory groups in the European Union would rely on each other's inspections for facilities making products for multiple markets, thus avoiding duplicating inspections, lowering costs, and concentrating resources in needed areas, such as China and India (10). The initiative is part of a trade agreement, however, which may be subject to additional scrutiny under the new administration.

FDA has worked to clear the backlog of generic-drug applications, but has been hindered by ongoing staff shortages. The 21st Century Cures Act should help FDA with some of its hiring issues, including a new pay scale for scientists, Woodcock said (6). As of September 2016, CDER had 700 job openings and was struggling to compete with drug companies to hire and retain talent. A lengthy hiring process, lower salaries, and federal requirements to divest of holdings in food or drug company stocks can deter quality candidates, agency spokespeople reported. Filling the vacancies is vital to the agency's ability to review and approve generic drugs and accommodate expedited applications (11).

Two key regulatory deadlines loom for drug manufacturers. The US Pharmacopeial Convention (USP) revisions to elemental impurities chapters—General Chapters <232> Elemental Impurities–Limits and <2232> Elemental Contaminants in Dietary Supplements—take effect on Jan. 1, 2018. The second phase of the Federal Drug Supply Chain Security Act (DSCSA) drug traceability requirements take effect beginning in November 2017, and require that pharmaceutical products are marked with a national drug code, serial number, lot number, and expiration date in machine-readable and human-readable form.

In addition, the reauthorizations of PDUFA and the Generic Drug User Fee Act are pending for Congressional action in 2017.

Next steps for drug development

The Cures Act, signed into law by President Barack Obama in December 2016, was a hopeful sign that progress can be made on the healthcare agenda. The legislation was passed with strong bipartisan support; however, some funding for the National Institutes for Health and FDA is authorized, but still must be appropriated.

The legislation includes support for research on regenerative medicine and development of antibiotics and treatments for rare conditions. Other provisions are designed to streamline the drug approval process using novel clinical trials designs and study modeling and permit drug companies to use real-world evidence to support approval of added indications for marketed medicines. One impact of the Cures Act will be elevating the role of the patient in the development of drugs, Woodcock said, giving patients a bigger voice developing treatments for their diseases.

References

1. A. Brown, *EP Vantage 2017 Preview*, Report, Evaluate Pharma (December 2016).
2. M. Egan, "Trump Warns Wall Street: I'm Going to Cut Drug Prices," *CNN.com*, Dec. 7, 2016, http://money.cnn.com/2016/12/07/investing/trump-drug-prices-time-man-year-biotech/, accessed Dec. 20, 2016.
3. C.A. Challener, *Pharmaceutical Technology* 41 (1) 26–29 (January 2017).
4. J. Jenkins, CDER New Drug Review: 2016 Update, Presentation, FDA/CMS Summit, Dec. 14, 2016.
5. K. Taylor, M. Stockbridge, and S. Shah. Balancing the R&D Equation, Measuring *the Return from Pharmaceutical Innovation 2016*, Report, Deloitte Centre for Health Solutions (London, 2016).
6. M. Tirrell, "FDA's Woodcock Speaks About One of the Agency's Most Controversial Decisions," *CNBC*, Dec. 14, 2016, www.cnbc.com/2016/12/14/fdas-woodcock-speaks-about-one-of-the-agencys-most-controversial-decisions.html, accessed Dec. 20, 2016.
7. FDA, Inspections, Compliance, Enforcement, and Criminal Investigations, www.fda.gov/ICECI/EnforcementActions/WarningLetters, accessed Dec. 20, 2016.
8. FDA, *Data Integrity and Compliance with CGMP Guidance for Industry*, Draft Guidance (Silver Spring, MD, April 2016).
9. FDA, *Submission of Quality Metrics Data, Guidance for Industry*, Draft Guidance, Rev. 1. (Silver Spring, MD, November 2016).
10. D. Corrigan, "The Mutual Reliance Initiative: A New Path for Pharmaceutical Inspections in Europe and Beyond," *FDA Blog*, Dec. 7, 2016 http://blogs.fda.gov/fdavoice/index.php/2016/12/the-mutual-reliance-initiative-a-new-path-for-pharmaceutical-inspections-in-europe-and-beyond/ accessed Dec. 20, 2016.
11. S. Lupkin and S.J. Tribble, "FDA's Drug Approval Team Copes With 700 Unfilled Jobs as Industry Lures Staff," *Kaiser Health News*, Nov. 3, 2016. **PT**

Global Drug Spending: A Look Ahead

The QuintilesIMS Institute, in its annual projections for global drug sales (1), estimates that global medicine spending will reach nearly $1.5 trillion on an invoice price basis by 2021; the total volume of medicines consumed globally will increase 3%. The types of therapies and use of innovator versus generic drugs, however, will vary depending on where patients live.

Consumption of newer drugs in developed markets, more generic drug use in pharmerging markets, plus patent expiries, discounts, and rebates will result in a 4–7% compound annual growth rate (CAGR) to 2021, slower than the nearly 9% CAGR in 2014 and 2015 when expensive new hepatitis drugs distorted the annual growth rates, but similar to the 5.9% growth during the past five years. Future growth will be generated by autoimmune, oncology, and diabetes treatments.

The report predicts that specialty drugs to treat chronic, rare, or genetic diseases will be more widely used, particularly the US and European markets, thanks to the approval of breakthrough medicines and a greater focus by payers on drug value and performance. Spending on such therapies, which was 20% of all medicines spending 10 years ago, will rise to 30% in 2016 and to 35% by 2021 and will represent half of the medicine purchases in the United States, Germany, United Kingdom, Italy, France, and Spain.

The US remains the top spender on drugs ($461.7 billion), followed by China ($116.7 billion), Japan ($90.1 billion), Germany ($43.1 billion), France ($32.1 billion), Italy ($28.8 billion), UK ($27.0 billion), Brazil ($26.9 billion), Spain ($20.7 billion), and Canada ($19.3 billion).

In the pipeline

More than one-quarter of therapies in the late-stage pipeline are focused on oncologic drugs, thanks to recent successes in cancer therapeutics and opportunities created by breakthrough therapy designations. Therapies for central nervous system disorders make up 12% of the pipeline, followed by anti-infectives and antivirals (8%), cardiovascular (6%), arthritis/pain (6%), immune system (5%), and genito-urinary and hormones (5%), according to IMS data.

An improved understanding of the underlying mechanisms of diseases, and maturity in the development of immunotherapies and targeted therapies, will drive innovation, the authors report. Regenerative cell therapies, blood components, the human microbiome, and gene editing will be emerging research areas.

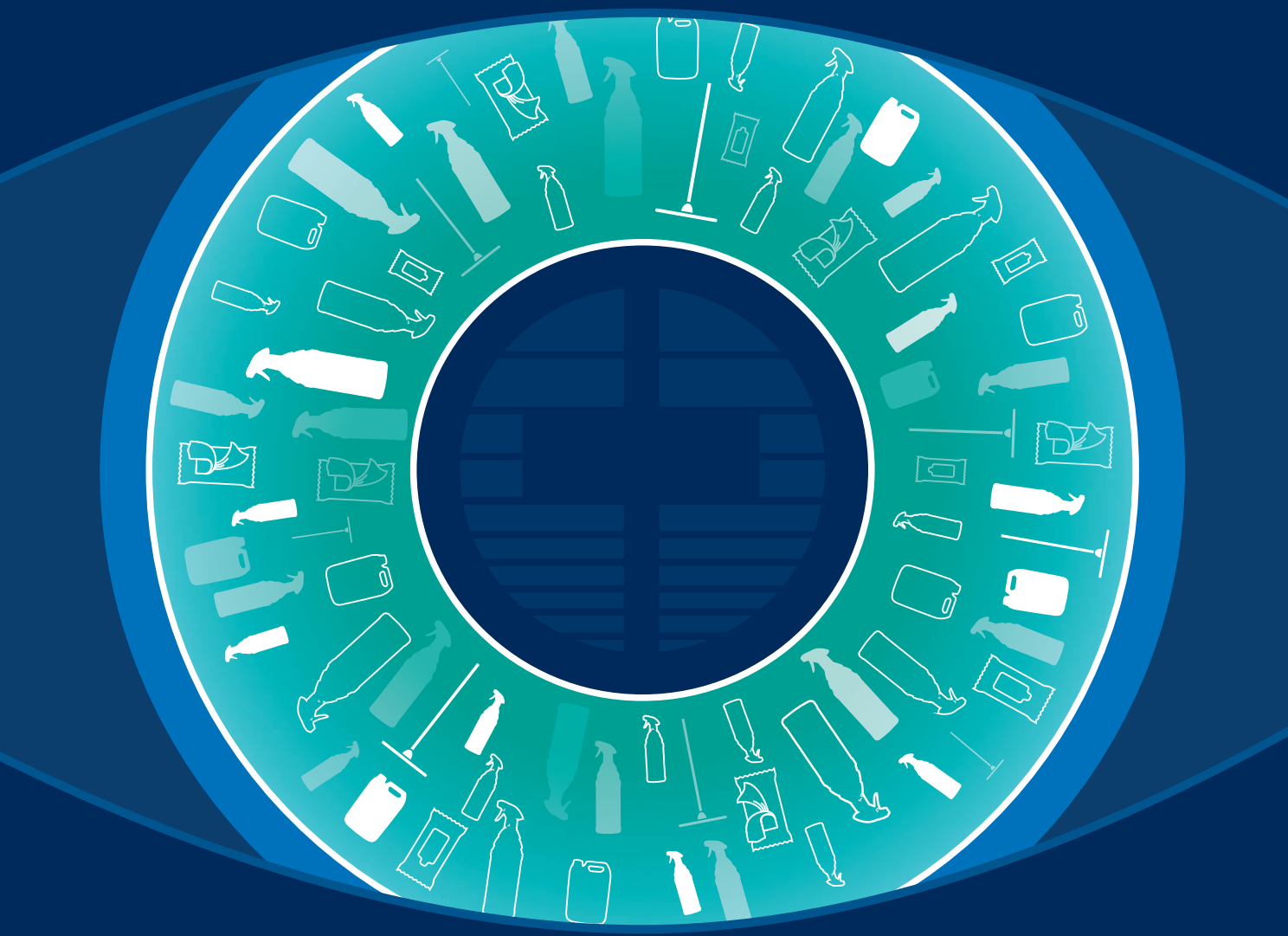
A mix of large, mid-size, and small companies have molecules in the oncology drug development arena. QuintilesIMS reports that while large companies are familiar with regulatory and logistical challenges, smaller companies have specific expertise with a specific mechanism of action or drug development platform that provides a research edge. Strategies moving forward include sale of assets, partnerships, or working independently. Outsourcing may also play a role.

US drug costs

The QuintilesIMS report estimates that the 12% US market growth in 2015 will be only 6–7% for 2016, and is forecast to average 6–9% through 2021. Factors for the decline include more patent expiries, historically high price increases for innovator and generic drugs before off-invoice discounts and rebates in 2014 and 2015, and the newly introduced hepatitis C drugs. When accounting for price concessions, spending growth is estimated to grow at 4–7% CAGR.

Reference

1. M. Aitken, M. Kleinrock, and D. Nass, *Outlook for Global Medicines through 2021, Balancing Cost and Value*, QuintilesIMS Institute, Parsippany, NJ, December 2016).



More than meets the eye

With one of the widest ranges of cleanroom wipes and mops available, plus a newly completed range of alcohols, disinfectants and detergents, there is definitely more to Contec than meets the eye. From patented Anticon wipes with particle attraction technology, or market leading presaturated wipes in a variety of substrates, Contec has a cleanroom wipe to suit every budget, application and facility. Contec has launched three new innovative mopping products, adding a curtain cleaner and sealed edge mops to their extensive mopping range. Visit our web site to view our newly launched Low Endotoxin wipes, mops and solutions.

For more information contact Contec at wipers@contecinc.com or by calling 1-866-855-4682

CONTEC®

www.contecinc.com

Drug Quality Key to Innovation and Access

Jill Wechsler

FDA plans to advance initiatives for ensuring reliable production of drugs and biologics in 2017.

Amidst multiple challenges to the structure and governance of the US healthcare system, bio/pharmaceutical manufacturers will face a host of issues in bringing safe and effective new therapies to patients. The demand for affordable personalized, or precision, medicines to treat lethal diseases requires efficient and cost-effective operations that promote innovation and avoid shortages. Similarly, modern, agile, and reliable production systems that adhere to standards and ensure data integrity are vital for development and access to biosimilars, cellular and gene therapies, complex dosage forms, innovative vaccines, and more combination therapies. And pressure to combat the devastating opioid epidemic across the US highlights the need for innovative methods to produce new formulations to treat pain that also resist abuse and misuse.

Innovation and reform

Pressure will mount on FDA under the new administration to make experimental therapies available to patients faster and more predictably. As 2016 came to a close, FDA officials reported that new drug approvals for the year would fall far short of the near-record set in 2015, raising concerns about current incentives and regulatory processes for bringing new drugs to market. FDA has approved numerous breakthrough therapies for cancer and critical conditions based on limited but convincing clinical data, a development highly applauded on all fronts. This patient-centric approach is expected to gain even more support from key provisions in the 21st Century Cures legislation.

These developments raise questions about how much data and what kind of evidence are needed to approve such products, and may require policy makers to grapple with new regulatory models. These issues were highly visible in the debate over FDA approval of Sarepta Therapeutics' treatment for Duchenne muscular dystrophy; reviewers and senior staffers in the Center for Drug Evaluation and Research (CDER) recommended against approval based on inadequate evidence that the drug had any positive effect on patients, while families of children with the condition claimed real benefit from the drug and convinced CDER director Janet Woodcock to recommend approval.

A similar situation recently emerged related to approving a new antibiotic that promises to address critical medical needs due to spreading antibiotic resistance, but has presented serious safety issues in clinical trials. Some regulatory officials and consumer advocates fear that pressure to provide early access to medicines, despite safety signals and limited evidence of efficacy, will undermine the FDA approval process more broadly.

Manufacturing challenges

Accelerated FDA approval of important therapies demands drug manufacturing systems able to scale up production quickly and efficiently and to maintain quality throughout the product lifecycle. These challenges apply to biosimilars and cutting-edge therapies, as well as to the need for modern aseptic processing methods able to reliably produce both new and generic sterile injectables. The increase in combination products, moreover, demands more coordinated oversight of manufacturing by FDA's centers for drugs, biologics, and medical devices.

FDA is responding with efforts to refine and clarify policies related to quality drug manufacturing, with an eye to avoiding onerous requirements that can increase production costs and cause delays. An important initiative involves collecting metrics data from drug makers that give a more precise picture of how reliably a drug facility produces quality products. In late November 2016, FDA revised a July 2015 proposal to address industry concerns about the scope and objectives of this quality metrics data submission initiative (1).

Under the new draft guidance, the program will be voluntary for a year and request three, instead of four, data elements, starting with lot acceptance rate, product quality complaint rate, and invalidated out-of-specification

Jill Wechsler
is *Pharmaceutical Technology's* Washington editor,
jillwechsler7@gmail.com.

rate. Manufacturers have the option of submitting data by product or by site and may add comments to reports. FDA, however, is looking for strong industry participation in this voluntary phase to be able to determine the value of this kind of data. If successful, FDA proposes to initiate a formal rulemaking process to establish a mandatory metrics reporting program, an approach likely to draw opposition from the Trump administration.

Contract manufacturers able to scale up quality production quickly have emerged as particularly important to the development of precision therapies and innovative dosage forms. The need for clear policies to ensure regulatory compliance and adherence to standards by contractors is reflected in a final guidance issued in November 2016 on establishing written quality agreements between commercial drug manufacturers and contractors (2). The final version revises a draft issued in 2013 and clarifies that the owner/manufacturer of a drug (and not distributors or retailers) is responsible for ensuring that drug substances and drug products are produced to meet GMP standards and how written agreements should map out the roles and responsibilities of each party in meeting those goals.

Industry and FDA will face challenges as they continue to implement drug supply chain monitoring programs, as required by the Drug Supply Chain Security Act (DSCSA) of 2013. An immediate task is to provide a barcode on packages by November 2017 that includes a National Drug Code (NDC), serial number, lot number, and expiration date in both machine-readable and human-readable form. A broad industry group adopted guidelines on using the Electronic Product Code Information Services (EPCIS) for lot-level management and item-level traceability of pharmaceuticals (3). Achieving standardized barcodes is a key step for establishing by 2023 a fully electronic system for item-level traceability of pharmaceuticals through the supply chain from manufacturer to wholesalers and distributors, and ultimately to pharmacies and patients.

Seeking harmonization

As manufacturers strive to meet the DSCSA goals for global tracking of prescription drug shipments, they will face multiple tracking and serialization systems under development in Europe, Asia, and South America. The lack of harmonization in these efforts reflects continued challenges in establishing worldwide standards for a wide range of operations involving drug testing, regulation, and production.

contin. on page 67

The Tide Stays High

Outsourcing Outlook for 2017

Jim Miller

Robust venture capital investment gives CDMOs and CROs a positive outlook for 2017.

A year ago, the outlook for contract services was a little uncertain. Equity markets' appetite for public offerings from emerging bio/pharmaceutical companies had significantly diminished: valuations of emerging bio/pharma companies, as measured by the NASDAQ Biotechnology Index (NBI), had declined by 15% from their highs in mid-2015, and by mid-February, they were off another 28%. Because contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) get so much of their business from externally-financed companies, the negative energy surrounding emerging bio/pharma did not bode well for the industry.

The valuations and levels of public offering activity in 2014 and 2015 were not sustainable, and the NBI has never gotten back close to the levels it reached in 2015. Nevertheless, fundraising by emerging biopharma companies held its own in 2016. Financing for emerging bio/pharma from venture capital, public equity, and partnering sources was ahead of 2013 levels, and those companies showed no fear of spending liberally to progress their pipelines though clinical development. Public reports for more than 300 companies tracked by PharmSource show that R&D spending by those companies has risen every quarter since the beginning of 2015.

Not surprisingly, this has been great news for CDMOs and CROs. Most publicly-traded services providers achieved revenue growth well in excess of 10% in 2016 (based on interim results), especially in those services that cater to clinical development (clinical supplies manufacturing, analytical services, clinical packaging, and clinical research). Many CDMOs have told PharmSource that they are operating near capacity, and customers may have to wait as much as six months for a manufacturing slot.

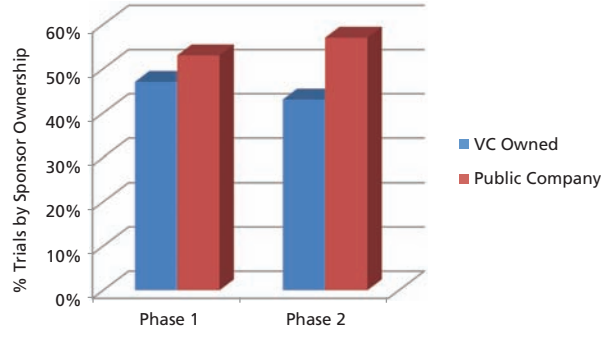
The significance of external funding can be seen by looking at early-phase clinical trials sponsored by emerging bio/pharma companies. Phase I and II clinical trial registrations by emerging bio/pharma companies, as recorded in clinicaltrials.gov, were up 55% higher in the first half of 2016 versus the first half of 2012 (see **Figure 1**) (1). Just over half of those companies (55%) are publicly-traded companies, while 45% are funded by venture capital. Clearly the tide of early development by emerging bio/pharma companies has risen thanks to the robust external funding environment.

The bio/pharma industry's recent performance is encouraging, but what is really important is what the industry can expect going forward. There is a sense that the outlook is positive but with some significant uncertainties.

US election impacts

Clearly, general economic sentiment since the November 2016 presidential election has been positive, with an expectation that the regulatory environment will be less restrictive and FDA will be approving more drugs more quickly. There have even been suggestions that a venture capitalist might be appointed to run the agency (no appointments had been announced at the time this column was written). However, emerging bio/pharma investors haven't

Figure 1: Ownership of emerging bio/pharma companies sponsoring clinical trials.



Source: clinicaltrials.gov; PharmSource analysis

Jim Miller is president of PharmSource Information Services, Inc., and publisher of *Bio/Pharmaceutical Outsourcing Report,* tel. 703.383.4903, Twitter@JimPharmSource, info@pharmsource.com, www.pharmsource.com.

COATINGS®

Coating Place

Innovative Controlled Delivery

Development through Commercial Manufacturing

Our manufacturing facilities are equipped with twenty proprietary, technically advanced Wurster fluid bed coating units, linear scaled for research and commercial production. No other CDMO offers a comparable record of bringing microencapsulated products to commercial viability as quickly and efficiently as Coating Place.

Coating Place, Inc., PO Box 930310, Verona, Wisconsin 53593 U.S.A. • 1-608-845-9521 • coatingplace.com

been moved much by this news as the NBI has remained at the same level it has been at for the past 12 months.

Enthusiasm for the bio/pharma industry may have been dampened by the president-elect's campaign promise to go after high drug prices, including allowing Medicare to directly negotiate drug prices. The dismantling of Obamacare could further reduce spending on drugs, especially in hospitals and other institutional settings. Coupled with the aggressive efforts by pharmacy benefit managers to reduce private sector spending on drugs by reducing utilization and prices, overall drug spending is likely to face considerable headwinds. That could dampen new investment in the industry, especially if it becomes more difficult for novel treatments to get formulary access.

Funding and investments

One positive indicator for CDMOs and CROs is the robustness of venture capital investment. Venture capital money has always been more dependable than public equity, even during the years of the global financial crisis. In 2016, even though public equity dropped considerably, venture capital maintained a pace that was close to what it was in 2015 and nearly 60% higher than it was in 2012. Looking ahead, according to the blog Life Sci VC, life-science venture funds are raising record amounts of new money that can sustain emerging bio/pharma companies for an extended period (2).

Of course, few venture capital or public equity investors place bets on emerging bio/pharma companies with the expectation that they will commercialize their pipeline candidates on their own. Rather, they hope their companies will be acquired, or at least have their candidates licensed by, a global bio/pharma company. Acquired or in-licensed products account for a third to a half of product approvals gained by global bio/pharma companies in recent years, and their reliance on externally-sourced candidates appears to be greater than ever. According to a report published by Deloitte in December 2016, global bio/pharma companies are getting only a 1% return on their investment in internal R&D (3).

So the stars seem to be aligning for a continued healthy environment for CDMOs and CROs. The biggest risks will come from what happens to drug pricing and coverage; and from a system-wide economic shock that negatively impacts the entire economy. The former is likely but over an extended number of years; and the latter can't be predicted.

References

1. clinicaltrials.gov
2. Life Sci VC, "Biotech Venture Capital Mythbusting Redux," Nov. 21, 2016, https://lifescivc.com/
3. Deloitte, Balancing the R&D Equation: Measuring the Return from Pharmaceutical Innovation 2016. **PT**

eppendorf

Flexible by Design

Comprehensive options for changing needs

The BioFlo® 320 offers a wide range of options to meet your ever changing needs. It controls both single-use and autoclavable vessels. Its universal gas control strategy allows for both microbial and cell culture applications. The BioFlo 320 can do it all.

- > Compatible with the BioBLU® Single-use Vessel portfolio
- > Extensive working volume range of 250 mL–40 L on a single bench-scale control platform
- > Multi-unit control of up to eight systems from a single interface improves efficiency

www.eppendorf.com • 800-645-3050

FDA New Drug Approvals Down Significantly in 2016

Cynthia A. Challener

As of mid-December, less than half the number of new drug approvals were issued by FDA in 2016 compared with 2015.

Following two years of near-record numbers of new drug approvals by FDA, with 41 in 2014 (1) and 45 in 2015 (2), 2016 appears to be seriously bucking the trend, with only 20 approvals issued as of Dec. 14, 2016 (3). The sharp decline was not expected. What might be the reasons? John Jenkins, director of FDA's Office of New Drugs, attributed the difference to a decline in the number of submitted applications, more complete response letters in 2016, and the fact that five approvals originally scheduled for 2016 were finalized earlier in 2015 (4). On a positive note, Jenkins reported that the number of applications received by FDA through Dec. 9, 2016 was 36, surpassing the average number (35) of new molecular entity filings for the past decade.

Notably, the decline in approvals does not seem to be having an impact on growth expectations for the global API market. Mordor Intelligence projects the global API market to expand at a compound annual growth rate of 6.5% from $154 billion in 2015 to $225 billion in 2021 (5).

While chemical compounds continue to account for the greatest percentage of APIs, biologic drug substances are growing at the fastest rate. APIs were intended slightly more often for branded drugs compared to generic drugs (43.5%) in 2015, and APIs for cancer treatments are experiencing the fastest growth vs. APIs for other therapies. North America remains the largest market for APIs, but demand is growing most rapidly in Asia-Pacific (5).

General observations

The 20 approvals in 2016 included treatments for asthma, type II diabetes, different cancers, hepatitis C, plaque psoriasis, multiple sclerosis, muscular dystrophy, and several rare diseases. Eight of the approvals were for biologics, including seven monoclonal antibodies (mAbs) and one hormone. Two were radioactive diagnostics agents and two were for the treatment of hepatitis C. Merck, Eli Lilly, and Sanofi each received two approvals. Half of the new drugs approved by FDA in 2016 received one or more special designations. Three are considered new classes of drugs, and three are the first-ever treatments for the diseases they target.

Special designations continue

With passage of the FDA Safety and Innovation Act (FDASIA) in 2012, FDA was granted authority to implement expedited review and approval programs to accelerate the introduction of novel medications to the market. Four programs are currently in use. Manufacturers can qualify for fast track and breakthrough therapy designations, and accelerated approval and priority review processes depending on the characteristics of their drug candidates. Breakthrough therapies provide substantial improvement over currently available treatments. Fast Track drugs meet unmet medical needs and treat serious conditions. Accelerated approval is available for similar reasons. Priority review is granted to drugs that have improved safety and effectiveness compared to current medicines.

Drug companies are utilizing these pathways. In 2014 and 2015, respectively, 66% and 60% of the 41 and 45 new drugs approved by FDA received one or more special designation or was granted an expedited review of some kind (6,7).

Cynthia A. Challener is a contributing editor to *Pharmaceutical Technology*.

The Parenteral Drug Association presents the...

2017 PDA Annual Meeting

Innovation in Manufacturing Science and Technology

April 3-5, 2017 | Anaheim, California

Anaheim Marriott

Exhibition: April 3-4 | Post-Meeting Workshop: April 5-6 | Courses: April 6-7

#PDAAnnual

Register before January 20, 2017 and save up to $600!

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

At the *2017 PDA Annual Meeting*, you'll receive the latest information and understand future trends related to pharmaceutical manufacturing and associated science and technology.

Plenary sessions will focus on advanced therapeutic strategies, including the emerging fields of immunotherapy and gene- and cell-based therapies. Breakfast sessions and Interest Group meetings provide opportunities for smaller group engagement on specific topics of interest.

And don't miss the Exhibit Hall, where attendees can meet one-on-one with service providers and vendors showcasing the latest in services and technologies.

Hear the latest on:

- Advances in Analytical Sciences & Quality Control Strategies
- Developments in Patient-Centered Precision Medicine
- Next Generation Manufacturing

Learn more and register at pda.org/2017Annual.

Following the Meeting, on **April 5-6**, PDA will be offering 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.***

In 2016, five of the newly approved drugs were awarded the breakthrough therapy designation, three received fast track status, five received accelerated approval, and eight underwent priority review. In addition, six of the newly approved treatments were classified as orphan drugs. One product—Exondys 51 (eteplirsen, Sarepta Therapeutics) for the treatment of patients with Duchenne muscular dystrophy (DMD)—received priority review for a rare pediatric disease. Notably, two of the approved drugs in 2016 had a total of five special designations (8).

Despite fewer approvals, the API market is expected to grow 6.5%.

Several first treatments

Several of the newly approved drugs are the first new therapies approved by FDA for the treatment of different diseases. Exondys 51 is the first drug approved to treat patients with DMD that have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the population with DMD (8).

In addition to receiving the seventh rare pediatric disease priority review voucher issued by FDA since the program began, Exondys 51 was granted fast track and orphan drug designations and was approved under the accelerated approval pathway based on the surrogate endpoint of dystrophin increase in skeletal muscle observed in some Exondys 51-treated patients. FDA is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit.

Nuplazid (pimavanserin) from Acadia Pharmaceuticals is the first drug approved to treat hallucinations and delusions associated with psychosis experienced by as many as 50% of people with Parkinson's disease. An estimated 50,000 Americans are diagnosed with Parkinson's disease each year, according to the National Institutes of Health, and about 1 million Americans have the condition. Nuplazid received priorty review and was designated a breakthrough therapy (9).

Defitelio (defibrotide sodium) marketed by Jazz Pharmaceuticals is the first FDA-approved therapy for the treatment of severe hepatic veno-occlusive disease (VOD), a rare and life-threatening liver condition that can occur in adults and children that receive a stem cell transplant from blood or bone marrow (hematopoietic stem cell transplantation or HSCT). Fewer than 2% of patients develop severe hepatic VOD after HSCT, but as many as 80% of patients who develop severe hepatic VOD do not survive. Defitelio was granted priority review and designated an orphan drug (10).

Epclusa (fixed dose combination of sofosbuvir and velpatasvir) from Gilead Sciences is the first regimen to treat all six major hepatitis C virus (HCV) genotypes and was approved for adult patients with chronic HCV. Velpatasvir is the new drug; sofosbuvir was approved in 2013. Epclusa was granted priority review (11).

Lartruvo from Eli Lilly is the first new therapy approved by the agency for the initial treatment of soft-tissue sarcomas (STS), cancers that develop in muscles, fat, tendons or other soft tissues and cannot be cured with radiation or surgery, since doxorubicin's approval more than 40 years ago. This platelet-derived growth factor (PDGF) receptor-alpha blocking antibody blocks PDGF receptors that cause tumor growth. The National Cancer Institute estimates that 12,310 new cases of STS and nearly 5000 deaths are likely to occur from the disease in 2016. Lartruvo (olaratumab) with chemotherapy drug doxorubicin was granted accelerated approval and priority review, as well as fast track, breakthrough therapy, and orphan designations (12).

New treatment pathways

Other drugs approved in 2016 fall into new classes of compounds that act by new pathways. Genentech's Tecentriq (atezolizumab) is the first FDA-approved PD-L1 inhibitor and the latest in the broader class of PD-1/PD-L1 targeted biologics approved by FDA in the past two years. This mAb was approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma, the most common type of bladder cancer. It blocks PD-1/PD-L1 interactions between the body's immune cells and some cancer cells, potentially helping the body's immune system to fight cancer cells. Tecentriq received priority review and accelerated approval and was designated a breakthrough therapy (13).

Venclexta (venetoclax) from AbbVie is the first FDA-approved treatment that targets the B-cell lymphoma 2 (BCL-2) protein, which supports cancer cell growth. The drug is for the treatment of patients with chronic lymphocytic leukemia (CLL) who have a chromosomal abnormality called 17p deletion and who have been treated with at least one prior therapy. According to the National Cancer Institute, CLL is one of the most common types of leukemia in adults, with approximately 15,000 new cases diagnosed each year. The relevant chromosomal abnormality occurs in approximately 10% of patients with untreated CLL and in approximately 20% of patients with relapsed CLL. Venclexta was granted priority review and accelerated approval and designated a breakthrough therapy and orphan drug (14).

Netspot from Advanced Accelerator Applications USA is the first kit for the preparation of gallium Ga 68 dotatate injection, a radioactive diagnostic agent for positron emission tomography imaging. The radioactive probe helps locate tumors in adult and pediatric patients with the rare condition somatostatin receptor positive neuroendocrine tumors by binding to receptors on the tumors, which develop in the hormone-producing cells of the body's neuroendocrine system. Netspot received priority review and was designated an orphan drug (15).

Other notable approvals

Several of the approved drugs in 2016 are intended for the treatment of diseases with existing therapies, but in some cases the new drug is of particular interest. For instance, Ocaliva (obeticholic acid) from Intercept Pharmaceuticals is only the second drug approved to treat patients with primary biliary cholangitis. Ursodeoxycholic acid, the only other approved drug, is effective in just over 50% of patients on its own and is not tolerated by many. An oral drug, Ocaliva binds to the farnesoid X receptor, a receptor found in the nucleus of cells in the liver and intestine, reducing bile flow from the liver and suppressing bile acid production in the liver. It received accelerated approval and fast track and orphan drug designations (16).

Merck's ZINPLAVA (bezlotoxumab) is approved for the reduction of the recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at high risk for CDI recurrence. CDI is caused by bacteria that produce toxins, including toxin B. Developed by researchers at the University of Massachusetts Medical School's MassBiologics Laboratory in conjunction with Medarex (now part of Bristol-Myers Squibb) and licensed to Merck in 2009, Zinplava, a human monoclonal antibody, binds to *C. difficile* toxin B and neutralizes its effects (17).

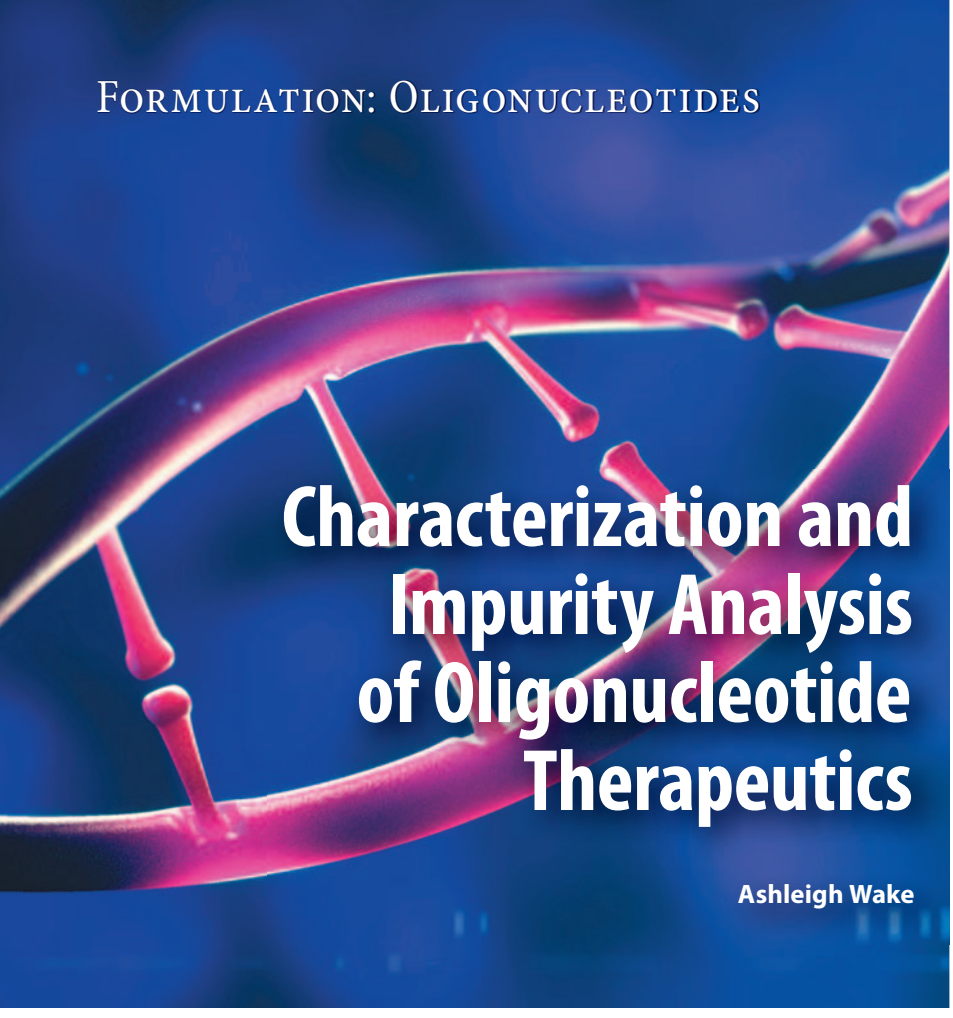
Developed by Elusys Therapeutics in cooperation with the US Dept. of Health and Human Services' Biomedical Advanced Research and Development Authority, Anthim (obiltoxaximab) is a mAb that neutralizes toxins produced by *Bacillus anthracis* and was approved for the treatment of inhalational anthrax in combination with appropriate antibacterial drugs. Inhalational anthrax is a rare disease that can occur after exposure to infected animals or contaminated animal products, or as a result of an intentional release of anthrax spores. Notably, the drug was approved under FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans (18).

North America remains the largest market for APIs, but demand is growing most rapidly in Asia-Pacific.

It is also worth noting that FDA's Center for Drug Evaluation and Research (CDER) approved 72 "first generic drugs" in 2016 as of Nov. 16, 2016 (19). "First generics" are the first approval by FDA that permits a manufacturer to market a generic drug product in the United States and receive prioritized review.

References

1. FDA, New Molecular Entity and New Therapeutic Biological Product Approvals for 2014, www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm429247.htm, accessed Dec. 14, 2016.
2. FDA, New Molecular Entity and New Therapeutic Biological Product Approvals for 2015, www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm, accessed Dec. 14, 2016.
3. FDA, New Molecular Entity and New Therapeutic Biological Product Approvals for 2016, www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm, accessed Dec. 14, 2016.
4. J. Jenkins, "CDER New Drug Review: 2016 Update," presentation at FDA/CMS Summit, Dec. 14, 2016, www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm533192.pdf, accessed Dec. 14, 2016.
5. Mordor Intelligence, "Global Active Pharmaceutical Ingredients Market–Growth, Trends & Forecasts (2016–2021)," September 2016, www.mordorintelligence.com/industry-reports/global-active-pharmaceutical-ingredients-api-market-industry, accessed Dec. 14, 2016.
6. FDA, Novel New Drugs 2014. January 2015, www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf, accessed Dec. 14, 2016.
7. FDA, Novel Drugs Summary 2015. January 2016, www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm474696.htm, accessed Dec. 14, 2016.
8. FDA, "FDA Grants Accelerated Approval to First Drug for Duchenne Muscular Dystrophy," Press Release (Silver Spring, MD, Sept. 19, 2016).
9. FDA, "FDA Approves First Drug to Treat Hallucinations and Delusions Associated with Parkinson's disease," Press Release (Silver Spring, MD, April 29, 2016).
10. FDA, "FDA Approves First Treatment for Rare Disease in Patients Who Receive Stem Cell Transplant from Blood or Bone Marrow," Press Release (Silver Spring, MD, March 30, 2016).
11. FDA, "FDA Approves Epclusa for Treatment of Chronic Hepatitis C Virus Infection," Press Release (Silver Spring, MD, June 28, 2016).
12. FDA, "FDA Grants Accelerated Approval to New Treatment for Advanced Soft Tissue Sarcoma," Press Release (Silver Spring, MD, Oct. 19, 2016).
13. FDA, "FDA Approves New, Targeted Treatment for Bladder Cancer," Press Release (Silver Spring, MD, May 18, 2016).
14. FDA, "FDA Approves New Drug for Chronic Lymphocytic Leukemia in Patients with a Specific Chromosomal Abnormality," Press Release, April 11, 2016.
15. FDA, "FDA Approves New Diagnostic Imaging Agent to Detect Rare Neuroendocrine Tumors," Press Release, (Silver Spring, MD, June 1, 2016).
16. FDA, "FDA Approves Ocaliva for Rare, Chronic Liver Disease," Press Release (Silver Spring, MD, May 31, 2016).
17. Merck & Co., "FDA Approves Merck's ZINPLAVA (bezlotoxumab) to Reduce Recurrence of *Clostridium difficile* Infection (CDI) in Adult Patients Receiving Antibacterial Drug Treatment for CDI Who Are at High Risk of CDI Recurrence," Press Release (Silver Spring, MD, Oct. 21, 2016).
18. FDA, "FDA Approves New Treatment for Inhalation Anthrax," Press Release (Silver Spring, MD, March 21, 2016).
19. FDA, First Generic Drug Approvals, www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/default.htm, accessed Dec. 14, 2016. **PT**



Characterization and Impurity Analysis of Oligonucleotide Therapeutics

Ashleigh Wake

Analytical technologies play a key role in the characterization and quantitation of oligonucleotide therapeutics.

The potential and anticipation surrounding oligonucleotides as therapeutics has been apparent in the pharmaceutical industry for more than 30 years (1). Until recently, however, the number of success stories has been limited with the actual level of growth failing to meet these initial expectations.

As of September 2016, three antisense drugs have been approved for use in the United States. The development pipeline for these therapies appears to be strong, with ClinicalTrials.gov detailing more than 140 active clinical programs for oligonucleotides in various stages of development.

Ashleigh Wake is director of Biological Services, Intertek.

This resurgence in oligonucleotide development can be attributed to a combination of factors including improved chemistries, a better understanding of the basic biology of oligonucleotides, more sophisticated delivery systems, and most importantly, increasing success in the clinic (2). Undoubtedly to support these developments, advancement in analytical technology has also been a fundamental aspect, specifically to facilitate characterization and quantitation of the oligonucleotide of interest as well as any synthetic contaminants (3).

Oligonucleotides are generally produced through a synthetic solid-phase chemical synthesis in a manner that likens them directly to traditional small-molecule pharmaceuticals. Oligonucleotides, however, display a diversity in mode of action, which on a cellular level involves interactions more typical of a biological moiety (3). This lack of ready definition as either a large or small molecule has led to many challenges from a regulatory perspective in terms of providing guidance, and subsequently, as yet, neither FDA or EMA have issued official documentation with respect to expectations surrounding quality control of oligonucleotides.

Despite the lack of formal guidance, FDA has issued papers detailing current thinking in respect to quality control (4). These documents provide an overview of the data required to support product registration in respect to identity, purity, quality, and strength. The actual analytics involved represent a diverse and complex analytical program. **Table I** provides an overview of a typical characterization program.

Identity testing

Given the complex nature of the molecule, as with many of the quality control analytics, it is recommended that orthogonal approaches be used to verify the identity of the test material.

Oligonucleotide structure and sequence

Determination of the molecular weight and confirmation of the nucleotide sequence of an oligonucleotide are fundamental criteria for analysis in terms of confirmation of the identity of the molecule and thus a regulatory expectation. Several methods can be applied to gain this information. Historically, digestion approaches such as enzymatic methods (e.g., Sanger) or chemical methods (e.g., modified Maxam Gilbert) followed by mass spectrometry have been widely used. Methods involving digestion are often complex and relatively time-consuming and the likelihood of success is restricted, in some ways, to the analysis of short chain length species. Mass spectro-

metric approaches, alternatively, can often be hindered by the polar nature, low thermal stability, complexity, and large molecular weights of oligonucleotides (5), which can hinder the ability to obtain good spectra and thus make clear assignments on mass and sequence.

Advancements in high-resolution mass spectrometry and in particular, tandem methods (MSMS), have provided a viable alternative for the determination of both mass and sequence of oligonucleotides. When considering intact mass, normal resolution instrumentation can only be used to obtain the average molecular weight; high-resolution mass spectrometry has, however, facilitated the determination of accurate mass. This method is based on obtaining negative ion spectra of the oligonucleotide followed by deconvolution. The accuracy of these measurements is typically less than 5 ppm, and as such, the mass can be used as an aid to establishing the empirical formula of the molecule, which is in turn used to postulate or confirm structure (6).

Such high resolution readily allows discrimination of nucleosides differing by only 1 mass unit, such as Cytidine monophosphate (CMP) (monoisotopic mass 323.05185 Da) and Uridine monophosphate (UMP) (monoisotopic mass 324.03587 Da), including distinguishing between the ^{13}C isotope of CMP and ^{12}C isotope of UMP, which effectively have the equivalent mass at a lower resolution (324 Da).

Quinn *et al.* (7) also detailed how tandem MS can be used to confirm the presence of truly isobaric nucleosides, such as Adenosine monophosphate (AMP) and Deoxyguanosine monophosphate (dGMP), both of empirical formula $C_{10}H_{14}N_5O_7P$ and a monoisotopic mass of 347.06308 Da). In discrimination between species of this type, structural differences are relied upon for definitive identification. In the case of AMP and dGMP, for example, the position of the oxygen atom differs, which can be distinguished by MS analysis and thus allow these isobars to be distinguished.

The benefit of these advanced MS-based methods is further demonstrated when considering identification of the position of modified nucleosides, a feature that could not be established from the earlier digestion/chromatography approaches.

Chain length

Despite improvements in the automation and understanding of the chemistries involved in oligonucleotide synthesis, and despite the most ardent post synthesis clean-up, it is inevitable that there will be some heterogeneity with regards to chain distribution in the final material. Monitoring of this distribution presents a further fundamental aspect of quality control.

Table I: Characterization of oligonucleotide drug substance.

Criteria	Analysis	Methodology
Description and physiochemical characteristics	Molecular weight	Mass spectrometry Size exclusion chromatography (SEC)
	Optical rotation (to clarify that stereochemistry is controlled)	
	pH	
	Moisture content	
	pKa	
	Hygroscopicity	
Assay/impurities	Assay	High-performance liquid chromatography (HPLC)
	Counter ion	Inductive coupled plasma (ICP) Atomic absorption (AA)
	Duplex content	SEC
Structure	Sequencing	Enzymatic method (e.g., Sanger) Chemical method (e.g., modified Maxam Gilbert) Enzymatic digestion followed by mass spectrometry (MS)
	Nucleobase composition	Enzyme digestion and HPLC of nucleosides. For enzyme-resistant oligonucleotides, transformation may be required; however, in these cases, the process should be shown not to affect other parts of the molecule.
	Melting temperature (T_m)	Nuclear magnetic resonance (NMR) Circular dichroism (CD)
	Chain length	Capillary gel electrophoresis (CGE) Polyacrylamide gel electrophoresis (PAGE) analysis
	Internucleoside Linkage	^{31}P NMR for assessment of phosphodiester, phosphorothioate, methlyphosphonate, and any other modified phosphate
	Molecular backbone composition phosphorothioate to phosphatediester (PS/PO) ratio	^{31}P-NMR plus strong anion exchange (SAX)–HPLC
	Chromatographic profile	HPLC SAX (for phosphorothiates)
	UV spectra	Lambda max and min for acidic, basic, and aqueous solutions. Determination of extinction coefficient
	Spectroscopic profile including stereochemistry	Fourier transform infrared spectroscopy (FTIR), ^{1}H-NMR, other NMR

The most accepted methodologies for performing this assessment are capillary gel electrophoresis (CGE) and anion exchange–high-performance liquid chromatography (SAX–HPLC), given both methods' inherent ability to separate truncated species. Each approach offers advantages over the other. CGE methods require little or no development to reach maximum performance and can generally be applied to larger oligonucleotides without loss of resolution over that can be prevalent with the HPLC approach. Alternatively, SAX–HPLC methods are generally more reproducible, the columns last longer, and the response of and amount of loading into the instrument are not affected by species of differing mass to charge ratios (8).

Internucleoside linkages

Introducing modification to a nucleoside linkage has been a critical feature in the advancement of oligonucleotide therapeutics. Such alterations help to overcome the two main challenges affecting the efficacy of these molecules, specifically, delivery to the target *in vivo* and increasing bioavailability. An example of the effect of this engineering is that introduction of phosphorthioate linkages increases resistance to nucleases, but the incorporation of too many bonds can reduce the function of the species.

Modifications are, however, a necessity, and as such, powerful techniques that allow continued monitoring of the distributions are required. SAX–HPLC and nuclear magnetic resonance (NMR) spectroscopy, in

particular ^{31}P NMR, provide powerful data in this respect to monitoring linkage. SAX–HPLC is particularly useful where quantitation is required (i.e., discrimination of the amounts of phosphate diester [P=O] or phosphorothioate diester). ^{31}P NMR can yield powerful data about the type of internucleoside linkers (phosphodiester P=O, phosphorothioate P=S, methyl phosphonate, phosphonate, or any other modified phosphate), the nucleobase, and oligo backbone composition. NMR also provides information on the ratios of various species such as that between the P=O and P=S; however, this technique is restricted to ratio and other techniques needed to give true amounts.

Melting temperature (T_m)

Melting temperature is often considered the most critical quality attribute of an oligonucleotide. This property relates to the temperature at which a double-stranded oligo denatures and separates into two single strands. The melt temperature, or T_m, is defined as the temperature at which 50% of the molecule is double stranded and 50% single stranded, also known as the molecule being classed as 50% annealed. Critically, T_m can be influenced by external factors, such as salt concentration, the presence of denaturants, and hybridization conditions. Altering the T_m by manipulating external or environmental factors is often used to increase solubility of a product or to enhance *in-vivo* stability of the material.

Many algorithms exist for determination of theoretical T_m. These theoretical values aid product development. For determination of actual T_m, however, NMR and circular dichroism (CD) provide the best methods for establishing the T_m of an oligonucleotide.

In addition to confirmation of core structural and physiochemical features, continued monitoring of the purity and levels of product- and process-related impurities presents a fundamental attribute for oligonucleotides in continued quality control.

Impurities determination

In addition to confirmation of core structural and physiochemical features, continued monitoring of the purity and levels of product- and process-related impurities presents a fundamental attribute for oligonucleotides in continued quality control.

Product-related impurities include the following:

- Addition sequences (n+1, n+2, etc.)
- Deletion sequences (n n-1, n+2, etc.)
- Phosphodiester analogs
- Depurinated sequences
- Partially deprotected sequences
- Aggregated sequences.

When considering impurities involving addition or deletion of sequence, the methods of choice are SAX–HPLC or CGE, when considering chain length. For the other potential product-related species, a combination of chromatographic and spectroscopic methods are applied to cover all relevant components.

Aside from product-related impurities, residual species originating from the process require monitoring, and if necessary, specifications set. Such species include:

- Organic volatile impurities (OVI) or residual solvents, typically quantified by gas chromatography (GC) with flame ionization detection (FID) or mass spectrometry (MS)
- Inorganic molecules metals, inorganic salts, catalysts, cleavage reagents, and counterions typically quantified by inductively coupled plasma (ICP), MS, or OES.

Conclusion

In support of continued quality control of oligonucleotide therapeutics, a vast array of analytics is required to comprehensively control structural, physiochemical composition, as well as the purity and impurities of the test material. Looking forward, some of the challenges facing the resurgence in these therapies and the growing pipeline of oligonucleotides can be effectively addressed through application of these sophisticated analytical approaches and continued advancements in analytical technology.

References

1. A. Aartsma-Rus, *Molecular Therapy* 24 (2) 193–194 (2016).
2. R.L. Juliano, *Nuclei Acids Research*, published online April 15, 2016, doi: 10.1093/nar/gkw236
3. B2B Labs, Oligonucleotides: Opportunities, Pipeline and Challenges, http://b2blabs.com/2016/06/oligonucleotides-opportunities-pipeline-challenges/, accessed Dec. 12, 2016.
4. Rao V.B. Kambhampati, Points to Consider for the Submission of Chemistry, Manufacturing, and Controls (CMC) Information in Oligonucleotide-Based Therapeutic Drug Application, presentation at DIA Industry and Health Authority Conference on: Oligonucleotide-based Therapeutics (Bethesda, MD, April 2007).
5. M. Smith, *Rapid Commun Mass Spectrom.* 25 (4) 511-25 (2011).
6. R. Houghton, "Oligonucleotides: The Next Big Challenge for Analytical Science," *Chromatography Today,* March 2011.
7. R. Quinn et al., *Mass Spectrom.* 48 (6) 703–712 (2013).
8. Analysis of Synthetic Deoxyoligonucleotides by Anion Exchange HPLC and Capillary Gel Electrophoresis, Waters Cooperation, poster at the 16th Annual Symposium of Column Liquid Chromatography (June 1992). **PT**

A Statistical Decision System for Out-of-Trend Evaluation

Niels Væver Hartvig and Liselotte Kamper

The authors present a set of statistical decision rules based on linear regression models that can be implemented in an automated trend system to assist stability studies. The models combine historical stability and analytical method data with data from stability studies, and allow the responsible person to routinely evaluate stability results based on statistical tools, without the need for expert statistical assistance. The system provides a fast and standardized framework for evaluating parameters that approximately follow a linear degradation path or are constant.

***Niels Væver Hartvig**, PhD, is a principal specialist, nvha@novonordisk.com, tel.: +45 30790913, and **Liselotte Kamper** is a chemist, both at Novo Nordisk A/S, Smørmosevej 17-19, DK-2880 Bagsværd, Denmark.

Submitted: Feb. 22, 2016. Accepted: Apr. 7, 2016.

Evaluation of data from stability studies is a central part of the control strategy of pharmaceutical products and is a GMP requirement (1). The purpose is to ensure the safety and efficacy of the product by confirming that the stability is as expected and that it will continue to meet quality specifications until expiry. Stability studies can be part of the development program for new products or the ongoing stability program for marketed products. The studies are typically conducted both at long-term storage conditions and at accelerated conditions.

For stability studies on marketed products, the objective is to confirm that the stability profile follows the trend of earlier batches. Unexpected results may either indicate that the batch is out-of-trend or that the result is out-of-trend (OOT). A typical approach to evaluate the data is to consider the following three questions (2):

- Is the latest result within the expected range, or is the result substantially different from what is expected? The latter is known as an *analytical alert* and would usually be related to the analytical procedure or the handling of the stability sample, and more rarely to the actual stability of the product.
- Does the stability of the batch follow the expected trend compared to historical stability data? Or are there indications that the batch degrades in a different manner than observed earlier, which could indicate a special cause event has occurred in the production of the batch? This is known as a *process control alert* and will often lead to the conclusion that the batch is OOT.
- Will the product comply with specifications throughout the shelf life? In the event of a process control alert, the batch is known to deviate from the historical expectations. The stability should be examined and evaluated to ensure that the batch stays within the specifications. When this stability is questionable, a *compliance alert* is raised.

The evaluation can be performed subjectively by an analyst, but it requires long experience with the analytical method and the product and its distinct properties. Also, different analysts or different laboratories may conduct the trending; they may have different experience and evaluate the data differently as a result. However, an

SHIMADZU
Excellence in Science

Nexera UC
Unified Chromatography

Unifying SFE/SFC Workflows

Sample Prep to Analysis in One Click

Nexera UC on-line SFE-SFC is the first system to break the technology barrier between automated sample pre-treatment and chromatographic analysis using supercritical mobile phase.

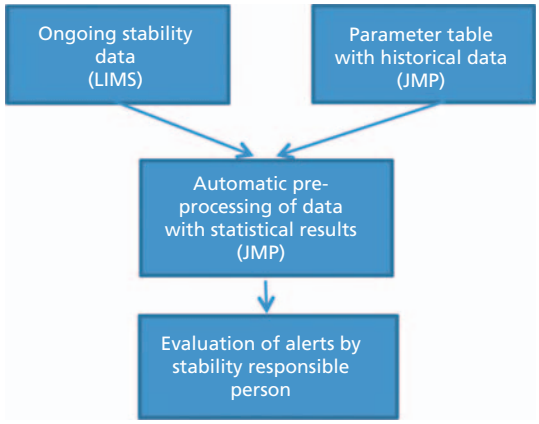
Learn more about Shimadzu's Nexera UC.
Call (800) 477-1227 or visit us online at
www.ssi.shimadzu.com/UC

Order consumables and accessories on-line at http://store.shimadzu.com
Shimadzu Scientific Instruments Inc., 7102 Riverwood Dr., Columbia, MD 21046, USA

Automatic extraction of up to 48 samples with seamless transfer to SFC/MS provides:

- Rapid separation harnessing the unique characteristics of supercritical mobile phase
- Efficient separation of isomers and enantiomers
- High-sensitivity detection using a variety of separation modes
- Split-less introduction to MS for enhanced trace analysis
- Reduced environmental impact and mobile phase cost compared to typical organic solvents

Figure 1: Illustration of the trend system. LIMS is laboratory information management system, JMP is the computer program by SAS Institute.



objective evaluation requires data from different sources to be combined, namely the precision of the analytical method and the stability trend of historical batches and their associated uncertainty, and this is a burden both practically and statistically.

Statistical tools can control the risks of false alarms, when the product and result are actually within the expected range, and the risk of overlooking an OOT. The factors of uncertainty that need to be considered are:

- How much historical data is available—how well is the expected slope determined?
- Are there historical batch-to-batch variations in the slope?
- What is the intermediate precision of the analytical method and how well is this determined?
- Is the variation in the current stability study comparable to historical intermediate precision, and if so, what is the combined estimated precision?
- How much data are available in the current study?
- How much confidence is there in the predicted value of the batch when extrapolating to end-of-shelf life?

Unless a system is in place that facilitates the combination and statistical evaluation of data in an automated and standardized manner, the evaluation of stability data will be laborious and may require expert statistical assistance, which is usually not readily available at all the facilities where data are generated and evaluated.

A number of different approaches for evaluating stability data from a statistical perspective have been proposed in recent years (2–5). In this paper, the authors consider only parameters that follow a linear stability trend (or are constant). In this approach, the analysis is based on linear regression models that combine the efficiency of a parametric statistical model with the practical aspect of being relatively simple and intuitive.

From the authors' experience, the vast majority of parameters that are followed in stability are approximated well by zero or first-order kinetic reactions, which lend themselves to linear regression analyses. Parameters that do not develop linearly must be evaluated, for instance, by tolerance interval methods by time point (3), or by more advanced kinetic models of the stability profile. These methods will not be considered here.

An overview of the system is provided in the following sections. Statistical details are deferred to the appendix.

System setup

The system is illustrated in **Figure 1**. The system supports a work flow where the stability responsible person routinely evaluates and releases results in a stability study as they are available. Stability data is stored in a laboratory information management system (LIMS). To evaluate the trend questions discussed in the previous section, historical data and data on the analytical variability of the method are needed. These data are stored in a database with tables for each product.

The combination of the two data sources and the statistical analysis and presentation of results is implemented in a computer program (JMP, SAS Institute) (6), but other systems for data analysis and visualization can be used. The evaluation of results and alerts is conducted on a computer screen.

The parameter table with historical data

Historical stability data is summarized in a parameter table (see **Table I**) for each product. The table should be based on batches and results that are representative of the current product and analytical methods.

The parameter table should be established based on statistical analysis of historical stability data that are representative of the current product. For new products, typically data from the new drug application (NDA) stability studies and other development stability studies will be used. For marketed products, the body of historical routine stability data can be used.

The analysis of the historical data should be based on a regression analysis, in which the average stability trend is determined. In the model, each batch should have its own intercept to account for batch-to-batch variation in the starting level. If the stability slope varies slightly from batch-to-batch due to random variations, for instance in raw materials or input factors, a mixed model with random slopes can be used (5).

The intermediate precision of the analytical method should preferably be estimated as the residual variation in historical stability data, because this estimate will cover long-term variation in the method and also any other variation in stability studies, for instance, due to sampling and handling of the samples. Alternatively, method validation data or variation in control samples can be used.

The construction of the parameter table is typically a large task and may require a cross-functional team

GEMÜ®

VALVES, MEASUREMENT AND CONTROL SYSTEMS

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*

550 Globe valve with 1434 positioner

Multiport

4212 Switch

650 Diaphragm valve with 4242 switch

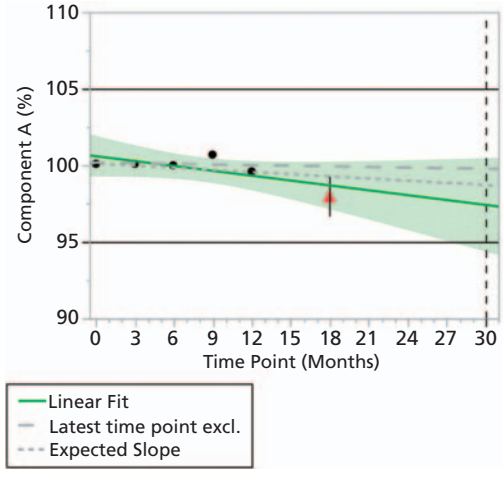
3800 Camp Creek Parkway • Building 2600 • Suite 120
Atlanta, GA 30331 • info@gemu.com • Tel: 678-553-3400

www.gemu.com

Table I: Information on specifications and historical data contained in the parameter table. The information is provided for each parameter and storage condition.

LSL	Lower specification limit
USL	Upper specification limit
Shelf life	Expected shelf life (months)
Expected slope	Expected stability slope in absolute units per month. This value is the estimated average slope from historical stability data from representative batches.
Std. err. slope	Standard deviation of the expected slope (in units per month). This value represents the uncertainty of the estimated slope and optionally also historical batch-to-batch variation in the slope.
Intermediate precision	Intermediate precision of the analytical methods in absolute units. This can be estimated as the residual variation in historical stability data, or alternatively, the analytical method validation study can be used.
D.f.	Degrees of freedom of the intermediate precision estimate. This depends on the number of results used to determine the intermediate precision.

Figure 2: Example of the graphical illustration of an analytical alert. The latest result is marked with a red triangle, because it, with high confidence (99%), does not follow the trend of the five previous results (marked with a dashed grey line). The vertical bar at the latest result indicates ±3 times the standard deviation of the analytical method



of analytical chemists, product responsible chemists, and statisticians. It is advisable to ensure careful documentation and control of the parameter table because it is the cornerstone of the stability trend evaluation.

Generally, the parameter table need only be established once for each product, but it may be necessary to update the table over time if there are changes to the stability profile of the product or to the analytical methods, or if the initial parameter table is based on a relatively small body of stability data and more precise estimates are obtained over time.

The parameter table summarizes all the historical knowledge of the product and the analytical methods in a single table. Thus, there is a wealth of information in the table, and the creation of the table ensures that the expectation of the stability study is clear across the organization. By using the same parameter table for trending, consistency in the evaluation of the data across persons, departments, and sites is ensured, which is an important benefit of the system.

Routine trend evaluation

When conducting routine trending, stability data are retrieved from the LIMS and combined with the parameter table. The system processes the data and presents a graph for each parameter, batch, and storage condition. The graphs illustrate the data and summarize the statistical evaluation of the three trend questions.

Is the latest result comparable with the results previously seen for the same batch in the study?

This trend is evaluated by a prediction interval based on the stability results for each batch, excluding the latest result. If the latest result falls within the prediction interval, it can be concluded that it follows the trend seen so far, within the expected uncertainty range.

Typically, a 99% prediction interval will be used to have a reasonably low risk (1%) of a false alarm. This interval corresponds approximately to ±3 standard deviations around the expected value.

The historical stability slope in the parameter table is not used in this evaluation, but the historical intermediate precision of the method is used to calculate the variance of the result.

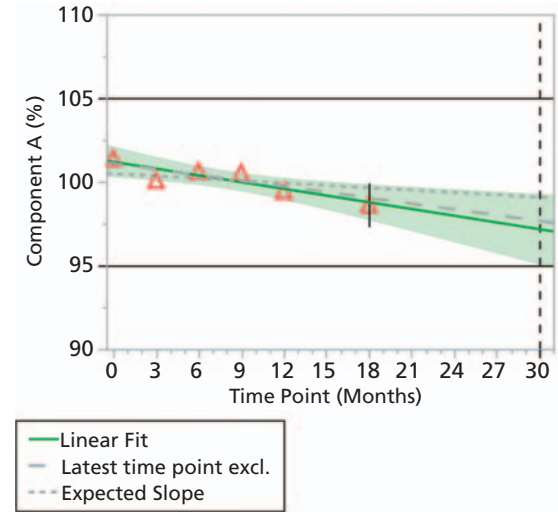
The result of the analysis is indicated graphically by plotting the data with the regression line, calculated with the latest result excluded, and by overlaying ±3 standard deviation error bars on the latest result. This approach provides a simple visual check for whether the result is within the expected range. The conclusion of the statistical analysis is illustrated visually by plotting the latest

result with a red symbol, if the result is outside the 99% prediction interval. An example is provided in **Figure 2**.

Is the development of the parameter comparable to the development of the same parameter in historical studies? This trend is addressed by a regression analysis, in which the estimated slope of the current batch is compared with the expected slope from the parameter table. Based on a t-test, the statistical significance of any difference can be assessed, accounting for the uncertainty of both the current estimated slope and the expected slope. The uncertainty of the expected slope can express both estimation uncertainty and, if relevant, random batch-to-batch variation in the slope (5). Typically, a significance level of 1% will be used to avoid too many false alarms, corresponding to the 99% intervals used above.

The result of the analysis is indicated graphically by plotting the regression line for the batch (the green line in **Figure 3**) as well as a line with the expected slope (dotted line in **Figure 3**). If a statistically significant difference is observed, all points can be plotted with a separate color to provide the stability responsible person with a clear visual indication that this statistically significant difference needs to be evaluated and possibly investigated further.

Figure 3: Example of a graphical illustration of a process control alert. The results of the batch are indicated with open red triangles to indicate that the slope of the batch is statistically significantly lower than the slope of historical batches at a 1% significance level (indicated with the dotted grey line). The statistical significance evaluation includes both the uncertainty of the slope of the current batch and the standard deviation of the historical slope estimate.



Can compliance with the specification limits be expected to be maintained until the end of study? This analysis is conducted following the principles in (7) by evaluating if the 95% confidence interval for the batch intersects the specification limit before the end of shelf life. A one- or two-sided confidence interval is used depending on whether the specification is one- or two-sided, respectively.

If the batch is confirmed to be OOT and there is less than 95% confidence that it will comply with the specification during shelf life, a compliance alert is raised (see **Figure 4**). The evaluation of criticality is not only a statistical exercise, but the statistical result may be used to evaluate the effect of reducing shelf life or other mitigations.

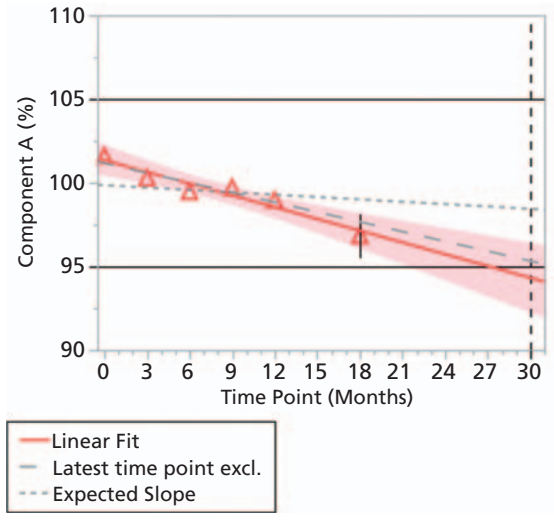
Practical use of the system

In the practical use of the system, all data for a given time point are evaluated and a graphical overview of the different parameters, batches, and storage conditions presented. The graphical illustrations of alerts make it easy to get an overview of the data. In case one or more alerts are identified, summary tables with estimates and statistical details are available to interpret the findings.

When evaluating alerts, the trend responsible person should be aware of a number of pitfalls and understand the limitations of the methods used:

- **Rounded and truncated results:** The trend analysis requires data with sufficient resolution. In particular, impurity data are often rounded to one decimal and truncated when they are below the limit of quantification. It is important that a database with the unrounded results is available for the trend analysis; if not, the trend system may not analyze impurity data correctly.
- **Non-linear trend:** The system assumes a linear trend over time (or no trend). This approach is typically reasonable, but complex biological reactions or physical parameters are not necessarily linear. In this case, the results of the system should be interpreted with much care, and trending may need to be conducted by other methods, for instance, the by-time-point method (2).
- **Multiplicity:** A number of statistical tests are conducted for each time point. For instance, if three batches are followed at three different storage conditions and five parameters are evaluated for each, a total of 45 tests are conducted. With a significance level of 1% for each test, there is a risk of $1-0.99^{45}=36\%$ of at least one false alert. Because there is no correction for this risk, it is important that the stability responsible person is aware of the risk of a false alert and uses good judgement when evaluating alerts.
- **Independent results:** It is an assumption in the analysis that all results are independent. When this is not the case, for instance, if two determinations are obtained in the same analytical run, there is a risk of over-interpreting findings and getting too many false alarms. The correlation between multiple results can be handled statistically using random effects models, but this method is difficult to automate in a system like this.

Figure 4: Example of a graphical illustration of a compliance alert. The trend line and 95% confidence region is colored red to indicate a process control alert, because the slope of the batch is significantly different from historical batches, and a compliance alert is issued because the confidence interval intersects the specification limit of 95% before end-of-shelf life (here 30 months). The confidence region for the slope is based on the data from the actual batch only.



- **Only the latest result is evaluated:** Previous OOT results in the same study should be excluded before the analysis; otherwise, these previous OOT results may mask new OOT results. The system supports a work flow where the OOT evaluation is conducted routinely after each result, and, therefore, only the latest result is evaluated.
- **Patterns across batches:** The system analyzes each batch, parameter, and storage condition separately, giving a relatively simple framework, but it means that patterns across similar batches or storage conditions are not discovered. These patterns must be evaluated subjectively or by more advanced statistical analyses in specific cases.
- **Number of results available.** The system can, in principle, estimate the stability slope based on two results, using the historical standard deviation as an estimate of the residual variation in the data. But clearly, the analysis will have low sensitivity until more time points are available.

The computer system should be validated for GMP-use. However, by building the system on existing validated computer systems, the validation effort is relatively smaller than if the system was built from scratch.

Comparison with other methods

As discussed, the methods presented rely on linear trend models with normally distributed errors. They are, therefore, less general than OOT methods that do not rely on these assumptions, such as the "change-from-previous" type methods and by-time-point methods presented in references 2 and 3, but they provide a simpler and more efficient setup when the assumptions are fulfilled.

The methods can be compared with other published regression methods as follows:

- **Analytical alert:** The method presented here is very similar to the regression control chart method (3–5) based on a prediction interval. A difference, however, is that the authors' method uses a pooled variance based on the historical variance and the variance in the present study. This approach will increase the power of detecting an OOT, provided that the variation in the historical data is comparable to that of the current study. If the historical variance is not entered in the parameter table, the authors' test simplifies to the regression control chart method.
- **Process control alert:** The method presented compares the slope of the current batch with the average slope of historical batches by a t-test, allowing for uncertainty in the estimated slopes and random batch-to-batch variation in the historical slopes. As such, the interpretation of the test is similar to the slope-control chart method (3), though the statistical framework is slightly different. If the standard error of the historical slope accounts for uncertainty in the slope only, the method is similar to the test for poolability of batches (7), except for the fact that all the historical batches are pooled before comparison with the current batch and the fact that a pooled variance is used in the test. If the standard error of the historical slope includes random variation between batches, the framework is similar to the random coefficient regression (6), where the model is used to set limits for individual results.
- **Compliance alert:** The method presented is the same as used in reference 7, where batches are not pooled and each batch is thus considered individually.

Conclusions and further development

The trend analysis system provides the trend responsible person with exact and reproducible results for evaluating stability data. It makes the evaluation of data objective and standardized, and provides greater flexibility in terms of who does the trending.

The system provides valuable summary measures for each batch, such as the estimated slope with confidence limits, a statistical test for whether the batch is comparable with historical batches, and the expected shelf life based on extrapolation of confidence intervals. The system makes it easy to account for the different sources of uncertainty in the evaluation of the data and thus provides control over the risk of false alarms and the risk of overlooking an OOT.

The system is relatively simple to implement, validate, and maintain, and can be based on a statistical software

YOUR EAST COAST PACKAGING CONNECTION

Come to **PACK EXPO East 2017** to connect with the packaging industry's biggest innovators and see their latest technologies in action.

- Investigate 400+ top suppliers' solutions in depth.
- Inspire your team and give your brand a competitive edge by exploring nearly 100,000 nsf of ideas.
- Interact with 7,000+ peers from food and beverage, pharma, personal care, household and other industries.

REGISTER TODAY AT
PACKEXPOEAST.COM

PACK EXPO® East

February 27–March 1, 2017
Philadelphia, PA USA

Produced by: PMMI

package such as JMP and existing database solutions, such as LIMS. The statistical methods strike a reasonable compromise between being relatively simple, based on linear regression model for each batch, yet sufficiently complex to handle, for instance, mixed effect models with random variation in the slope between batches.

Generating the database of parameter tables for all products requires analyses of historical data. Though this effort is a prerequisite for conducting a trend analysis, whether a trend system is used or not, the practical work of establishing, documenting, and maintaining the parameter tables in a system such as this should not be underestimated.

The system is not designed to encompass all parameters, and some level of "manual" trending should, therefore, be expected even with this system. Parameters that do not follow a linear pattern or ordinal responses cannot be analyzed by the system currently. Also, impurity data that are truncated below limit of quantification may need to be trended by other methods. One could extend the system, for instance, by including functionality for transforming responses to linearize the trend, or to include tolerance intervals methods. Still, it is important that the results of the analyses are intuitive and easy to interpret, and this feature should be a cardinal point when extending the system.

Acknowledgement

The system has been developed by a team of stability responsible persons in Novo Nordisk. In particular, the authors acknowledge valuable discussions and input from Marika Ejby Reinau, Jens Krogh Rasmussen, Helle Lindgaard Madsen, Lone Steenholt, Carsten Berth, and Karin Bilde.

References

1. EudraLex, *The Rules Governing Medicinal Products in the European Union,* Volume 4, Chapter 6.
2. PhRMA CMC Statistics Stability Expert Teams, *Pharm. Technol.,* 29 (10), 66 (2005).
3. PhRMA CMC Statistics and Stability Expert Teams, *Pharm. Technol.* 27 (4), 38–52 (2003).
4. A. Torbovska and S. Trajkovic-Jolevska, *Pharm. Technol.,* 37 (6), 48 (2013)
5. ECA, *Laboratory Data Management Guidance; Out of Expectation (OOE) and Out of Trend (OOT) Results* (draft, Aug 15, 2015).
6. JMP Statistical Software, SAS Institute Inc.
7. ICH, Q1E, *Evaluation for Stability Data* (Step 4 version, 2003).

Appendix: Statistical details

The following section contains the statistical details.

Consider data from a single parameter, a single batch at a single storage condition. Let $Y_1,\ldots,Y_n$ be the results available for analysis and let $x_1,\ldots,x_n$ denote the corresponding storage time in months. For simplicity, it is first assumed that only a single result is obtained per time-point, and that x_n is the latest time point.

The underlying statistical model is a linear regression model,

$$Y_i = \alpha + \beta x_i + \varepsilon_i,\ \varepsilon_i \sim N(0, \sigma^2),\ i = 1,\ldots,n$$

with all observations independent. Let $\bar{x}$ and $\bar{Y}$ denote the averages,

$$\bar{Y} = \frac{1}{n}\sum_{i=1}^{n} Y_i,\quad \bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i,$$

and let SPD_{Yx} and SSD_x be given by

$$SPD_{Yx} = \sum_{i=1}^{n} Y_i(x_i - \bar{x}),$$

$$SSD_x = \sum_{i=1}^{n} (x_i - \bar{x})^2.$$

The maximum likelihood estimates of the parameters α and β are then given by

$$\hat{\beta} = \frac{SPD_{Yx}}{SSD_x} \sim N\left(\beta, \sigma^2 \frac{1}{SSD_x}\right),$$

$$\hat{\alpha} = \bar{Y} - \hat{\beta}\bar{x} \sim N\left(\alpha, \sigma^2\left(\frac{1}{n} + \frac{\bar{x}^2}{SSD_x}\right)\right),$$

and the residual variance σ^2 is estimated by

$$s^2 = \frac{1}{n-2}\sum_{i=1}^{n} (Y_i - \hat{\alpha} - \hat{\beta}x_i)^2 \sim \sigma^2\chi^2(n-2)/(n-2).$$

Evaluation of shelf life

The (1-α)-confidence limit for the regression line at time point x is given by

$$\hat{\alpha} + \hat{\beta}x \pm t_{1-\alpha/2,n-2}\, s\sqrt{\frac{1}{n} + \frac{(x-\bar{x})^2}{SSD_x}},$$

where $t_{p,f}$ is the upper p-quantile of the t-distribution with f degrees of freedom, and s is the square-root of the estimated residual variance s^2.

The estimated shelf-life is established by looping over values of x and determining the largest x where both the upper and the lower 95% confidence limits are within the specification limits.

If the specification is two-sided a two-sided 95% confidence interval is considered by setting $\alpha = 0.05$. If the specification is one-sided, a one-sided 95% confidence interval is calculated by setting $\alpha = 0.1$.

Pooling of variances

For the OOT-tests a pooled variance is used,

$$s^2_{pool} = \frac{(n-2)s^2 + f_{ip}s^2_{ip}}{f_{pool}},$$

$$f_{pool} = n - 2 + f_{ip}.$$

Here s^2_{ip} is the intermediate precision variance and f_{ip} is the degrees of freedom, both provided in the parameter table.

For early time points, *n-2* will be small, and the intermediate precision variance provided in the parameter table has to be used to conduct tests for OOT. In this case, s^2_{pool} will primarily be given by s^2_{ip}. On the other hand, for late results, the residual variance contains valuable information on the precision of the analytical method in practice. As n becomes larger, the residual variance will weigh increasingly more in the pooled variance. A prerequisite for pooling the variances is that the provided intermediate precision represents the current variation in the method.

When f_{ip} is set to missing in the parameter table, it is interpreted as $f_{ip} = \infty$ and therefore $s^2_{pool} = s^2_{ip}$. If s^2_{ip} is missing in the parameter table, only the residual variance is used, i.e. $s^2_{pool} = s^2$.

OOT test for slope

The test for whether the batch is OOT is based on the expected slope $\hat{\beta}_0$ and the standard error of this, s_0, both provided in the parameter table. It is assumed that the expected slope follows a normal distribution, $\hat{\beta}_0 \sim N(\beta_0, \sigma_0^2)$, where the normal distribution expresses the uncertainty of the expected slope and/or an expected batch-to-batch variation in the slope.

In the parameter table, the degrees of freedom f_0 for the standard error s_0 could be entered if relevant. It was found that in practice, this parameter was often difficult to obtain, and the degrees of freedom are, therefore, by default set to missing, which is interpreted as $f_0 = \infty$.

The OOT test for the slope is a t-test for the hypothesis: H_0: $\beta = \beta_0$. The t-test is given by

$$t = \frac{\hat{\beta} - \hat{\beta}_0}{\sqrt{\frac{s^2_{pool}}{SSD_x} + s_0^2}}$$

Under H_0, this will approximately be t-distributed with *f* degrees of freedom, where *f* is calculated by Satterthwaite's approximation

$$f = \frac{\left(\frac{s^2_{pool}}{SSD_x} + s_0^2\right)^2}{\left(\frac{s^2_{pool}}{SSD_x}\right)^2 / f_{pool} + \frac{s_0^4}{f_0}}.$$

Notice that when one or both of the degrees of freedom are infinite, some of the terms in the denominator will be 0. If both degrees of freedom are infinite, *f* will also be infinite, and *t* follows a normal distribution.

The p-value is calculated as

$$p = 2\left(1 - F_{t(f)}(|t|)\right),$$

where *F* is the cumulative distribution function of a t-distribution with *f* degrees of freedom.

OOT test for latest result

The OOT test for the latest result is conducted by first fitting the above model, but with the latest time point (x_n, Y_n) excluded. Let $\hat{\alpha}_{(n)}$, $\hat{\beta}_{(n)}$, $s^2_{pool,(n)}$ etc. denote the estimates thus obtained. If the latest result deviates significantly from the predicted value based on the previous data, $\hat{\alpha}_{(n)} + \hat{\beta}_{(n)}x_n$, it is an indication that the result is out-of-trend; either because of a laboratory error, an error in the handling of the sample, or for other reasons.

It is initially assumed that $Y_n \sim N(\mu_n, \sigma^2)$ and the test for OOT is then a t-test for the hypothesis H_0: $\mu_n = \alpha + \beta x_n$. The t-statistic is given by

$$t = \frac{Y_n - \hat{\alpha}_{(n)} - \hat{\beta}_{(n)}x_n}{\sqrt{s^2_{pool(n)}\left(1 + \frac{1}{n-1} + \frac{(x_n - \bar{x}_{(n)})^2}{SSD_{x,(n)}}\right)}}$$

which follows a t-distribution with $f_{pool,(n)}$-degrees of freedom.

Multiple results at each time point

When multiple results are given for one or more time points, it is assumed that all observations are independent. The analysis is conducted as described above, and an OOT test for the time point is conducted for each individual result. **PT**

Predicting Moisture Uptake in Solid-Dosage Packaging

Johan Remmelgas

Modeling tools help define storage and handling requirements for oral solid-dosage drugs.

In the pharmaceutical industry, considerable effort is made to develop products that are stable and have a long shelf life. It is well known that moisture uptake is the most common cause for a product failing to meet its specification (1), and during development particular attention is, therefore, paid to moisture. Uptake of moisture by oral solid-dosage forms, such as tablets or capsules, is well known to increase the mobility of chemical species, which causes an increase in the rate of degradation of the drug substance and an increase in the rate of production of undesired byproducts (2). Moisture can also have an effect on the physical attributes of the product, such as its drug release rate or appearance.

In cases where moisture causes an increased rate of degradation, it is possible to model the rate of reaction using an Arrhenius-like expression that also includes moisture (as shown, for example, by He *et al.* [3]). The parameters in this model can be determined using accelerated stability tests, as described by Waterman *et al.* (4, 5), and the amount of degradant can then be predicted provided that the temperature and the moisture content of the product or the relative humidity to which it is exposed are known. In this article, however, only moisture is considered, with the implicit assumption that this factor can be used to predict degradation.

The product may absorb moisture during handling and storage, and the fact that the product has adequate stability during its shelf life is demonstrated experimentally for a number of different packaging configurations at selected environmental conditions. Tablets in bottles can also absorb moisture during use by the patient, because bottles with a broken seal can have a much higher moisture permeability than sealed bottles and because the repeated opening and closing of a bottle to remove tablets may increase the rate of moisture transport into the bottle relative to a closed bottle. **Figure 1** shows how the moisture content of the product can change from the point of manufacture to the point of administration by the patient. Two cases are shown in **Figure 1**: one where the moisture content starts at a low value and then gradually increases during packaging, handling, storage, and use; and one where it is packaged in a consumer bottle with a desiccant so that it starts at a higher value but decreases almost immediately after it is packaged. As **Figure 1** shows, the moisture content of the product when it is administered by the patient can be controlled either by selecting the packaging components so as to include a desiccant in the container or by introducing a drying or conditioning step in the manufacturing process so that a desiccant is not required. To develop a supply chain that is cost effective and guaranteed to deliver a high-quality product to the patient, it is therefore of interest to consider moisture uptake during the entire lifetime of the product.

Outlining the constraints on the supply chain from the point of view of stability is not straightforward because there are a number of unknowns. Fortunately, by examining the overall process and by introducing predictive models for each stage, it is easier to understand what parameters are important and to what extent they can be expected to affect the quality of the product. In this article, it is shown how simple experiments along with simple modeling tools can be used to help define requirements for storage and handling in the end-to-end manufacturing process and supply chain.

Using predictive tools to define the packing and handling process

As shown in **Figure 1**, the product may absorb moisture during packing, during storage in bulk and consumer containers,

Johan Remmelgas is associate principal scientist in Manufacturability, Pharmaceutical Technology & Development, AstraZeneca, Gothenburg, Sweden.

From Bench to Clinic:
Preclinical and First-in-Man Drug Development Strategies

BONUS CONTENT: Attend to receive a FREE executive summary of the webcast

ON-DEMAND WEBCAST Aired January 18, 2017

Register for free at

www.pharmtech.com/pt/Strategies

EVENT OVERVIEW:

Every year, hundreds of drug candidates are abandoned during preclinical testing studies. Physical characterization, salt selection and polymorph screening, and formulation become key enabling technologies for ensuring continued development. Preclinical-stage formulations drive meaningful efficacy and toxicity assessment by maximizing exposure. Once the compound passes preclinical assessment, focus shifts to choosing the right human dosage form.

For most early phase companies, reaching first-in-man quickly is critical, especially for companies with limited budgets or investor milestones tied to this step. Of equal importance is the company's choice of formulation strategy. A poorly formulated drug can lead to negative clinical data, severely tripping up development plans.

Over-development at this phase, however, can be just as detrimental when timelines and resources are tight. Therefore, an early phase development strategy should start with a thoughtful analysis of the drug substance, pre-formulation data, desired clinical outcomes, and the strategic goals of the company.

Join industry experts to discuss several factors that impact early phase development and clinical success. Discussion will include case studies and methods for developing a sound, phase-appropriate formulation with scientifically supportable data to help progress development to the next phase in a timely and cost-efficient manner.

Key Learning Objectives:

- Preclinical and first-in-man formulation strategies for oral and injectable drugs.
- Understanding how different formulation strategies contribute to the short- and long-term success of your compound.
- Compound characterization and preformulation techniques to elucidate the best path forward for a drug candidate and to access chemical and physical stability risks.
- Benefits and impact of physical characterization and salt selection and polymorph screening, on the druggability of a compound.

Presenters

Anthony Leone
Director, Preformulation
Merck

Nathan Barksdale
Scientist
Catalent

Dr. Pingyun (P.Y.) Chen, PhD
Director, Early Development
Catalent

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Who Should Attend:

- CEO & Presidents
- Director/VP Drug Development, CMC, Manufacturing, Analytical Development, Formulations or Formulation Development
- Director/VP Quality Assurance and Regulatory
- Technical Section Managers
- Principal Analytical Chemists
- Team Leaders
- Formulation Development Scientists
- Consultants for Drug Development, CMC, and Regulatory

Sponsored by

Catalent

Presented by

Pharmaceutical Technology

For questions, contact Kristen Moore at kristen.moore@ubm.com

Figure 1: Example of moisture content in a product during its lifetime. 1: Storage in internal bulk container, 2: Bulk packing process, 3: Storage in bulk packaging, 4: Primary packing process, 5: Storage in consumer container, 6: During use by end consumer. Solid line: the product has been dried in a final manufacturing step before any packing. Dotted line: desiccant dries product in the primary consumer container.

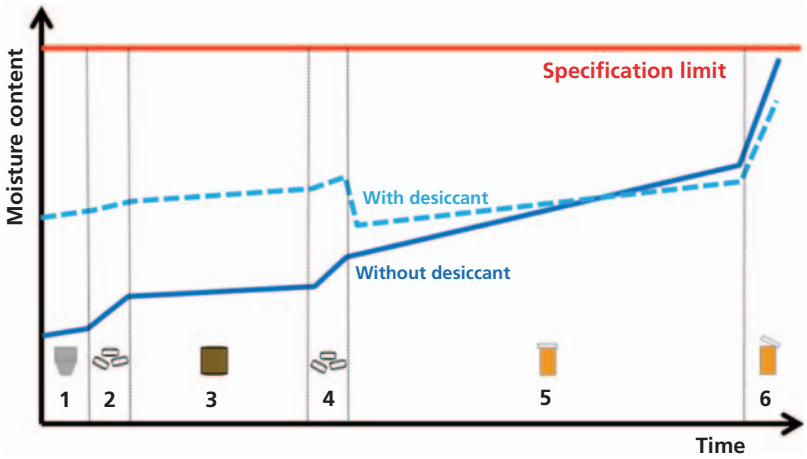
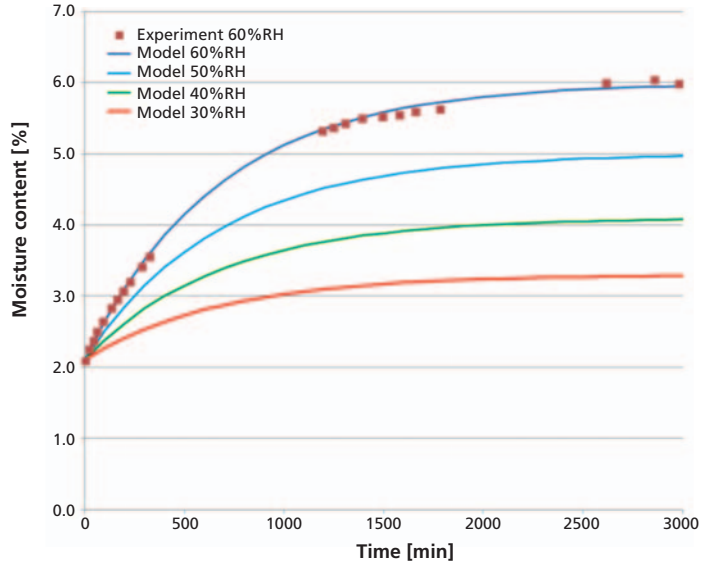


Figure 2: Measured and predicted moisture uptake of tablets during exposure. RH is relative humidity.



and during use by the patient. Moisture uptake by the product during these stages can be predicted using simple models.

Predictive model for water uptake due to exposure during packing

A simple and useful model for the moisture uptake of a product due to exposure during packing can be obtained by assuming that the rate of moisture uptake is proportional to the driving force for moisture uptake. The tablet moisture content, X_T, can thus be modeled using an ordinary differential equation (**Equation 1**):

$$\frac{dX_T}{dt} = k_T\left(X_T^* - X_T\right) = \frac{1}{\tau_T}\left(X_T^* - X_T\right) \quad \text{[Eq.1]}$$

where τ_T is the time constant for moisture uptake, which is closely related to the mass transfer coefficient k, and X_T^* is the equilibrium moisture content. The solution to **Equation 1** is given by **Equation 2**:

$$X_T(t) = X_T^* - \left(X_T^* - X_T^0\right)e^{-t/\tau_T} \quad \text{[Eq.2]}$$

where X_T^0 is the moisture content of the tablets before exposure. To determine the time constant for moisture uptake, a simple experiment may be performed that takes into account how the tablets are exposed. For example, in many cases tablets become exposed appreciably only when the packaging line has to be stopped during packing. If the tablets during this period have already been filled into bottles, the time constant for this mode of exposure may be characterized by measuring the weight increase of tablets in uncapped bottles in an environment with a known relative humidity. The experimental data can then be used to determine the time constant by fitting **Equation 2** to the data, as shown in **Figure 2**. Packing into blisters can be handled in a similar fashion.

To model moisture uptake in a climate with a different relative humidity, it is reasonable to assume that the major effect is a change in the equilibrium moisture content, and that a change in the relative humidity has a much smaller effect on the time constant. The dependence of the equilibrium tablet moisture content on the relative humidity can be obtained by performing a separate experiment to measure the moisture sorption isotherm. The model in **Equation 2** can then be employed to make predictions for any climate, as also indicated in **Figure 2**, and to construct a look-up table that shows the maximum exposure time that can be allowed for the moisture content not to exceed a critical value. **Table I** is an example of a look-up table for a case in which the initial moisture content of the tablet is 2% and the maximum allowed value is 4%.

As discussed previously, the experiment to determine the time constant should take into account the mode of exposure, and it can then be used to

ALL FIGURES ARE COURTESY OF THE AUTHOR.

Figure 3: Moisture uptake of tablets stored in a high-density polyethylene bottle with desiccant.

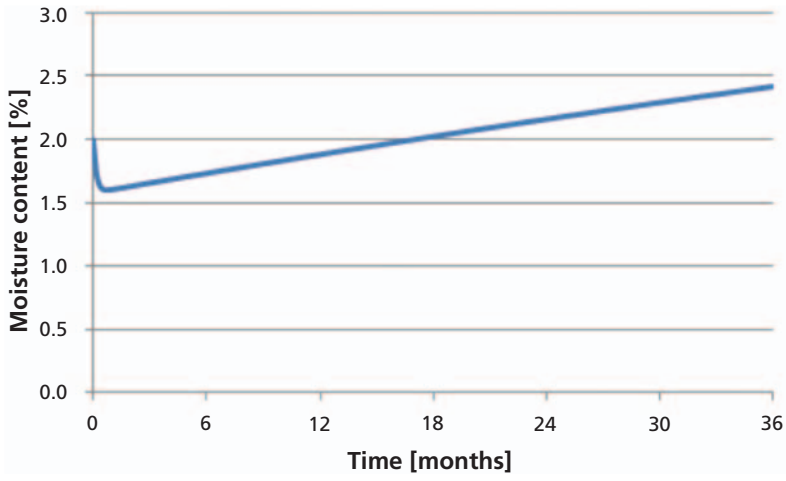


Table I: Look-up table for the allowed exposure time for a case in which the initial moisture content is 2% and the maximum allowed moisture content is 4%.

RH [%]	Max. exposure time [min]
45	1360
50	870
55	650
60	520
65	420
70	360
75	300

model a similar situation. The rate of moisture uptake by the tablet is determined by the rate of transport inside the tablet as well as the rate of transport in the air surrounding the tablet. Ideally, one should determine these rates independently and then employ a model to predict the combined effect. In the experiment outlined previously, the rate of moisture transport in the tablet can be expected to be much slower than the rate of transport to the tablet via diffusion in air. The result obtained from this simple experiment may thus serve as a useful approximation in describing the rate of moisture uptake in other situations, such as in the models for the moisture uptake of tablets in bottles or in bulk packages that are described in the following section. It is important to consider that the temperature can be expected to have an effect on this time constant.

Predictive model for moisture uptake during storage

Models for moisture uptake by packaged tablets during storage have been described by Chen and Li (6), Vaczek (7), Possumato (8), and Waterman and MacDonald (9). These models rely mainly on the sorption isotherm of the product and the moisture permeability. In one model, the relative humidity of the headspace, φ_H, and the moisture content of the tablets and the desiccant, X_T and X_D, respectively, are described using three ordinary differential equations (**Equations 3–5**):

$$\frac{M_W V_H p_{SAT}}{RT}\frac{d\varphi_H}{dt} = P p_{SAT}(\varphi_A - \varphi_H) - \frac{m_T}{\tau_T}(X_T^* - X_T) - \frac{m_D}{\tau_D}(X_D^* - X_D) \quad \text{[Eq.3]}$$

$$\frac{dX_T}{dt} = \frac{1}{\tau_T}(X_T^* - X_T) \quad \text{[Eq.4]}$$

and

$$\frac{dX_D}{dt} = \frac{1}{\tau_D}(X_D^* - X_D) \quad \text{[Eq.5]}$$

In **Equations 3–5**, M_W is the molar mass of water, V_H is the headspace volume, p_{SAT} is the saturation pressure, R is the gas constant, T is the temperature, P is the moisture permeability of the container, m_T is the mass of tablets, and m_D is the mass of the desiccant. In addition, X_T^* and X_D^* represent the equilibrium moisture contents of the tablets and the desiccant, while τ_T and τ_D represent the time constants for moisture uptake by the tablet and the desiccant.

In the context of this model, it may be noted that the time constants for moisture uptake by the tablets and the desiccant may be determined as described previously. It is not always necessary to include this detail because moisture uptake by the tablets is almost always much faster than moisture transport into the container. In addition, it is usually also possible to neglect moisture in the headspace of the container because the amount of moisture in the headspace is usually negligible compared to the amount of moisture in the tablets.

Along with appropriate parameters and initial conditions, **Equations 3–5** can be used to predict the moisture content of the tablets. One example of such prediction is given in **Figure 3**, which shows the moisture content of tablets packaged in a high-density polyethylene bottle with desiccant. The results show that the desiccant dries the tablets initially and that there is then a slow increase in the moisture content of the tablets due to the permeability of the bottle. In this context, it should be pointed out that the short-term predictions may not be entirely accurate because the model assumes quasi-steady moisture transport into the container; it is well known that there is an initial induction period during which this quasi-steady state is established.

Predictive model for bulk storage

Bulk storage differs from storage in consumer bottles mainly because the number of tablets per container is much larger in a bulk package, the

Figure 4: Computational fluid dynamics (CFD) model for prediction of moisture transport and uptake during bulk storage with a desiccant. The contour plot shows that the moisture content is lower near the desiccant pouch at this point in time.

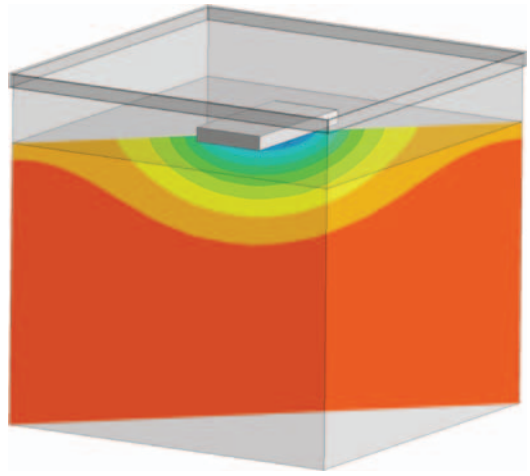
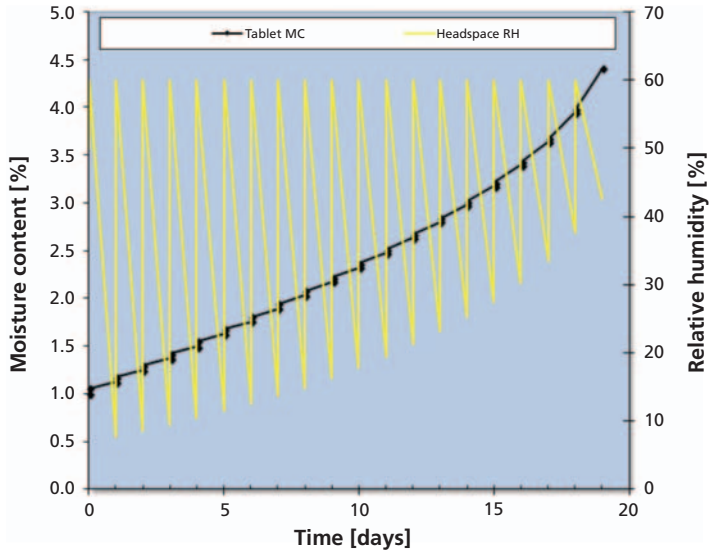


Figure 5: Example showing one possible scenario for the relative humidity in the headspace and the moisture content of the tablets during use.



type of packaging material differs, and the bulk package is larger than a consumer bottle. Because the time required to transport moisture a distance L by diffusion is proportional to L^2, moisture equilibration inside a bulk container is slower than in a small bottle. For bulk storage, it is therefore not always appropriate to assume that the tablets have the same moisture content throughout the container.

Fortunately, it is possible to develop models to predict moisture transport in bulk packages as well. In such a model, the bulk package can be considered to be a bed of tablets. Moisture transport can then be modeled as a diffusive process with volumetrically distributed sources/sinks to represent moisture uptake or loss by the tablets. A desiccant can also be included. Since diffusion of moisture in the air between the tablets is modeled explicitly, it is, in this case, important that the rate constants for moisture uptake by the tablets and the desiccant include only the transport resistance in the tablet/desiccant. An example of such a prediction is shown in **Figure 4**, which shows a contour plot of the tablet moisture content in a cross-section of a bulk container some time after the tablets have been placed in the container along with a desiccant pouch.

Predictive model for in-use moisture uptake

It is also possible to employ predictive tools for moisture uptake during use. One such model is described by Simonutti *et al.* and Remmelgas *et al.* (10, 11). The main feature of this model is to account for moisture that enters the bottle each time it is opened and the subsequent moisture uptake of the tablets between openings. This model requires information about the amount of air that is exchanged with the environment every time the bottle is opened and about the permeability of a bottle with a breached seal (which may be much higher than a for a sealed bottle). Beyond these two pieces of information, however, this model does not require any experimental data that has not already been discussed.

A likely scenario for this process is sketched in **Figure 5**, which shows that the relative humidity in the headspace fluctuates significantly due to opening and closing the bottle, whereas the moisture content of the tablets increases slowly (albeit more quickly than for a closed bottle). In this context, it is of interest to note that the rate at which the tablets absorb moisture increases as tablets are removed from the bottle because fewer and fewer tablets are left to absorb the incoming moisture (which also increases due to the increased headspace).

Simulating moisture uptake during the entire supply chain

These models can be put together to simulate moisture uptake by the product from the point of manufacture to the point when it is administered by a patient. This approach to modeling moisture uptake in the end-to-end manufacturing and supply chain may be used to specify requirements on the

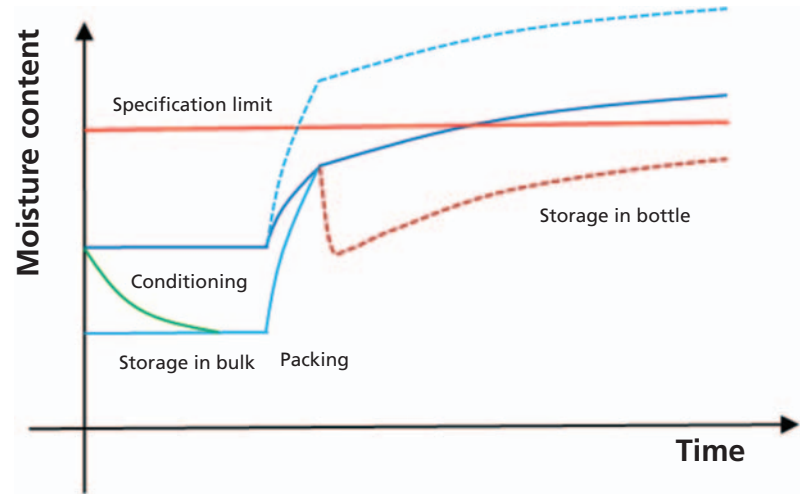
manufacturing process, any conditioning steps, the packing process, and the packaging configuration. For example, there is frequently a specification on the end-point moisture content, and this specification can be used to back-calculate the requirements on the supply chain, as discussed in the following paragraphs.

The dark blue curve in **Figure 6** shows a hypothetical example of a process for which the tablet moisture content is not within the specification limit after storage in a bottle. This situation will result in a substantial decrease in the shelf-life of the product unless a desiccant is included in the bottle, as indicated by the dashed red curve in **Figure 6**. It is straightforward to use prediction tools to select the amount of desiccant that will keep the moisture content below the specification limit. Such a predictive ability may be even more valuable for formulations in gelatin capsules because it is then necessary to also keep the moisture level above a certain lower limit to keep the capsule shells from becoming brittle.

The dark blue curve in **Figure 6** represents tablets manufactured and packaged in one facility. However, tablets are frequently manufactured at one site and packaged at another, and not all facilities have the same ability to control environmental conditions during packaging. The dashed light blue curve in **Figure 6** thus shows the moisture content of tablets that are packaged at a facility where exposure to a humid environment during the packing process increases the tablet moisture content beyond the specification limit. One solution to this problem is to simply not consider this site for packaging into consumer bottles. If tablets are, nevertheless, to be packaged at this facility, the tablets either have to be manufactured with a lower moisture content, as indicated by the solid light blue curve in **Figure 6**, or somehow conditioned so that their moisture content is lower before the packing process, as indicated by the green curve in **Figure 6**.

Although in the vast majority of cases, it is more practical and less expensive to manufacture tablets with a lower moisture content, it is not always possible. For example, tablets may not always be able to withstand the added handling that an extra drying step would imply. The green curve in **Figure 6** thus represents a conditioning step in which the tablets are packaged into bulk aluminum bags with a desiccant. In this case, it is important that all tablets have an acceptable and approximately the same moisture content after conditioning. A predictive model can be valuable in determining and justifying the necessary conditioning time and the required amount of desiccant. Conditioning using a desiccant is not a method of choice, but that is precisely the point: by considering moisture uptake and degradation during the entire supply chain one can design a process that is cost effective and guaranteed to deliver a high-quality product.

Figure 6: Example showing different ways of handling and storing a product.



Conclusion

It has been shown how predictive tools can be used to simulate the moisture uptake of oral solid-dosage forms from the point of manufacture to the point when it is administered by a patient. The model for moisture uptake can be coupled with a model for degradation in order to predict chemical degradation. By considering moisture uptake of the product in the end-to-end manufacturing and supply chain it is thus possible to select the most appropriate measures to ensure that the product meets its specification when it is administered by the patient.

References

1. J. Barry, et al. "Basis for Using Moisture Vapor Transmission Rate per Unit Product in the Evaluation of Moisture-Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms," PQRI (September 2004), http://pqri.org/wp-content/uploads/2015/08/pdf/WhitePaper.pdf, accessed Sept. 29, 2016
2. C. Ahlneck and G. Zografi, *Int J Pharm* 62 (2-3) 87-95 (1990).
3. X.Y. He, G.K. Yin, and B.Z. Ma, *ActaPharm. Sinica* 25 (7) 543–550 (1990).
4. K.C. Waterman, *AAPS Pharm Sci Tech* 12 (3) 932-937 (2011).
5. K.C. Waterman et al., *Pharm Res* 24 (4) 780-790 (2007).
6. Y. Chen and Y. Li, *Int J Pharm* 255 (1-2) 217-225 (2003).
7. D. Vaczek, "Modeling Moisture Control. Desiccants help stabilize drugs, and may get them to market faster," *Pharmaceutical & Medical Packaging News* (July 2006).
8. A. Possumato, "Psuedoempirical Modeling Ensures effective drug Packaging. Pharmaceutical stability and sorbent technology can be calculated in advance" *Pharmaceutical & Medical Packaging News* (April 2007).
9. K.C. Waterman and B.C. Macdonald, *J Pharm Sci* 99 (11) 4437-4452 (2010).
10. A.L. Simonutti, *Moisture barrier prediction modelling.* M.Sc. Thesis, Luleå University of Technology, (2010) http://epubl.ltu.se/1402-1617/2010/116/LTU-EX-10116-SE.pdf, accessed Nov. 16, 2016.
11. J. Remmelgas et al., *Int J Pharm* 441 (1-2) 316-322 (2013). **PT**

Validating a Method for Point-of-Use Leak Testing of Single-Use Bag Assemblies

Carole Langlois, Marc Hogreve, and Jean Marc Cappia

The authors describe the development and validation of a highly sensitive point-of-use pressure decay test.

Single-use technologies have transformed biopharmaceutical manufacturing by providing opportunities to reduce costs, improve flexibility, and shorten cycle times. Manufacturers of biopharmaceuticals want to maximize the benefits they can derive from single-use technologies and are becoming increasingly confident when integrating single-use assemblies into processing steps that have a greater impact on product quality. Today, the expansion of such technologies into more critical applications, such as drug substance and drug product storage, has naturally raised new challenges for the industry to address. Industry surveys show that these challenges include quality assurance, supply chain reliability, supplier change control, raw material transparency, and maintaining the integrity of assemblies (1, 2). "A lack of robustness can lead to contamination of process fluids or drug products and, subsequently, loss of time and materials," Weibing Ding, PhD, principcal scientist, Process Development at Amgen said in a statement. The cost of bag failures could be between $100,000 to $1 million per bag.

To avoid these costs, established suppliers of single-use bags provide assurance of container-closure integrity across the entire product lifecycle. They do this by applying quality-by-design principles, performing process validation, and ensuring process control. Quality control policies ensure the integrity of the film, the welds, and the bag chamber.

As part of their quality risk management strategy and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q9 biomanufacturers can reduce the risk of losing high-value product and enhance patient and operator safety by performing a non-destructive point-of-use leak test on all single-use bags used in critical process steps (3). This ensures no damage occurred to the single-use bags during shipping, storage, and handling at the user site.

In this article, a leak test method was validated to detect leaks by means of pressure decay for 2D storage bags (Flexboy 2D, Sartorius Stedim Biotech). This article describes the validation of a pressure decay test method used for the point-of-use leak test at the user site of Flexboy bags from 50 mL to 50 L with the FlexAct BT and the Sartocheck 4 plus Bag tester. A preliminary parameter study was first performed to pre-determine the test pressure, stabilization time, and test time. A complete validation study was then carried out to validate the parameters, the maximum allowable pressure decay, and the leak detection limit.

Materials and methods

Bag Integrity test hardware and instrument. Test method development and validation were performed using the FlexAct BT system with Sartocheck 4 Plus Bag tester. The bag tester was equipped with two bag holders, each consisting of two metal plates with porous spacers. By using porous spacers, the film surface of the bag is not in direct contact with the stainless steel holder during the test. Any potential masking effect is eliminated and environmental heat transfer is reduced. The holders allow performance of the leak test with a small and reproducible inflating bag volume and at a higher test pressure. This is critical for achieving the test sensitivity and reliability required. Furthermore, the holders protect the bag from mechanical stress during the test.

2D bags from 50 mL to 50 L. The designs of 50 mL to 50 L Flexboy 2D bags for pre-use have been adapted to meet the specific requirements of critical process applications and pre-use leak testing. This requires the installation of a sterile vent filter line to permit the performance of the test under conditions that maintain the integrity and the sterility of the system (**Figure 1**).

Carole Langlois is senior product manager, Fluid Management Technologies; **Marc Hogreve** is senior engineer Integrity Testing Solutions; and **Jean Marc Cappia** is group VP Marketing & Product Management Fluid Management Technologies all at Sartorius Stedim Biotech.

Pressure decay test method. The test method was derived from *ASTM F2095-01: Standard Leak Test for Pressure Decay Leak Test for Non-porous Flexible Packages with and without Restraining Plates* (4). Once the test pressure has been set and allowed to stabilize, the system measures the pressure decay and compares the result to an acceptance criteria determined during the development and validation of the method (**Figure 2**). The pressure decay test method developed detects defects according to the leak-rate specification on the film, welds, and ports of the bags. Because the validated test method is non-destructive, it is compatible with performing pre-use leak tests on 100% of bags used at a biologics production facility.

Figure 1: Flexboy 2D standard bag design for pre-use leak test.

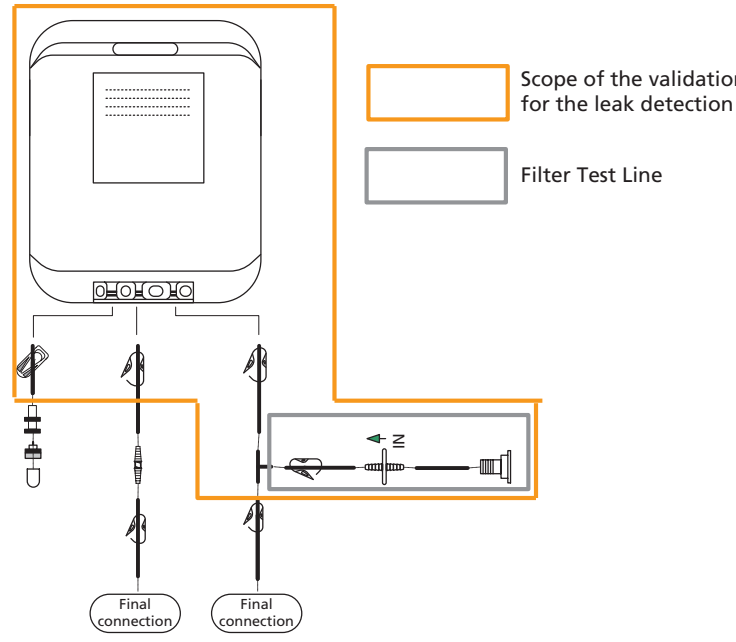
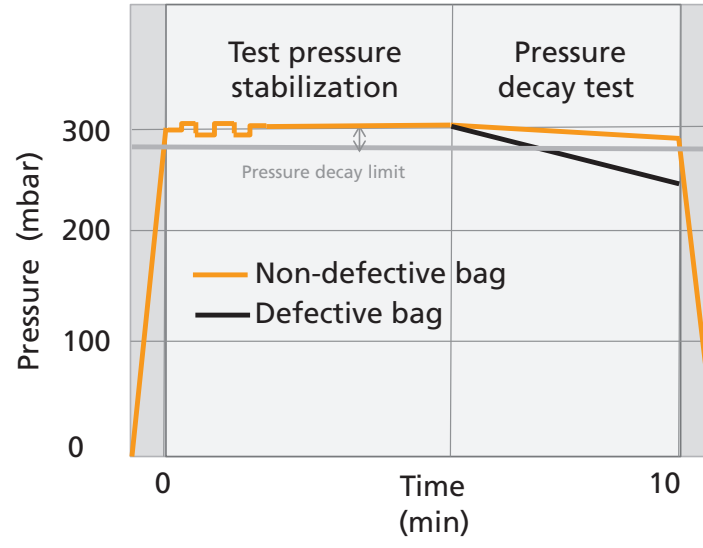


Figure 2: Pressure decay test.



Results

Test method development. The aim of the initial phase of the study was to predetermine the stabilization time and test time parameters necessary to detect a defect reliably over the volume range of the bag configurations. The range contains bags with 10 different volumes from 50 mL to 50 L. For each of the 10 bag sizes, three non-defective test samples, and three defective test samples were prepared. Defects were introduced into film samples with a laser drill and flow calibrated hole.

All 60 samples were tested at a fixed 300-mbar test pressure. For each test run, four different stabilization times of 60 seconds, 120 seconds, 180 seconds, and 240 seconds were used. The pressure drops were continuously measured and reported every second across the entire test time from 0 to 240 seconds during the four different stabilization time test runs.

The minimum, the mean, the maximum, and the standard deviations (σ) of the measured pressure drops were calculated for the four different stabilization times separately, with non-defective and defective test samples for each different bag volume. The optimum stabilization time and test time were chosen to provide a selective test method capable of differentiating defective bags form non-defective bags (i.e., the points where the error bars [± 3 σ] from the defect is distinguished from the error bars [± 3 σ] from the non-defective measurements). Initial results showed that, for tests performed with a 120-second stabilization time and 90-second test time, a difference between the observed pressure drops of defective and non-defective test samples could be detected with a probability of 99.9%. A safety margin was then applied by doubling the stabilization and test times to avoid false positive and false negative results during normal operations. These timings were selected for the subsequent validation study.

Test method validation. The purpose of the validation study was to verify the ability of the pre-established test

Figure 3: Pressure drop intervals of ± 3 σ around the mean values for defective and non-defective test samples at 240 second stabilization and 180 seconds test time.

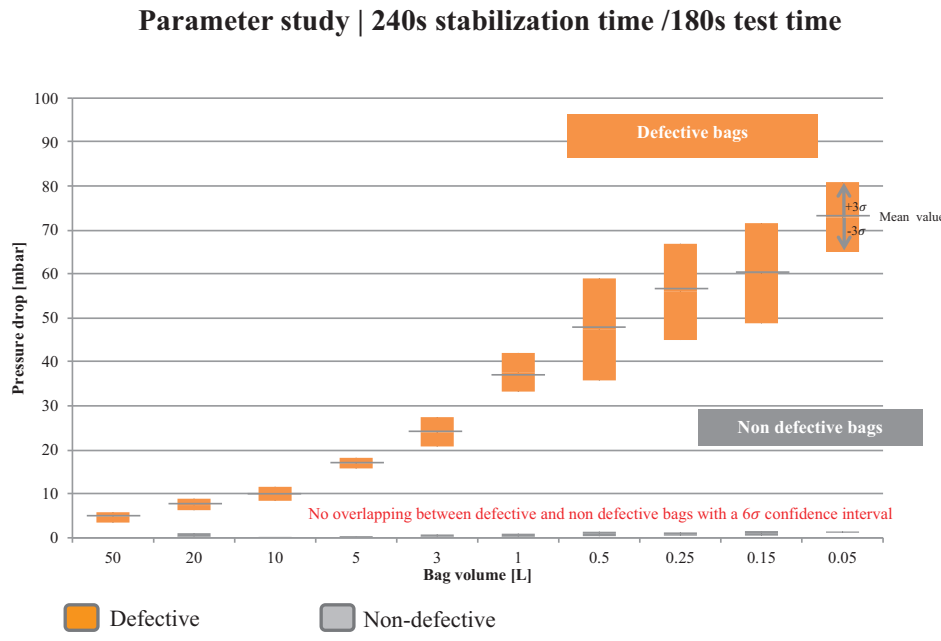


Table I: Final test parameters from the validation study.

Test Pressure [mbar]	300
Stabilization Time [sec]	240
Test Time [sec]	180
Max. Pressure Drop [mbar]	3.1

method and test parameters to detect a defect reproducibly and accurately over the volume range of the bags. The validation study was performed with a statistically significant number of bags from different routine production lots to provide a robust validation and test method. For each of the 10-bag volumes, 32 non-defective test samples from production with representative raw material and process variability, and 32 test samples with a defect were used. This represented a total of 640 samples tested during the validation study. Every defect film sample was checked for its calibrated hole size before it was used. Tests were performed using the pre-determined test pressure of 300 mbar, stabilization time of 240 seconds, test time of 180 seconds, and a defect size.

This study allowed the validation of the pre-established test parameters and the setting of a maximum allowable pressure decay specification at 3.1 mbar. The validated pressure decay method was capable of reliably detecting defective bags from non-defective bags with a given leak detection limit in less than 10 minutes including installation and testing.

The 3.1 mbar maximum pressure decay specification was established with a 6σ interval of confidence for the full range of bags from 50 mL to 50 L to avoid false positive or false negative results under real testing conditions (**Figure 3**). The final test parameters established during these studies are provided in **Table I**.

Conclusion

The authors developed and successfully validated a pressure-decay leak test for 2D bags using commercially available equipment and proved that it is a robust and predictive method for the reliable detection of leaks. Using the method, non-defective bags gave results below the maximum pressure drop specification. The bags into which a defect was deliberately introduced gave results above the maximum pressure drop specification and failed the test. The method is, to the authors' knowledge, the first point-of-use leak test capable of detecting down to 10 µm defects in 2D bags, irrespective of their volume. The sensitivity of the test is independent of 2D bag size.

References

1. Aspen Brook Consulting LLC, *6th Annual Survey of the Single Use Bioprocessing Market 2014* (Aspen Brook Consulting LLC, 2014).
2. Bioplan Associates, *12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (Bioplan Associates, 2015).
3. ICH, *Q9 Quality Risk Management* (ICH, 2005).
4. *ASTM F2095-01: Standard Leak Test for Pressure Decay Leak Test for Nonporous Flexible Packages with and without Restraining Plates* (West Conshohocken, 2001). **PT**

EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

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

Courtesy of
Fette Compacting

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**

The Transition to Electronic Records

Christian Fortunel

A four-stage process to successfully make the switch from paper to electronic batch records is presented.

Challenges associated with using paper-based processes to manage pharmaceutical manufacturing are leading pharma companies to adopt technology solutions. The following is a practical guide to migrating from paper-based records to electronic batch records (EBRs) in pharmaceutical manufacturing. The author considers factors that are driving the adoption of technology and outlines a four-stage process to successfully make the switch.

A changing landscape

The transition from paper-based processes to the use of technology to manage operations is becoming more and more common within the pharmaceutical manufacturing industry. The increased adoption of manufacturing execution system (MES) technology can be attributed to the limitations and challenges associated with using paper-based systems. Paper-based recording is a lengthy process. Data needs to be located manually and transcribed into a system before being analyzed; in some cases, the information is no longer relevant by the time it is recorded.

Lack of information visibility can cause problems in planning production activities. Paper-based systems can also lead to documentation errors, which affect regulatory compliance and can be costly to the business, both in time and in money.

With paper-based systems, data are not recorded and reported in real-time, which can increase product waste and the time spent investigating deviations. Potential issues are also not identified and recorded as they happen, meaning a delay in resolving these issues.

The time lag between using materials and updating the system can also cause issues as the inventory is not always up-to-date. Operations teams may have to manually count items due to inaccurate recording or late reporting of important information such as materials issues and materials receipts transactions. Furthermore, paper-based systems can delay production if, for example, production operators are left waiting for materials and quality approvals.

MES technology can help eradicate many of these issues. Electronic data capture allows for real-time visibility of information, which saves time at all stages of the process.

Regulatory compliance is also dramatically increased as EBRs raise any issues as they occur, so that they can be dealt with promptly and effectively. MES technology helps ensure that information can flow smoothly around a manufacturing plant. This flow produces quality products and ensures 'right-first-time' production.

To ensure smooth integration of this technology, there are four key stages to success. The migration from paper to electronic reporting may seem daunting, but there are steps that can be taken to simplify the process.

Stage one: Establish a business case

The transition to an electronic system affects all aspects of production, from planning and execution, through to control, monitoring, and documentation. The deployment of the technology can disrupt the organization in critical ways, meaning that if this is not handled properly there can be negative consequences. One must think ahead to how the new systems and processes may affect staffing, training, and organizational roles and plan how to make necessary changes.

The first step is to have a champion within the organization to take a lead

Christian Fortunel is vice-president at LZ Lifescience.

and help socialize the new project to its stakeholders. This person will drive the process to develop the business case in the beginning but will also take responsibility for ensuing that each future project stage is handled properly.

A valid business case will help convince all stakeholders (e.g., finance, operations, quality, IT, engineering) that the investment is worthwhile and will bring the desired benefits to the organization, such as improving documentation compliance or reducing operational costs.

Return on investment (ROI), which helps to quantify the value of the business case in a meaningful way, should also be determined. In the author's experience, cloud-based systems, for example, prove to be cost effective as they can be scaled up or down to meet customer requirements, typically generating ROI in 12–18 months. Furthermore, MES technology has been proven to improve productivity by 25% in some cases.

Although EBR is the typical functionality used to justify investments in MES systems, their broad functional coverage makes them quite attractive. European regulatory agencies, for example, require the submission of a Summary of Product Characteristics before any medicinal product is authorized for marketing. The data collection and reporting capabilities of MES make it easy to achieve this. The savings achieved in that area become one more component of building the business case for the entire solution. The functionality to track overall equipment effectiveness (OEE) is another example where a small increase in investment can lead to significant returns.

Finally, improving process compliance is another factor when companies are establishing their business case. MES technology can be used to issue electronic work instructions and track process performance.

Stage two: Plan your course of action

The next stage is to review best practices for planning and identify the correct course of action for implementation. Once the decision to move to using MES technology has been made, the key is to approach the project in a well-informed and well-planned manner.

To ensure success, goals should be put in place and a project charter developed. This will allow all parties involved in the MES integration process to fully understand the project objectives. Key performance indicators (KPI) should also be established to allow for specific measurements and establish accountability to the entire team.

Key performance indicators should also be established to allow for specific measurements and establish accountability to the entire team.

For the new system to be effectively integrated, the entire organization needs to work together. An effective way to do this is through a concept of operations (COO), which establishes production policies. This document outlines how daily operations will be managed and by whom, identifies any benefit that will be gained from the migration to an MES system, and defines the role of each organizational department.

With the COO and project charter in place, all key stakeholders must be introduced into the process. Involving management, planning, production, quality, and IT staff will ensure that they are prepared for the upcoming changes. This process allows for the communication of the benefits to the organization as well as explaining how the changes will shape their roles. There are many ways to do this, for example through training and internal communications. Employees need to fully understand their new role and

responsibilities to allow them to focus on making products 'right first time'.

It is within this planning stage that it is important to also create a detailed IT strategy. This strategy must consider how the new system will integrate with any peripheral systems, including automation systems, so that communication flows are minimized.

This cohesive approach to planning is key to eliminating any potential negative side effects and reducing the project implementation timeline. There will be some unavoidable disruption when implementing new systems, but with effective planning many issues can be avoided.

Stage three: Implementation

The next step is to implement the MES, and the success of this will depend on the project plan and IT strategy. An analysis phase is advised here, as this will allow existing business processes to be converted into workflows and the necessary software functions and configurations to be established. At this stage, interfaces with other systems can be developed against formal specifications.

After the configuration process, the software must be qualified in accordance with the International Society for Pharmaceutical Engineering (ISPE) GAMP-5 validation model, an established industry standard (1). This process includes factory acceptance testing (FAT), installation qualification (IQ), and site acceptance testing (SAT). Depending on the type of software configuration, the level of qualification documentation and cooperation between the organization and vendor will vary. This is typically described in the master validation plan for the project.

Once the MES solution is available, it needs to be configured to migrate paper records to electronic format. This task is a significant opportunity to harmonize business processes and establish corporate standards, particularly if the system is expected to be deployed in multiple locations.

Next, the organization must validate the solution against its user requirements and business use. This is the stage at which the functionality of the software is tested, known as the operational qualification (OQ).

Standard operating procedures (SOP) must be updated to allow for the fact that paper systems are no longer being used. Here, the company must decide what information should be included in its SOPs versus what should be included in a batch record. For example, the EBR may include GMP and patient-related data, while SOPs may be more suited to information for operators (i.e., equipment assembly instructions).

The final stage of implementation is for training to be delivered to operators. All those that will be affected by the new system (i.e., electronic record designers, quality supervisors, production operators, and IT administrators) must be fully educated on their new role and responsibilities.

As can be seen, there are many facets to designing and configuring an EBR solution; the more planning you can do beforehand, the better.

Stage four: Launch and evaluation

Before the project can go live, master and inventory data need to be loaded into the production system. This loading may involve a fair amount of preparation to clean up master data and start the MES system with accurate inventory information. Any data loading tool that is used will need to be validated ahead of time. It is important to remember that there may initially be lower production output when a system first becomes operational. The organization may take some time to adapt to the new ways of working and employees will be settling into their changed roles. Taking this into account, consider increasing production in the run up to the changeover to counteract the diminished performance during the learning period. It is also essential to manage any customer expectations during this time.

Monitoring that the MES is performing as expected is important at this stage to create accountability and a true success story. This is the time when KPIs defined during the early planning phase of the project are measured and published to the organization.

Software upgrades are the next step to consider now that the system is live. Its lifecycle has only just started so one may want to take advantage of new features or functionality that may be introduced. Vendors must be very clear on the process that is required to upgrade the MES. It is important to determine the impact of any upgrade upon the exiting solution and the dependence on the vendor to perform the upgrade. Ideally, one should require as little support from the vendor as possible.

Consider allowing the vendor to access data remotely so that problems or investigations can be handled quickly and efficiently. An online ticket submission system is now the preferred option to obtain system support.

Conclusion

Before making the transition from paper-based reporting to EBRs with the implementation of an MES, it is important to think about the impact that the technology will have across the entire organization. Changes will affect all aspects of the company's operations (e.g., change management, operations, quality, IT, engineering, training, validation, SOPs), as well as having an impact on its people. The success of the project will rely on a holistic approach to planning, with potential issues considered ahead of time.

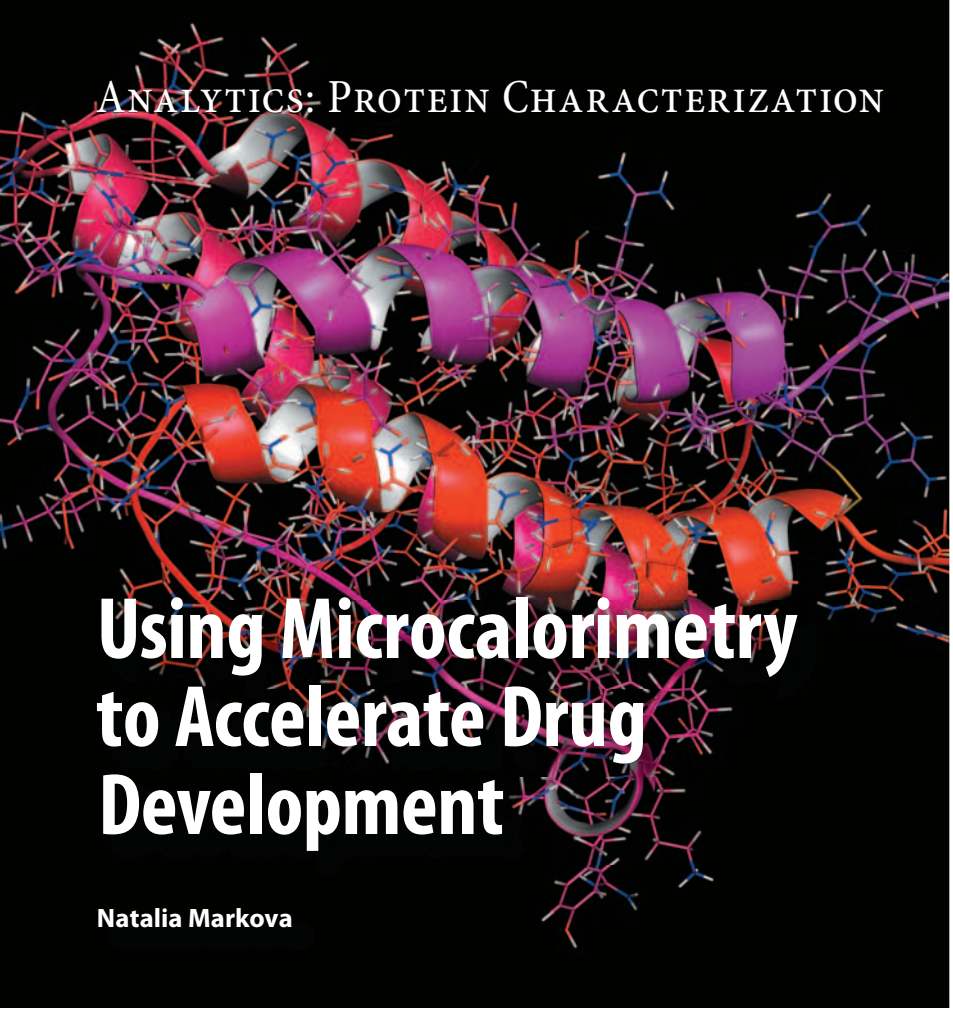
Perhaps surprisingly, the actual implementation of an MES system represents approximately 25% of the total project costs. The remainder of the project consists of:

- IT infrastructure (10%)
- Process engineering and paper batch record migration (30%)
- Change management (communication, training, SOPs) (10%)
- Validation activities (25%).

Each of the stages outlined here will help to efficiently and successfully migrate from paper-based records to a more effective MES system, improving compliance and ensuring 'right-first-time' production.

Reference

1. ISPE, *Gamp 5: Compliant GxP Computerized Systems* (ISPE, February 2008), www.ispe.org/gamp-5 **PT**



Using Microcalorimetry to Accelerate Drug Development

Natalia Markova

MOLEKUUL_BE/SHUTTERSTOCK.COM

Isothermal titration calorimetry and differential scanning calorimetry are valuable tools that can help accelerate drug development.

Calorimetry is the science of measuring heat changes that result from chemical reactions or physical events. The "micro" in microcalorimetry refers to the extremely small scale at which experiments can be conducted, because of its ultrasensitive technology. The ability to make highly precise, information-rich measurements using as little as 10 µg of protein/drug substance (depending on the properties of the sample) makes microcalorimetry a powerful technique for investigating the biochemical interactions that underpin drug efficacy and safety. This article provides an overview of how microcalorimetry works, and the value and application of the data this technique produces.

Natalia Markova is principal scientist, MicroCal, Malvern Instruments.

How does it work?

Microcalorimetry can be subdivided into isothermal titration calorimetry (ITC) and differential scanning calorimetry (DSC), both of which are valuable for pharmaceutical/biopharmaceutical applications. These techniques share similar principles of operation but differ in terms of instrumentation and experimental setup, and as a result, offer different but complementary analytical capabilities.

The thermal core of a microcalorimeter consists of two cells: a reference cell and a sample cell (see **Figure 1**). When a reaction or binding event takes place in the sample cell, heat is either released or absorbed, inducing a temperature differential (ΔT) between the two cells. This differential is eliminated through automatic control of the energy input to the sample cell. The magnitude of the resulting change in energy input correlates directly with the enthalpy (ΔH) of the interaction that has taken place and can be used to determine a range of parameters, depending on the specific technique applied and the experimental setup.

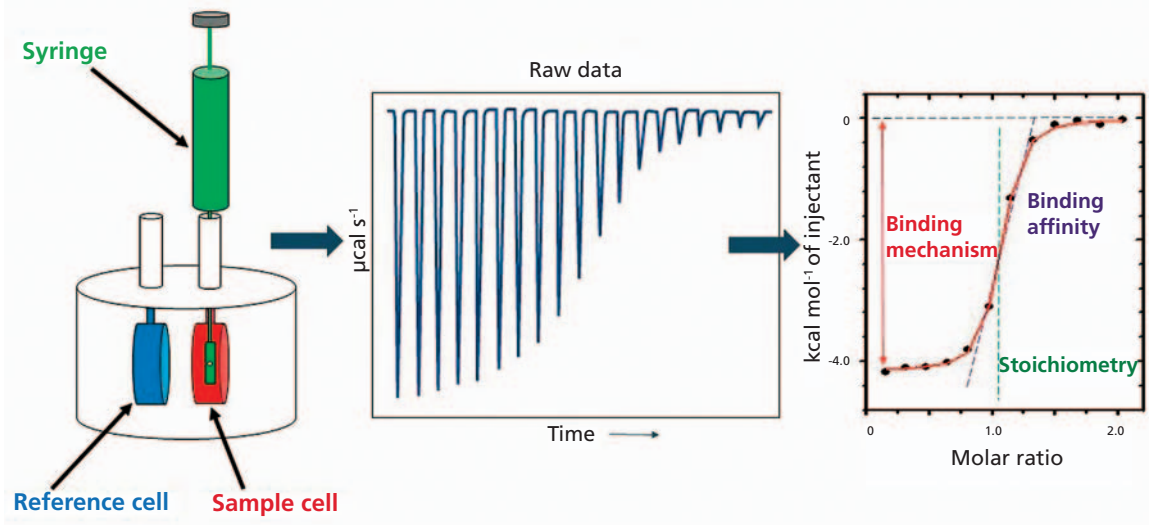
In an ITC system, the reference cell and sample cell are set to the desired temperature, with one reactant, in solution, loaded into the sample cell. The experiment is performed at constant temperature by titrating the second binding partner or reactant into the solution in the sample cell using an automated syringe capable of injecting precisely metered aliquots. As binding or reaction occurs, temperature changes of a few millionths of a degree Celsius are detected and measured, to determine the heat released or absorbed. Injection continues until the binding or reaction has reached equilibrium, to generate a complete thermodynamic profile for the reaction, including information about binding affinity (i.e., the strength of interaction between the first and second binding partner or reactant).

In a DSC experiment, the reference cell is typically filled with buffer, and the sample cell is filled with a solution of the entity under investigation; both cells are then heated at a constant known rate. Here, it is the sample undergoing a thermally-induced change that creates the temperature difference between the cells. Enthalpy values and changes in specific heat capacity are directly determined from the power drawn to correct this imbalance.

What can ITC measure?

ITC enables a robust, label-free evaluation of the mechanisms of intermolecular interactions between a drug candidate and a target molecule. These interactions are an indicator of

Figure 1: An isothermal titration microcalorimeter with an example of the raw data output for a binding experiment, and its conversion to detailed information about the binding reaction.



bioactivity, a critical determinant of drug efficacy. Quantifying binding affinity is, therefore, an important way of ranking bioactivity. In addition, by providing a complete thermodynamic profile of a molecular interaction, ITC more broadly supports the optimization of a drug candidate(s). Specifically, it can be used to quantify the following parameters:

- Equilibrium dissociation constant (KD): a measure of the strength of bimolecular interactions, with smaller values indicating a stronger affinity between a ligand and a target molecule
- Reaction stoichiometry (n): the ratio of biomolecule to ligand involved in a binding interaction/reaction; this parameter quantifies how many drug molecules can be attached to the target site before saturation is achieved
- Enthalpy (ΔH): the energy released or absorbed per mole of ligand as bonds are broken and created; a measure of the type and strength of bond changes during binding, especially changes in hydrogen and van der Waals bonding
- Entropy (ΔS): the change in degrees of freedom of the interacting species relative to the complex; most usefully indicative of hydrophobic interactions and conformational changes.

What about DSC measurements?

DSC measurements directly address a different but equally important aspect of drug performance: stability, specifically thermal stability, which is a major concern for biopharmaceuticals. DSC is especially useful for the measurement of the following:

- Melting point (T_m): In a protein solution, a native (folded) protein that exhibits two-state reversible unfolding behavior is present in equilibrium with the analogous unfolded protein. T_m is the temperature at which the size of these two populations is identical. A higher T_m is, therefore, indicative of higher stability
- Onset temperature (T_{onset}): This is the temperature at which substantial unfolding of the protein begins to occur, so as with T_m, a higher value is associated with greater stability
- ΔH of unfolding: This is the enthalpy change associated with breakage of the non-covalent bonds that stabilize the protein and can, therefore, provide insight into unfolding mechanisms.

Via measurement of these parameters (see **Figure 2**), DSC can elucidate the factors that contribute to the folding and stability of native biomolecules, including hydrophobic interactions, hydrogen bonding, conformational entropy, and the nature of the physical environment, for example, pH or exposure to oxidation.

Microcalorimetry is particularly valuable in the early stages of drug development.

Applications in drug development

Drug candidate choice is often guided from the outset by the affinity between a therapeutic and target molecule, with high bioactivity maximizing efficacy and/or minimizing the amount of drug required to achieve the desired therapeutic effect. While advantageous for all pharmaceuticals, high bioactivity is particularly important for biophar-

maceuticals because of its ability to alleviate the difficulties associated with high-concentration drug delivery via injection or infusion. Stability is also a crucial early screen for biopharmaceutical molecules because of the risk of reduced efficacy and/or immunogenicity associated with a compromised protein being delivered to the patient.

Such requirements make the informational output of microcalorimetry closely aligned to the early stages of drug development, to candidate validation, and to early formulation development. The practicalities of the techniques are equally well matched to this stage of the pipeline, with modern systems offering:

- Fully automated operation with the capacity for unattended running of industry standard 4 x 96-well plates
- High signal-to-noise ratios for excellent data quality with minimal sample volume required
- Automated washing for high reproducibility
- Compatibility with a broad range of sample types, solvents and buffers, including systems that are highly concentration, colored, and/or turbid
- Simple assay development.

In terms of specific applications, ITC has become the gold standard technology for studying intermolecular interactions, and its attributes make for a highly efficient screening tool. The level of hydrogen bonding between a drug candidate molecule and its target molecule is directly quantified by ΔH, which can consequently be an effective predictor of efficacy, more so than the hydrophobic interactions quantified by ΔS. Optimizing ΔH is a strategy applied to an increasing extent in candidate validation and early stage formulation.

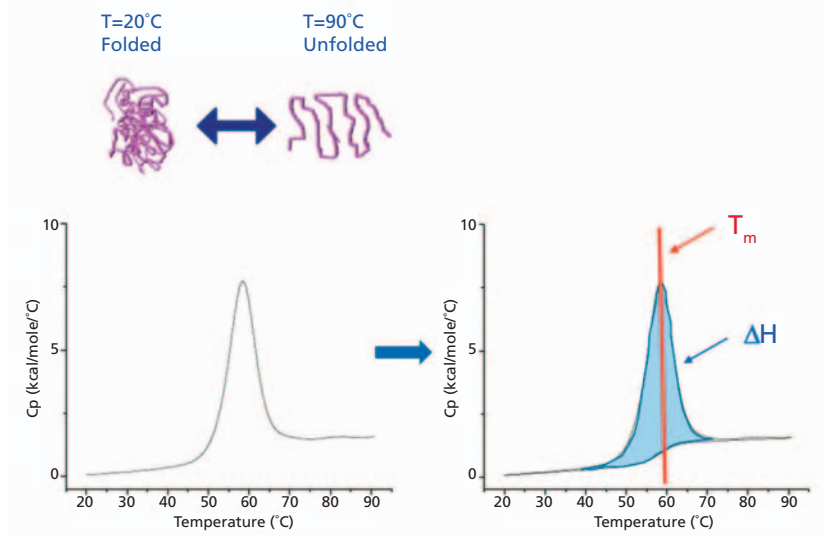
However, the application of ITC can begin even earlier—in drug discovery—and extend into processing and manufacturing support. At these stages, ITC helps to:

- Quantify binding affinity to support initial candidate selection and optimization
- Confirm intended binding targets in small molecule drug discovery
- Validate IC_{50} (drug concentration causing 50% inhibition of the desired activity) and EC_{50} (drug concentration causing 50% of the maximum of a measured biological effect) values during hit-to-lead
- Confirm the bioactivity of an as-manufactured product and/or equivalence in a biosimilar.

The application of DSC to detect and study changes in protein structure, and determine pre-folding events is focused on the early stages of the biopharmaceutical drug pipeline, and for biosimilars, in the area of biocomparability studies. In all of these applications, the ability to study formulations without dilution to realistically explore the mechanisms of oligomerization and aggregation is particularly valuable. However, the use of DSC also extends into process development and manufacturing support, where it may be applied:

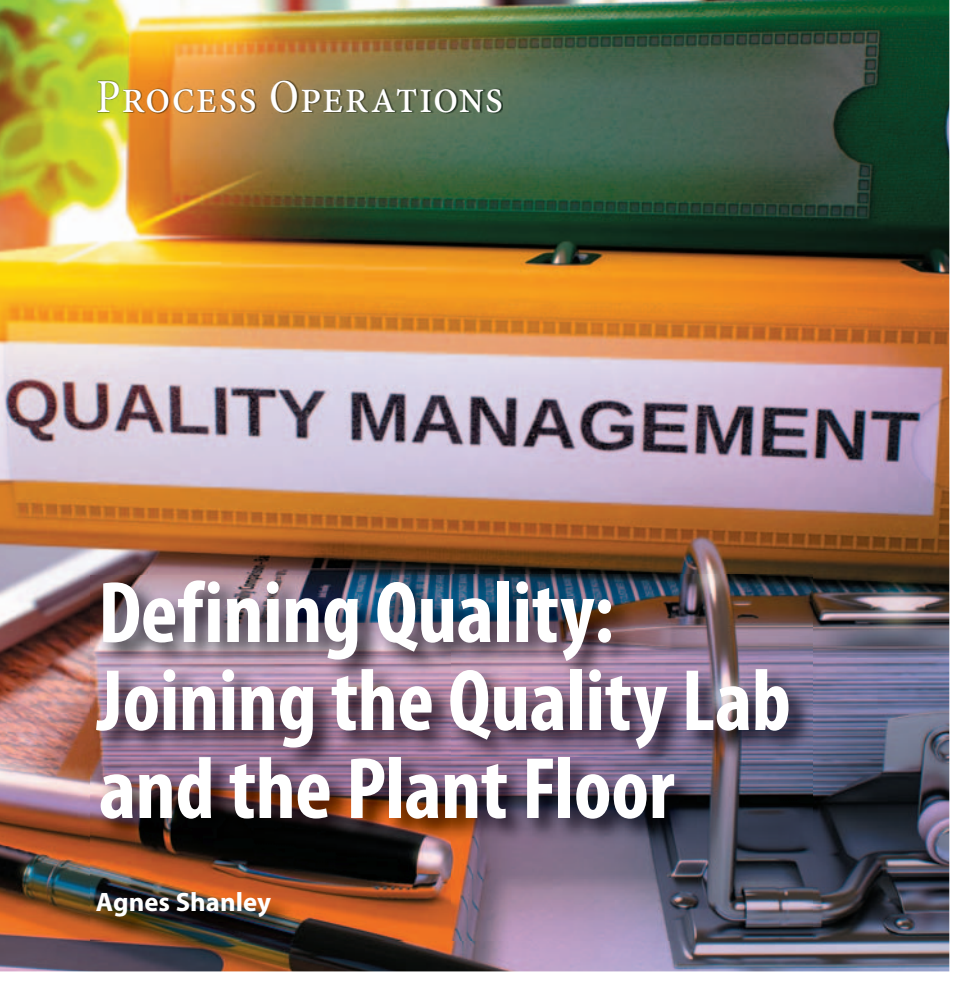
- To optimize purification and manufacturing conditions
- For lot release and/or to compare the consistency of lots produced at, for example, different manufacturing sites.

Figure 2: Differential scanning calorimetry measures the temperature at which conformational changes occur, directly supporting assessments of protein stability.



Conclusion

Microcalorimetry technology has developed considerably in recent years, and the resulting instrumentation is particularly valuable in the early stages of drug development. By providing a complete thermodynamic profile of a molecular interaction, ITC goes beyond binding affinities to provide elucidation of the mechanisms responsible for the interactions that underpin drug activity. Such insight supports the rational design and optimization of both small and large candidate molecules, to ensure a highly efficacious product. DSC is an efficient tool for stability detection and elucidation, an important activity in biopharmaceutical candidate validation, and is similarly useful during manufacturing support for lot release. Powerful and easy-to-use, both techniques boost the analytical capability accessible to drug developers helping to accelerate their work to a commercially successful conclusion. **PT**



Defining Quality: Joining the Quality Lab and the Plant Floor

Agnes Shanley

As pharmaceutical quality metrics evolve, they will need to incorporate more of the principles of operational excellence, says consultant Prabir Basu.

For the past few years, to help pharmaceutical manufacturers improve and sustain better product quality, FDA has been working with industry to define the metrics and key performance indicators that are most critical to product quality (1). This work actually began in 2008, with the release of the International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use's (ICH) Q10 (2), which articulated the need for a systemic approach to quality that would get beyond the case-by-case approach of current good manufacturing practices (cGMPs) and final product testing.

After FDA released initial guidance on quality metrics in 2015 (3), there were complaints about its broad scope. FDA had asked that manufacturers collect data for 10 metrics. In November 2016, FDA released a second version of the guidance (4), which focuses on the following three main metrics:

- Lot acceptance rate, or the number of accepted lots within a timeframe divided by the total number of lots started, for primary and secondary distribution and packaging, during a given timeframe. Included will be number of lots started, released, and rejected.
- Product quality complaint rate, or the number of complaints received divided by the total number of dosage units of that product distributed during that time frame.
- Invalidated out-of-specification (OOS) rate, or the number of OOS batch-release test results and long-term stability test results that were invalidated due to measurement process issues at the facility, divided by the total number of such tests performed at the facility during the time frame. Every OOS result will trigger an investigation, and the guidance specifies best practices.

Long term, the agency's goal is to furnish metrics that will help process operations and manufacturing teams, quality control departments, and regulators (especially plant inspectors) focus on key principles that determine product quality. These principles should drive, not only day-to-day operations, but also investment in new technology. In addition, they should help regulators prioritize inspections to focus on facilities and companies that are at the highest risk of quality or compliance failure.

In July 2016, FDA began to fund research that aims to analyze existing quality metrics, and to see whether new measurements that incorporate more of the language of the manufacturing plant floor and the principles of operational excellence might help achieve better results in the future (5).

Working on this project is a team at the University of St. Gallen in Switzerland, led by Thomas Friedli, who has spent the past 15 years studying the application of continuous improvement techniques across different industries. Collaborating with Friedli is a team from the Dublin Institute of Technology, led by Nuala Calnan, and, based in the United States, pharmaceutical industry consultant Prabir Basu, who, for more than 10 years, was head of the National Institute for Pharmaceutical Technology and Education (NIPTE).

Friedli's team has been analyzing pharmaceutical manufacturing for well over a decade, based on the universal metrics used in automotive, aerospace, and other industries, which include "on-time delivery" and inventory levels. St. Gallen's surveys of pharmaceutical manufacturing operations look at such things as whether the facility or company uses total predictive maintenance, or how effectively the workforce is engaged in, or how strongly senior management supports, total quality improvement.

Some pharmaceutical companies have been reluctant to embrace such universal manufacturing excellence metrics, with some insisting that "pharma is different," due to the special requirements for product safety and testing. There has been debate over this topic for decades, and, even today, one sees uneven acceptance of such concepts as "process capability analysis" or process analytical technology (PAT) among drug manufacturers.

At this point, FDA wants to see whether the language of operational excellence can further enrich the industry's understanding of quality. Research is still in a preliminary stage, and could not be discussed for this article, but Prabir Basu shared some of his thoughts on what the industry will need if it is to redefine, and transform, pharmaceutical quality control.

Operational excellence

PharmTech: Why is operational excellence (OpEx) so important to improving both pharmaceutical manufacturing and quality?

Basu: Quality and operational excellence cannot be separated. Operational excellence metrics show how motivated people within a company are to improve overall performance, and quality with it.

FDA has, in the past, taken an approach that has separated the two, as if quality were not a part of operations. The point is, that if a company is not investing in quality, that will show up in the operational excellence parameters, and they will have quality problems too.

A great example is preventive maintenance. If you don't have a corporate mandate and policy for this activity, you are very likely to have problems with product quality.

PharmTech: How does all this affect regulators?

Basu: Having links to existing OpEx quality parameters would be very helpful in ensuring that FDA can get pertinent information underlying deviations or batch rejections.

Today, most manufacturing is taking place outside of the US, and FDA has limited ability to inspect all the facilities involved. Having indicators in place that are operations related and that suggest which facilities and companies might pose a higher risk of noncompliance or low quality will allow FDA to prioritize inspections. But it would be ideal if we could get to the stage where quality and operational excellence are considered as one. ICH Q10 gives us indications of how to get there.

So, we are beginning a journey that has much potential, and we can get to this goal of a unified definition of quality, if we continue for the next three to five years.

At this point, we are collecting data using benchmarking questionnaires, correlating between existing operational excellence measurements and quality metrics. We hope to expand the

questionnaire to reflect on real quality information.

PharmTech: In the past decade, we've heard more people in pharma talk about Deming's approaches to excellence, yet concepts as basic as process capability don't seem to have been widely embraced. Why is that?

Basu: Some companies are working with the concept of process capability, but they tend to be the larger companies, such as Amgen and Pfizer. And even the larger companies don't employ this approach for all products.

We need to come up with metrics that will be attractive for all companies.

PharmTech: How about cost of goods?

Basu: That measure is too variable, because the cost of capital varies so dramatically depending on which country the facility or company is based in.

Quality metrics

PharmTech: How about the metrics that FDA is focusing on in its latest version of the draft guidance, including out of specification? Are these adequate?

Basu: The metrics are okay but they aren't yet tied to processes so they won't necessarily reflect what is going on internally. For example, lot acceptance rate seems okay, but what happens if lots have to be reworked? Will the figure then be a true reflection of the facilities' processes?

PharmTech: What are some concepts that might be more helpful?

Basu: I think that Six Sigma value could provide a better indicator. In the early 2000s, a number of thinkers used to talk about doing this, but it hasn't yet been fully accepted.

Even if we were to use the lot acceptance rate as a quality metric, ideally some measure of accuracy could be factored in, for example, of the number of batches started, how many came out right the first time, without the need to rework them?

PharmTech: What role should quality complaints play?

Basu: This is an important metric, but first we need to define very clearly what the complaints are and where they are coming from. Are they coming from the warehouse? From distributors? From patients? From regulators?

"The most important question is whether the facility's or company's processes are in a state of control. "

— Prabir Basu

Some of the metrics that are currently being discussed may not adequately reflect internal processes. The beauty of operational excellence metrics is that they measure how well processes are performing, so they are much better reflections of the actual situation within a given facility or company.

Some of the important operational excellence metrics to consider are on-time delivery and customer satisfaction. These measurements reflect internal processes.

In addition, I believe that metrics must incorporate more of the spirit of ICH Q10, to determine the company's quality culture, and such things as whether the firm has a continuous improvement program in place, whether its senior management is involved in quality, the degree of employee involvement, and how the company prioritizes projects for improvement (ie, whether it uses ICH Q9 and principles of risk assessment to help make those decisions).

The most important question is whether the facility's or company's processes are in a state of control. Here, key indicators are measures of variability of the critical process attributes. Even if process capability information is not available, at a minimum, trending of critical process variables and data on process drift such as shifting of the averages or changes in slopes of the trend, degree of implementation of ICH-Q9, etc. We need metrics to measure these areas, and also to identify facilities and companies that are at the greatest risk of quality and compliance failure.

In the end, the number of rejected batches may be more important to screen than lot failures. In addition, relative numbers are more important than absolute numbers. For instance, the top 25% should have good systems in place, and the bottom 25% should receive more attention from FDA

It might be most beneficial to use the pillars that St. Gallen has been using to measure performance: total predictive maintenance, total quality management, and just-in-time inventory levels.

Keeping a focus on process operations will ensure that companies and regulators are monitoring operational principles, looking at stabilizing systems, and developing frameworks for knowledge management and risk management. By definition, these efforts can only make any organization more focused on product quality.

References

1. Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment, Meeting Summary, *brookings.edu*, www.brookings.edu/wp-content/uploads/2014/05/Quality-Metrics-Meeting-Summary.pdf, May 2014.
2. ICH, *ICH Q10, Pharmaceutical Quality System (PQS)*, 2010, *ich.org*, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Presentation/Q10_General_Presentation.pdf
3. M. Mezher, "FDA Releases Long-Awaited Quality Metrics Guidance," *raps.org.*, July, [2015, www.raps.org/Regulatory-Focus/News/2015/07/28/22939/FDA-Releases-Long-Awaited-Quality-Metrics-Guidance/ July 28, 2015.
4. FDA, *Submission of Quality Metrics Data, Draft Guidance for Industry*, November 29, 2016, *FDA.gov*, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455957.pdf, November, 2016.
5. T. Friedli and P. Basu, "Measurement of Pharmaceutical Quality in an Operational Excellence Environment," in CPhI Annual Industry Report, 2016, p. 15. **PT**

INTRODUCING

3 days of programming
24 in-depth conference sessions
40+ hours of industry insights
Partnered with **InformEx**

CPhI CONNECT

CPhI Connect delivers the latest conference content sessions on drug development, manufacturing, pharmaceutical outsourcing and specialty chemicals.

@

CPhI north america

In Partnership With

ICSE FDF InnoPack informEx

May 16-18, 2017 | Philadelphia, PA, USA

The newest edition of CPhI is coming to Philadelphia in May 2017!

Featuring an all new conference program focused on drug development, manufacturing and outsourcing trends across the complete pharma supply chain. Located adjacent to the 33rd edition of InformEx a so you can take advantage of unprecedented access to the complete pharmaceutical and specialty chemical industries— all under one roof!

Register for the conference today and get access to **both** programs - CPhI Connect and InformEx Connect - 48 sessions in total!

Go to www.cphinorthamerica.com/register and use PROMO Code PHARMTECH to receive an additional 10% discount off your conference pass!

In Partnership With:

ACS Chemistry for Life™ | BioPharm International | Pharmaceutical Technology | SOCMA Society of Chemical Manufacturers & Affiliates

*Discount applicable to non-exhibiting badge types only.

UBM

TETRA IMAGES/GETTY IMAGES

PharmTech.com/pack

Blister Packaging Moves Forward

Hallie Forcinio

Advances in materials and equipment for pharmaceutical blister packaging protect quality and enhance shelf life.

Blister packaging, a common format for solid-dosage forms, continues to evolve. Equipment advances combine flexibility, servo controls, compact size, and integration with upstream and downstream equipment. Material and quality-control innovations focus on protecting product quality and maximizing shelf life. Pouch options wait in the wings to replace cartons.

A new entry in the North American market, the MHI Eagle blister packaging machine from Maruho Hatsujyo Innovations (MHI), is an American version of its parent company's best-selling machine. Established in 2014, MHI provides US-based installation, maintenance, spare parts, and 24/7 technical support. Parent company, Kyoto-based Maruho Hatsujyo Kogyo, ranks as the second largest pharmaceutical packaging machinery company in Japan and has installed nearly 400 blister packaging machines there. "There is no child-resistant (CR) requirement in Japan, so we had to design sealing for CR lidding (push, peel/push, and peelable)," reports Gregory Zaic, president and CEO of MHI.

The MHI Eagle blister packaging machine (see **Figure 1**) operates at speeds up to 100 blisters per minute at a maximum index length of 90 mm and maximum index width of 130 mm. Designed for lower volume runs, the compact, servo-driven machine with inline inspection and multi-zone preheating is especially well-suited to copackers and lines with frequent changeovers (1). With hand screws to expedite tooling changes, changeover takes less than 10 minutes and requires no tools. Other quick changeover features include recipe-driven format change and a feeder station on wheels that plugs into the main unit. "We sell two feeder stations for the price of one-and-a-half so feeders can be swapped at changeover," says Zaic. Swapping units moves feeder cleaning off-line and minimizes downtime for cleaning. The Eagle blister packager accepts feeders from other manufacturers and is easily integrated with a printer or cartoner.

A fully integrated, modular line from Körber Medipak's Mediseal thermoforms, doses, seals, punches (perforates and embosses), diecuts, and feeds inserts and cartons. Direct product transfer eliminates fault-prone intermediate stacking units and minimizes change parts. Cameras confirm an insert is placed on every other blister before pairs of blister cards are stacked for cartoning. A display at Pharma EXPO (Nov. 6–9, 2016) showcased an integrated line on its way to a factory acceptance test. The one-lane CP400 blister packager integrated with a P1600 cartoner featured hot-melt carton sealing but also could accommodate tuck carton closure. Other potential variations include a P3200 cartoner with dual stacking devices, integration of a printer from HAPA for online printing of lidstock, various dosing systems (brush box, roller dosing, automatic spiral conveyor, or dedicated feeder) and choice of roller or platen sealing. Maximum speed of the servo-driven line is 400 blisters per minute (2). A sophisticated human/machine interface (HMI) groups functions for ease of use and helps reduce changeover time to less than 30 minutes. "All the information is in the HMI, which provides detailed instructions by system for format changes," Kai Trepte, area service manager at Mediseal, explains.

Blipack, a company based in Argentina, also supplies integrated blister forming and cartoning lines. The centerpiece, the Blistera 200-240 blister packaging machine, combines heavy-duty construction with user-friendly operation and quick and easy changeover and maintenance. The system can be electromechanical or driven by a programmable logic con-

We'll be seeing more ...

- Integrated equipment
- Compact systems
- Robotics
- Quick changeover features
- In-line inspection
- Non-destructive leak testing
- Pouches replacing cartons
- Advanced materials for improving or tailoring the package barrier.

Hallie Forcinio is *Pharmaceutical Technology*'s Packaging Forum editor, 4708 Morningside Drive, Cleveland, OH 44109, tel. 216.351.5824, fax 216.351.5684, editorhal@cs.com.

Purillex™ The New Standard in Single-Use BDS Containers

Don't trust your API with anything else.

The new Purillex PFA and FEP fluoropolymer bottles are designed precisely for biopharma use. The unique stretch blow molding technology gives Purillex bottles superior sealing capability, under extremes of pressure and temperature, to greater safeguard valuable contents. Stretch blow molding also eliminates the extrusion process which can produce particles of carbon that become embedded in bottle walls.

- ☐ Manufactured and inspected in a Class 10,000 ISO 7 cleanroom
- ☐ Only virgin fluoropolymer resin used
- ☐ Complies with USP 87, 88, 661 & 788
- ☐ Every lot is FTIR tested and ships with a certificate of conformance
- ☐ Sizes range from 50 mL to 2000 mL

Savillex
Purillex

Read the complete Purillex for Biopharma Technical Note at www.savillex.com/biopharma

Figure 1: A removable feeder module on the MHI Eagle blister packaging machine enables off-line cleaning and cuts downtime.

Figure 2: In a Pharma EXPO demonstration, the standalone AMI 120 leak detector from Pfeiffer Vacuum checked cold-formed foil blisters.

troller and is compatible with thermoforming or cold-forming and a wide range of accessories including printers and semiautomatic, automatic, dedicated, and universal feeders (3). Blipack's integrated Estuchadora ACM 150 intermittent-motion cartoner loads cartons horizontally. Carton sizes range from approximately 0.6 x 0.5 x 2.0 in. to 3.5 x 2.8 x 7.9 in. (4).

Another turnkey blister packaging line integrates the TF1e thermoformer and the TC1 cartoner from Pharmaworks. The unified system results in a compact footprint, operates from a single control system, and produces up to 100 blisters/80 cartons per minute. A robotic pick-and-place module transfers blisters from die punch to cartoner flights and eliminates the need for change parts. The number of blisters transferred to the cartoner flights is controlled from the operator interface (5).

Robotics also play an important role in the Integra 520 V integrated blister packaging line from Marchesini Group. The servo-driven system fits in 10 m of floor space and features a balcony design for the thermoforming and cartoning sections. Capable of producing 520 blisters and up to 500 cartons per minute, the Integra 520 V line succeeds the Integra 320 model and incorporates an innovative pusher, a drum-type carton-opening system to manage higher speeds, and a new leaflet pickup and insertion system. Separating product loading from electrical and mechanical zones ensures quick and straightforward cleaning and changeover. An enclosed oil bath system protects mechanicals from wear and tear and extends service life. Maximum forming depth measures 9 mm, although a 12-mm option is available. Carton sizes range from 35 x 16 x 75 mm to 90 x 90 x 150 mm (6).

Uhlmann Packaging Systems, which has offered integrated blister packaging lines for some time, offers three models: the single-lane BEC 300 model for up to 300 blisters/150–300 cartons per minute; the dual-lane BEC 500, rated at 500 blisters/300–500 cartons per minute; and the three-lane BEC 700, capable of outputting 700 blisters/300–500 cartons per minute. Upgraded in 2015, the BEC 300 model features the latest control and drive technology, tool-free format changeover, and smooth surfaces for faster line clearance (7).

Existing BEC 300 systems can be retrofitted to shorten the forming cycle, simplify cleaning, and minimize abrasion marks on forming materials. Uhlmann's Rebuild Packaging Systems Center performs electrical and mechanical retrofits using genuine Uhlmann parts to extend equipment lifespan and meet the latest GMP requirements and legal regulations. Upgraded equipment comes with detailed rebuild documentation, validation services, and one-year warranty. Rebuilding typically saves 30–70% compared to the cost of a new machine (8).

Carton alternatives

Cartons are the traditional secondary package for blisters, but CR pouches provide a lightweight, flexible packaging option. To simplify adoption of a CR pouch, the Child-Guard CR track and slider from Presto Products has a Drug Master File listing. In use, the caregiver moves the Child-Guard slider over a notch, pushes down on a tab and pulls back the slider to open the pouch (9). CR pouches from Impak meet ASTM (American Society for Testing and Materials) D3475 CR standards. Sliding tab or press-to-close CR designs require two-handed dexterity to open, making access difficult for toddlers but not for seniors (10).

Quality control

Quality control systems confirm blister packaging equipment is working properly. Systems, such as the camera-based IBIS inline blister inspection system from Pharmaworks, check product and print on sealed blisters. Installed inline or off-line, the vision system identifies flaws such as mis-shaped, damaged, missing, or rogue product, as well as incorrect color and foreign objects (11).

Seal integrity is checked on units such as the AMI 120 leak detector from Pfeiffer Vacuum (see **Figure 2**). The leak detector requires no tracer gas to nondestructively detect holes as small as five microns, a sensitivity up to 1000 times better than the traditional destructive blue dye dunk test. "Using helium as a tracer gas boosts sensitivity even more," says Dennis Seibert, head of business development, Leak Detection, at Pfeiffer Vacuum. Time spans for the offline test range from 10–60 seconds. Calibrated orifices quantify the leak rate and provide an alert if seal quality is deteriorating. Compatible with thermoformed or cold-formed blisters, testing a different blister only involves a simple fixture change.

The VeriPac UBV leak detection system from PTI Packaging Technologies and Inspection combines vacuum with volumetric imaging to detect leaks in multi-cavity blister packs. The nondestructive test involves three steps:

FIGURES ARE COURTESY OF THE AUTHOR.

input the number of blister cavities; place the blister pack on the inspection plate; press start. In seconds, the display shows pass or fail, the volumetric measurement reading, and the location of any defective cavity. The technology provides rapid detection of defects as small as 10 microns in a test cycle that lasts less than 15 seconds (12).

Innovative materials

Activ-Blister material from CSP Technologies heat-stakes absorbent material to the interior of blister cavities. Silica gel and molecular sieve technology absorb tailored amounts of water vapor, oxygen, or a combination of the two to control the internal atmosphere of each cavity and protect product shelf life. The active feature can be adopted without changing the footprint of the packaging line (13).

Another option for sensitive products, Pentapharm LiquiGuard film from Klöckner Pentaplast, offers protection from package leaching and moisture gain or loss. The crystal-clear, autoclavable laminate accommodates hot-fill liquids, gummies, and other emerging dosage forms. Features include a customizable moisture barrier, excellent deep-draw properties for complex blister geometries, high heat stability (the glass transition temperature of the contact layer is 120 °C), high slip for quick release and increased productivity, and low leachability and extractability, with excellent odor and flavor retention. Applications include chewables, formulations sensitive to flavor or odor loss, nutraceuticals, pharmaceuticals, unit-dose liquids, and veterinary products (14).

References

1. Maruho Hatsujyo Innovations, "At Pharma Expo, Maruho Hatsujyo Innovations to Introduce Blister Machine Specifically for U.S. Market," Press Release, Aug. 25, 2016.
2. Mediseal, "Flexibility All Along the Line," Brochure, undated.
3. Blipack, "Blister Packaging Machine 200-240," www.blipack.com.ar/eng/factory/200.htm, accessed Nov. 23, 2016.
4. Blipack, "Cartoning Machine ACM 150," www.blipack.com.ar/eng/factory/acm150.htm, accessed Nov. 23, 2016.
5. Pharmaworks, "TF1e/TC1 Line (New!), the All-in-One Solution," www.pharmaworks.com/index.php?id=210, accessed Nov. 23, 2016.
6. Marchesini Group, "All4Pack Paris: Marchesini Group Showcases the Amazing Integra 520 V Line and Two New Stand-Alone Machines," Press Release, Sept. 22, 2016.
7. Uhlmann Packaging Systems, "Blister and Cartoner Module in One Productive Unit," www.uhlmann.de/products/blister-lines.html, accessed Nov. 23, 2016.
8. Uhlmann Packaging Systems, "Uhlmann USA to Ramp Up Machine Rebuilding Services at New Jersey Facility," Press Release, Aug. 24, 2015.
9. Presto Products, "Slide-Rite Child-Guard Track & Slider," http://fresh-lock.com/product-list/slide-rite-child-guard-slider-zippers/, accessed Nov. 27, 2016.
10. Impak, "Impak Offers the Largest Selection of Child Resistant Pouches, Plus the Option for Labeling and Custom Print," www.impakcorporation.com/flexible_packaging/child-resistant-pouch, accessed Nov. 27, 2016.
11. Pharmaworks, "IBIS Inline Inspection," www.pharmaworks.com/index.php?id=271, accessed Nov. 23, 2016.
12. PTI Packaging Technologies and Inspection, "Introducing New Non-Destructive Technology for Blister Package Testing at PACK EXPO International," Press Release, Nov. 2, 2016.
13. CSP Technologies, "CSP Technologies, Inc. Introduces Activ-Blister Solutions for Customizable Product Protection at INTERPHEX NYC," Press Release, April 28, 2016.
14. Klöckner Pentaplast, "Pentapharm LiquiGuard Films from Klöckner Pentaplast," Press Release, Oct. 26, 2016. **PT**

DRUG QUALITY KEY TO INNOVATION AND ACCESS— *contin. from page 21*

The International Council for Harmonisation (ICH) has changed its name to reflect expanded involvement of health authorities from additional regions and of manufacturers representing additional industry components in its standards-setting activities. An important new quality guideline on lifecycle management of pharmaceuticals (Q12) is moving forward slowly, and should complement the series of ICH quality standards developed to encourage manufacturer adoption of modern production methods.

Expanded global sourcing of pharmaceutical ingredients and products will continue to build support for regulatory mutual reliance initiatives able to streamline agency oversight while assuring quality drug production in multiple regions. A growing collaboration involves GMP inspections of APIs by FDA and regulatory authorities in Europe, Japan, Australia, Canada, and by the World Health Organization (WHO). FDA and the European Medicines Agency also seek to avoid duplicate inspections by expanding a program for information sharing on planned site visits and on inspection outcomes from pre-approval and routine GMP inspections of drug manufacturers in both regions. While increasing its own oversight of foreign drug manufacturers, FDA will continue to support reliance on other inspectorates and on policies that promote quality drug production globally.

References

1. FDA, *Submission of Quality Metrics Data, Guidance for Industry, Draft Guidance* (CDER, CBER, November 2016), www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM455957.pdf
2. FDA, *Contract Manufacturing Arrangements for Drugs: Quality Agreements, Guidance for Industry* (CDER, CBER, CVM, November 2016), www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM353925.pdf
3. GS1 US DSCSA Implementation Suite, www.gs1us.org/industries/healthcare/gs1-healthcare-us-initiative/dscsa/implementation-guide **PT**

GE Healthcare Looks to Boost Biopharmaceutical Production with Synpromics Partnership

In an attempt to battle low production volumes of hard-to-manufacture biopharmaceuticals, GE Healthcare announced in January 2017 that it will partner with Synpromics on the development of synthetic promotors. The goal of the collaboration is to identify promoters that will work most effectively with GE's existing expression system for optimal transcription.

GE will couple its cell line with a library of bar-coded synthetic promoters from Synpromics to improve platform performance. Promoters drive stronger expression levels of a desired protein, so the partnership could help GE strengthen its platform for future manufacturing projects. Synthetic promoters are said to be capable of driving higher expression levels than do naturally occurring promoters.

"One of the attractive features of our technology is that we can design synthetic promoters to be active at the desired expression strength ... our technology essentially allows us to find the optimal expression level for the particular protein of interest in the environment and cell type of interest," David Venables, CEO of Synpromics, wrote via email.

In December 2016, Synpromics announced a similar deal with Sartorius Stedim Cellca. Both the Sartorius and GE projects focus on the discovery of promoters in Chinese hamster ovary (CHO) cells, but Sartorius and GE each have their own proprietary platforms. Synpromics has also created promoters specific to other human cell types, such as liver, skin, lung, cells of the eye, muscle, and cancerous cells.

Lonza to Acquire Capsugel

After a brief lull in contract services mergers and acquisitions activity, 2016 closed with a major announcement from Lonza that it will acquire Capsugel for $5.5 billion in cash, including refinancing of existing Capsugel debt of approximately $2 billion. The transaction has been approved by the boards of directors of both companies and is expected to close in the second quarter of 2017.

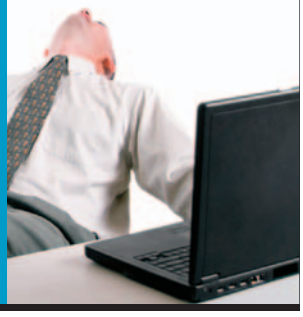
The integrated company will offer a portfolio of APIs, excipients, dosage forms, delivery technologies for both small- and large-molecule drugs. In a press statement announcing the acquisition, Lonza noted that the transaction is "fully in line with Lonza's stated strategy to accelerate growth and deliver value along the healthcare continuum by complementing its existing offerings and by opening up new market opportunities in the pharma and consumer healthcare and nutrition industries."

The acquisition also will allow Lonza to expand the market reach of its contract development and manufacturing organization (CDMO) and products businesses. The deal is expected to strengthen the company's position in consumer healthcare and nutrition as an integrated service provider of active ingredients, oral dosage forms, development services, and delivery technologies.

The press statement noted that the acquisition of Capsugel "will allow cross-selling of existing products, combine manufacturing solutions and services, and create an integrated value offering that merges Lonza's ingredients with Capsugel's dosage forms."

The initial focus of the transaction is to ensure a seamless integration while continuing the growth trajectory of the Capsugel business. The transaction will be financed with a combination of debt and equity financing, Lonza reports.

Ad Index



MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

Staffing and Preparation for Audits

Siegfried Schmitt, PhD, principal consultant, PAREXEL, discusses how to handle audits and inspections during business expansion.

Q: Our quality unit is responsible for hosting audits and inspections for our manufacturing site. We are a contract manufacturer and due to our expanding client base, we are experiencing a growing number of customer audits and regulatory inspections. Can you provide advice for how to best accommodate this increased workload?

A: First, congratulations on your growing business. In terms of managing this rising number of audits and inspections, we would recommend developing procedures. Formalized processes, in addition to using the right tools, can help make the job more predictable, improve planning, and provide a higher chance of success. You may call this a playbook, or simply "Good Guide to Audits/Inspections." Being prepared and having a defined process helps reduce uncertainty and drives efficiency.

Being prepared and having a defined process helps reduce uncertainty and drives efficiency.

It is good practice to start putting together this document by getting input from all parties involved. We recommend starting at the moment an audit or inspection is announced, and then structuring it by phase, such as preparation/planning, hosting, follow up/post event, and close out.

The guide should include roles, rather than name-specific individuals, when explaining responsibilities involved in the inspection, as this eliminates the need for many updates or changes. For each role, it is beneficial to describe each person's particular involvement in the inspection (e.g., active or stand by/back up), what and when they are needed, where (e.g., front office or back office "war room"), and any other pertinent information. Note that some roles may only be required occasionally, such as translators.

This playbook can be in any format suitable for your needs, but often it is in the form of a spreadsheet. A spreadsheet allows activities to easily be added into sequence and the ability to select tasks for individual roles or locations. Furthermore, completed tasks can be ticked off, together with any comments or feedback as required.

Information for auditors

A number of documents and data are typically requested by auditors and inspectors; including, but not limited to:

- Number of deviations
- Number of batches manufactured
- Number of out-of-specification (OOS) results
- List of standard operating procedures (SOP)
- Organizational structures
- Annual quality reports
- Number of complaints
- Number of recalls (if applicable).

Having a spreadsheet to refer back to, therefore, is crucial to staying organized and up to date with inspections. Having a running tally readily available in electronic format will greatly reduce the effort with preparations. It can also be beneficial to keep a set of printed copies of all SOPs handy, making these available upon request, which reduces time and effort during the audit or inspection.

Being prepared is key

Ultimately, the key to being prepared for audits and inspections is to follow the old adage: preparation, preparation, preparation. Furthermore, with practice comes experience, and with experience comes perfection. Maintaining procedures and metrics will be helpful for any inspection, especially as you expect to experience more inspections due to a growing client base. PT

Your opinion matters.

Have a common regulatory or compliance question? Send it to susan.haigney@ubm.com and it may appear in a future column.

Pharma&Biotech

Lonza

Focused on Your Success

Committed to Global Innovation for Human Health

Lonza has been a reliable partner in the life sciences industry for over 30 years. Our experience in biological and chemical development and manufacturing has allowed us to create a broad platform of technologies and services for fine chemicals, advanced intermediates, active pharmaceutical ingredients (APIs), functional ingredients, biologics, cell and viral therapies.

We are committed to continued innovation with a focus on future scale-up technologies and emerging markets. Whether you are an established pharmaceutical company or an emerging biotech, Lonza is prepared to meet your outsourcing needs at any scale.

Why Outsource with Lonza?

- Full range of services from preclinical risk assessment to full-scale commercial manufacturing
- Advanced technologies and optimized processes to streamline your product pipeline
- 10 contract development and manufacturing sites worldwide
- Experience with worldwide regulatory authorities
- Track record in meeting accelerated timelines associated with breakthrough therapy designated products
- Dedicated project teams committed to comprehensive and timely communications
- Lean, sustainable processes that minimize waste and environmental risk

For more information, contact us at:
North America: +1 201 316 9200
Europe and Rest of World: +41 61 316 81 11
custom@lonza.com

www.lonza.com/oursites

SCREEN FORMULATE DESIGN

Catalent®
DEVELOPMENT

NEW
Catalent Acquires Pharmatek
EARLY DEVELOPMENT & SPRAY DRY CAPABILITIES

your molecule has so much potential. we share your passion to unlock it.

As the #1 global leader in drug development and delivery, we have a passion to help you bring better treatments to your patients, faster.
Our broadest expertise and superior technologies helped optimize thousands of molecules from pre-formulation through all development stages. Our integrated analytical, clinical, and manufacturing services along with patient-centric dose design streamlines and accelerates your path to patients.

- PRE-FORMULATION / FORMULATION
- OPTIFORM® SOLUTION SUITE
- BIOAVAILABILITY ENHANCEMENT
- STABILITY & SCALABILITY
- DOSE FORM DESIGN
- MODIFIED RELEASE
- COMPLETE ANALYTICAL SUPPORT
- SEAMLESS SCALE-UP

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™
US + 1 888 SOLUTION (765-8846) **EU** + 800 8855 6178 catalent.com/development