OCTOBER 2018 Volume 30 Number 10

Advancing Development & Manufacturing

Pharmaceutical Technology® EUROPE

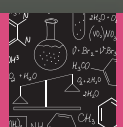
PharmTech.com

New Dose Forms Break the Mould

UBM

FORMULATION
Lipid-Based Formulations

PEER-REVIEWED
Internal Release Limits



API SYNTHESIS
Advances in API Labs

PDA Europe Conference, Exhibition, Education

PDA
Parenteral Drug Association

Pharmaceutical Freeze Drying Technology

Freeze Drying of the Future

PDA EXCHANGE SERIES
WITH THE 11TH WORKSHOP ON MONOCLONAL ANTIBODIES

27-28 November 2018

pda.org/EU/FreezeDrying2018

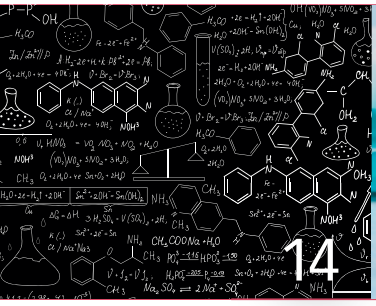
MELIÁ Hotel
Seville | Spain

Pharmaceutical Technology Europe 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.

October 2018

Advancing Development & Manufacturing
Pharmaceutical Technology EUROPE
PharmTech.com

Cover: Dan Ward
Art direction: Dan Ward



PharmTech.com

Features

Peer-Reviewed

Columns and Regulars

Pharmaceutical Technology
EUROPE

PharmTech Group
Editorial Director
Rita Peters
rita.peters@ubm.com

PharmTech Europe
Editor
Felicity Thomas
felicity.thomas@ubm.com

Senior Editor
Agnes Shanley
agnes.m.shanley@ubm.com

Managing Editor
Susan Haigney
susan.haigney@ubm.com

Manufacturing Editor
Jennifer Markarian
jennifer.markarian@ubm.com

Science Editor
Feliza Mirasol
feliza.mirasol@ubm.com

Associate Editor
Amber Lowry
amber.lowry@ubm.com

Contributing Editor
Cynthia A. Challener, PhD

Global Correspondent
Sean Milmo
(Europe, smilmo@btconnect.com)

Art Director
Dan Ward

Publisher
Michael Tracey
mike.tracey@ubm.com

Sales Manager
Linda Hewitt
Tel. +44 (0) 151 353 3520
linda.hewitt@ubm.com

Senior Sales Executive
Stephen Cleland
Tel. +44 (0) 151 353 3647
stephen.cleland@ubm.com

Sales Operations Executive
Barbara Williams
barbara.williams@ubm.com

C.A.S.T. Data and List Information
Michael Kushner
michael.kushner@ubm.com

Published by
UBM
Hinderton Point
Lloyd Drive
Cheshire Oaks
Cheshire CH65 9HQ, United Kingdom
Tel. +44 151 353 3500
Fax +44 151 353 3601

UBM Americas:
Chief Executive Officer
Scott Schulman

Chief Operating Officer
Brian Field

Head of Legal
Michael Bernstein

EVP & Senior Managing Director, Life Sciences Group
Thomas W. Ehardt

Senior VP, Finance
Tom Mahon

EVP & Managing Director, UBM Medica
Georgiann DeCenzo

VP & Managing Director, Pharm/Science Group
Dave Esola

VP, Marketing & Audience Development
Joy Puzzo

UBM PLC:
Chief Executive Officer
Tim Cobbold

Chief Financial Officer
Marina Wyatt

EDITORIAL ADVISORY BOARD

Above is a partial list of the *Pharmaceutical Technology* brand editorial advisory members. The full board, which includes advisory members of *Pharmaceutical Technology* North America, can be found online at www.PharmTech.com/pharmtech-editorial-advisory-board. *Pharmaceutical Technology* publishes contributed technical articles that undergo a rigorous, double-blind peer-review process involving members of our distinguished Editorial Advisory Board. Manuscripts for editorial consideration should be sent directly to Susan Haigney, managing editor, susan.haigney@ubm.com.

SHIMADZU
Excellence in Science

Rookie of the year

Small size. Massive impact.

The MALDI-8020 is the newcomer in the Shimadzu family of MALDI products. This linear MALDI-TOF mass spectrometer combines talents and skills such as outstanding speed, accuracy and performance. It targets researchers developing MALDI-based diagnostic methods as well as labs where quality control methods or rapid screening of intact samples are routine.

Small size
due to benchtop design with a compact footprint

Massive impact
through performance similar to larger, more expensive devices

Multi-talent system
for analysis of proteins, peptides, polymers and other analytes

Additional 'Rookie of the year' talents
such as TrueClean automated cleaning source, barcode reader and MALDI Solutions software for Pharma quality control labs

www.shimadzu.eu/rookie-of-the-year

Hygienic Connection Box Range

Flexicon's new range of stainless-steel connection boxes are suited for applications requiring high levels of hygiene and ingress protection. The boxes offer high ingress protection with IP66, IP67, IP68, and IP69 performance, and provide reliability in areas requiring frequent wash-down routines where connections will be subject to extended wet and/or damp conditions.

According to the company, the stainless-steel construction offers improved corrosion resistance and has been hygienically designed to prevent the buildup of microorganisms and bacteria using the principles of BS EN 1672-2 and EN ISO 14159.

The company states that the round boxes are designed to be secure and easy to install with fixing holes provided for easier mounting. The design consists of a base and lid construction with blue, high-visibility polyester elastomer seals, and provides quick access to cabling routed through connecting conduits. Slots in the lid also allow for secure tightening and aid opening during maintenance to reduce downtime.

Flexicon
www.flexicon.uk.com

Low-Profile, Sanitary Screener

A new Low-Profile, Flo-Thru Sanitary Screener from Kason scalps oversize particles and foreign matter from dry bulk materials and solids-laden slurries at high rates in low headroom areas.

The screener uses two unbalanced-weight gyratory motors mounted on opposing exterior sidewalls of the screening chamber instead of one motor positioned beneath it, reducing minimum height requirements significantly, according to the company. The screener's design is mounted on suspension springs and allows vertical alignment of the top inlet and bottom outlet, enabling on-size material to rapidly descend through the screen in a straight-through path at high rates into downstream equipment or receiving vessels. Oversize material is ejected through a spout at the periphery of the screen.

The unit is available in a diameter range of 460 to 2540 mm with interchangeable screens that allow sifting of on-size materials as fine as 38 microns (400 mesh). Quick-release clamps allow rapid removal of screens and tool-free disassembly of frames for thorough wash down of components (including the motors), as well as rapid interior access for inspection and screen changes. All material contact surfaces are of stainless steel with continuous welds polished to cGMP, US FDA, or industrial standards.

Kason
www.kasoneurope.com

Custom Multi-Shaft Mixer

Ross, Charles & Son added a custom 150-gallon Triple Shaft Mixer, the Ross VersaMix Model VMC-150, with elaborate automation and safety functions.

Customized features include six pneumatic clamps rated for 4000 lbs., each for remote locking of the mix vessel to the mixer cover designed for 29.5-in. Hg vacuum and 5-psi internal pressure. The clamps function as redundant limit switches, allowing for operation only when secured. The mixer also includes automated valves for powder feed and clean-in-place liquids, a resistance-temperature detecting multi-point temperature sensor, built-in vacuum pump assembly, load cell system, and a centralized human machine interface.

The three independently-driven agitators of the company's Triple Shaft Mixers include a high-speed saw-tooth dispersing blade for quick product wet out, a three-wing anchor for efficient transport of viscous product throughout the mixing zone, as well as a third shaft, frequently a high shear rotor/stator homogenizer for emulsification. Instead, this VMC-150 model features a helical auger screw for submerging floating agglomerates. When reversed, the auger screw surfaces air pockets resulting in decreased batch cycle time. The sides and bottom of the mixing vessel are jacketed and insulated for operation up to 100 PSIG at 250 degrees.

Ross, Charles & Son
www.mixers.com

Mass Spectrometer for Analyzing Complex Samples

The LCMS-9030 quadrupole time-of-flight (TOF) liquid chromatograph mass spectrometer from Shimadzu is a research-grade mass spectrometer suited to deliver high-resolution, accurate-mass detection with fast data acquisition rates, allowing scientists to identify and quantify more compounds with greater confidence.

The instrument provides a new solution for analyzing complex samples and integrates quadrupole technology with TOF architecture to improve high-mass accuracy workflows by maintaining high-sensitivity, high-speed, and high-resolution detection, as stated by the company. Features include less need for calibration and easy switching between ionization units. Core ion beam technologies transition towards a unique approach in ion gating using UFaccumulation to create a precise pulse of ions in the flight tube optimized for high sensitivity and high resolution using iRefTOF reflectron technology.

Shimadzu
www.ssi.shimadzu.com

MOVE PRODUCTS NOT CONTAMINATION

CART 2 CORE

ELIMINATE CART WHEEL DISINFECTION

- Reduces safety concerns with cleaning.
- Provides the ability to steam sterilize bases & wheels.
- Eliminates the over use of disinfectants, reducing corrosion and pitting.
- Reduces garment contamination and gloves ripping.
- Available in 3 styles: Mircro Cart, Can & Bottle Cart, and Tray Cart. **Custom Built Carts also available.**

For more information visit: **sterile.com/cart2core**

vai

Veltek Associates, Inc.
15 Lee Boulevard
Malvern, PA 19355
Patents: sterile.com/patents

STERILE.COM

Sean Milmo
is a freelance writer based in Essex, UK, seanmilmo@btconnect.com.

Curbing Drug Shortages in Europe

A European task force outlines its upcoming efforts to combat drug shortages.

The European Union is stepping up its efforts to sort out the chronic problem of drug shortages, which has now been a priority for the EU's medicines agencies for several years.

In late August 2018, a joint EU task force on the issue of unavailability of authorized medicines published its work programme for the next two years. The task force was set up in December 2016 by the European Medicines Agency (EMA)—responsible for centrally approved drugs—and the Heads of Medicines Agencies (HMA), which deals with authorizations at the national level.

The programme shows that if all goes to plan, by 2020 the task force will have laid a foundation for a regulatory and supplies management framework that could curb the increasing number of incidents of drugs shortages across Europe. The sudden acceleration in activity on the issue comes as two events loom on the horizon that could cause—temporarily at least—major disruptions to drug supplies.

The task force's purpose is to put forward long-term solutions.

Bracing for Brexit

The biggest of these is Brexit, under which the United Kingdom is due to depart from the EU on 30 March 2019 with the status of a third country independent of the Union's regulations, including those covering medicines. The UK government revealed in August that it is working with the country's pharmaceutical sector to stockpile next spring an additional six weeks supply of medicine if the UK exits the EU without a withdrawal agreement. A 'no-deal' Brexit with customs barriers being erected between the UK and the remaining 27 EU member states would also impact not only medicines imports from mainland Europe but also the considerable number of medicine exports from the UK to its European neighbours.

The UK and the EU 27 countries seem likely, however, to avoid a no-deal by reaching an agreement this November on measures to soften the regulatory effects of Brexit, including allowing a transition period for a full implementation of the departure by the end of 2020.

Nonetheless, since the country will still legally become a third country at the end of next March, pharmaceutical companies in the UK will have to make regulatory changes, such as transferring quality control activities and the marketing authorization holder (MAH) status of their medicines to a EU state. Small and medium-sized enterprises (SMEs) in the UK are already admitting they may not be able to meet these obligations on time so that the post-Brexit marketing of their drugs in the EU next spring would be illegal.

Serialization pressure

The other event threatening medicines supplies—although to a lesser extent than Brexit—is the implementation on 9 Feb. 2019 of an EU mandatory scheme for the serialization or barcode identification of individual packs of medicine. The new regulation is being introduced to combat counterfeiting of drugs under the EU's Falsified Medicines Directive.

There are dangers that the IT infrastructure necessary for the operation of the scheme across the EU may not be fully in place by the deadline. Also, SMEs throughout the EU may have failed to upgrade their packaging lines or arranged to have access to modernized equipment on time.

The EMA–HMA task force, whose members represent the agencies in the EU's medicines regulating network, is planning to provide a co-ordination and communications platform to deal with any medicine supplies difficulties next spring, particularly relating to Brexit. It is already drawing up its own guidance on the implementation of post-Brexit regulatory changes like MAH transfers.

Keeping medicines available

But the main impetus behind its work programme for the next two years is the need to fulfil the objectives of the five-year year strategy, launched in 2015, of the medicines agencies network. Dealing with the lack of availability of authorized medicines is a prime aim of the strategy.

The task force will be guided by a reflection paper of the network, also issued in August 2018, on medicines availability. The paper aims to "provide an oversight of initiatives (and to) propose and explore intended actions to be considered by the network" (1).

The work programme, which is mainly focused on putting into effect actions agreed by the task force in early 2017, covers three main areas: facilitating the authorization and marketing of medicines to minimize shortages, the prevention and management of supply chain disruptions, and the communication of information on availability issues.

The task force's purpose is to put forward long-term solutions. But what happens to medicines supplies next spring after Brexit and the introduction of the serialization

regulation could show that other aspects of the whole issue of drug availability may need to be given equal or even greater importance.

In its new work programme, the task force's first major job is to complete by the end of 2018 the drawing up of EU-wide common definitions of medicine shortages and what types of specific shortages should be considered to be reportable.

"Until (uniform) definitions are in place we cannot compare shortages/supply disruptions across the EU," says the reflection paper (1). The paper shows that there is no harmonized definition or approach to the management of shortages in the EU, particularly at the national level. "There is a lack of clarity of what, when, and to whom reports of shortage/unavailability/supply chain disruption should be made," according to the paper.

The timeframes laid down by the national regulatory authorities for reporting shortages or supply chain disruptions ranges from up to 12 months in some EU states to 96 hours in Belgium and 72 hours in France. At the same time, there are approximately 20 different definitions of shortages in use across the EU, says the paper.

One difficulty facing the task force is that stakeholder groups have different views on what constitutes a shortage. For healthcare professionals and patient representatives, the definition should be determined by how much the lack of availability of a medicine impacts patients. Industry representatives want a distinction between shortages that affect patients and supply disruptions that could be managed with or without regulatory action, according to the paper.

A joint report issued in 2018 by manufacturers, distributors, and health professional associations stressed the importance of a common definition of a suspected medicine shortage (2). This definition would then be used to establish a simple mechanism for assessing a 'signal' of a suspected shortage and for deciding whether it is an actual medicine shortage.

It suggested the definition of a suspected shortage as being "the inability for a community or hospital pharmacy, as a result of factors beyond their control, to supply a medicinal product to a patient within a defined period." The report emphasized the importance of all suspected shortages being recorded, whether they are single or multi-source products.

The reflection paper advises that definitions should consider "availability in a wider sense," with distinctions, for example, between worldwide non-availability and shortages of a medicine which is available in some EU states but not in others.

By the end of this year, the task force is also due to provide metrics for measuring the extent of shortages so that they can be more easily managed and monitored. Metrics would enable benchmarking of shortages due to causes such as manufacturing problems and distribution difficulties.

Over the next few months, the task force is scheduled to review existing guidance to network agencies on managing shortages, including those that may arise as a result of Brexit. It is also investigating—possibly in preparation for any supply disruptions in the spring—existing ways regulatory agencies communicate to the public information on medicines availability.

Work on other issues in the task force's programme, scheduled to be finished between next summer and the end of 2020, include matters such as sharing information within the network and setting up single contact points.

In 2019, the task force is tackling potentially thorny questions involving interaction with industry. Guidance for companies on reporting shortages will be completed by mid-2019 and ways of encouraging best practices by industry in preventing shortages will be finalized by the end of next year.

It will be considering ways of introducing authorized medicines into certain national markets that some pharmaceutical companies avoid often because of costs or low returns.

By the end of 2020, it is due to complete work on an initiative on the use of multilingual packages so that medicines with the appropriate translated patient information can be distributed in countries experiencing shortages.

The task force is also scheduled to complete a review in two years of the existing procedures for withdrawals of medicines from markets to enable adequate transition periods for ensuring sufficient supplies of alternative products.

The network's reflection paper indicates that in the longer term it may be necessary for supply standards to be covered by good manufacturing practice (GMP). This could be done by amending chapter one of the EU GMP guide, which details all matters that individually or collectively influence the quality of a product (1).

MAHs could be required to identify products at risk from potential supply chain disruptions. With medicines deemed to be of critical importance, MAHs may have to draw up plans for preventing shortages. These prevention plans could be the subject of future guidance documents from the agencies network, according to the reflection paper.

The paper warns about the size of the challenge facing the EU. There are a wide range of causes behind shortages, some of which are global in scope, it says. Resolving the problem is going to be a long haul.

References

1. Heads of Medicines Agencies (HMA) and European Medicines Agency (EMA), ''European Union regulatory network reflection paper on the availability of authorised medicinal products for human and veterinary use.'' EMA/565780/2018 (Brussels, 23 Aug. 2018)
2. The European Association of Euro-Pharmaceutical Companies (EAEPC), Medicines for Europe, The European Association of Hospital Pharmacists (EAHP), European Healthcare Distribution Association (GIRP) and four other industry and professional associations. ''Joint Supply Chain Actors' Statement on Information and Medicinal Products Shortages.'' (Brussels, February 2017). **PTE**

New Dose Forms Break the Mould

Innovative technologies, such as drug-loaded devices and 3D printing, bring patient focus to drug delivery.

Jennifer Markarian

The pharma industry is increasingly focusing on patients as it considers drug development. Both innovative dosage forms, such as implantable drug–device combination products, and novel manufacturing methods, such as three-dimensional printing, are creating opportunities for solving drug-delivery challenges.

Drug-loaded implants

Interest from both pharmaceutical companies and medical device companies in developing drug-device combination products, such as drug-loaded implants for local delivery, is growing. Device makers in this arena typically seek to add a drug functionality to a device, such as a steroid-eluting pacemaker lead or an antimicrobial-eluting catheter, notes Jim Arps, director of Pharma Services at ProMed Pharma, a contract manufacturer of polymer-based, drug-releasing dosage forms and combination device components. Pharma manufacturers, on the other hand, are typically looking for a drug-delivery format, particularly for controlled release. "The beauty of these systems is their capability for long-term, consistent release," says Arps.

Drug-loaded implants can improve patient compliance by reducing dosing and side effects. "Side effects are minimized because the drug is delivered at the site of action and does not have to travel through the many natural barriers in place in the human body (e.g., stomach and other organs), and dosing can be reduced because the implants deliver the dose over a long period of time (e.g., weeks or months) as opposed to hours for oral dosage forms," says Tony Listro, vice-president of Technical Business Development at Foster Delivery Science.

One of the commercial uses for drug-loaded implants is ocular drug delivery; ocular indications are difficult to treat with oral dosage forms, and the eye itself has many barriers to protect it from topical treatment, notes Listro.

Approved uses are expanding into other areas. Titan Pharmaceuticals, for example, produces the Probuphine (buprenorphine) Implant, a six-month subdermal implant for long-term maintenance treatment of opioid addiction that was approved by the United States Food and Drug Administration (US FDA) in 2016. The product is being commercialized by Titan in the US and, upon approval by the European Medicines Agency, will be commercialized in Europe and certain other territories by Molteni Farmaceutici of Italy. The company says that the proprietary ProNeura implant technology has the potential to be used in developing treatments for many chronic conditions such as Parkinson's disease, Type 2 diabetes, hypothyroidism, and others for which consistent, around-the-clock dosing is important.

Some of the earliest commercial drug-loaded implants were contraception products that are matchstick-sized rod-shaped implants injected subcutaneously into the arm, where they release

Dan Ward

Capsugel | Lonza Pharma & Biotech

Spray dried to perfection.

Capsugel

Dry-Powder Inhalation capsule portfolio

Tailored to achieve the desired performance

Gelatin

Coni-Snap® Gelatin

Coni-Snap® Gelatin-PEG

HPMC

Vcaps®

Vcaps® Plus

Consistent powder release

Customized approach to guarantee optimal performance of the end product

Compatible with a large selection of device principles and opening systems

Ideal puncturing and cutting performance

Made better. By science. ™

Want to know more?
Visit www.capsugel.com

the drug for multiple years and then are surgically removed. For years, researchers have hoped to develop biodegradable implants that would eliminate the need for surgical removal.

Most recently, Hera Health Solutions, a start-up out of the Georgia Institute of Technology, is developing proprietary, biodegradable implants for extended-release drug delivery using existing generic drugs in combination with FDA-approved structural materials, notes company cofounder and CEO, Idicula Mathew. All of the company's potential products use bioresorbable excipients and are intended to eliminate the need for an implant removal procedure, and the company's biodegradable contraceptive arm implant, Eucontra, is currently concluding *in-vitro* testing. The company's proprietary manufacturing process creates a layered drug-excipient matrix that erodes over a long period of time and retains its shape, strength, and flexibility, notes Mathew.

Biodegradable and biodurable matrices

Drug-loaded devices deliver controlled release of a drug either by diffusion or by an erodible matrix. "In diffusion-controlled drug delivery, the polymer matrix remains intact while the drug is gradually deployed to the therapeutic site, either by encapsulating the drug in a polymer shell or coating, or by distributing the drug throughout a non-degradable (i.e., biodurable) polymer matrix," explains Listro. "Erodible matrix implants are produced through the encapsulation or distribution of the drug in an erodible polymer, such as a water-soluble or bioresorbable polymer. As the polymer erodes in the body, the drug is released."

Biodurable polymers that can be used as matrices for drug-loaded devices include low density polyethylene (LDPE); ethylene co-vinyl acetate (EVA), at various levels of vinyl acetate; polyurethanes; and silicone. Polymer excipients used for hot-melt extrusion of oral dosage forms (e.g., polyvinylpyrrolidones, cellulosics, and acrylics) can also be used. Bioresorbable polymers include polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polydiaxanone (PDO), and others. PLA and PGA are commonly used, but they degrade by hydrolysis into acidic byproducts; other polymers that have enzymatic degradation pathways may work better with certain APIs, notes Arps.

Manufacturing considerations

Drug-loaded implants are typically manufactured by mixing the API into the excipients before forming the final shape, using extrusion to make simple shapes (e.g., fibers, monofilaments, rods, tubes, sheets, or other profiles) or injection moulding to make either simple or complex, three-dimensional shapes. An alternative method sometimes used with silicones is to form the implant and then infuse it with the drug.

High-precision injection moulding creates tight dimensional tolerances (controlled within a few microns) and good surface finishes, says Arps. "In addition to complex shapes, such as stents, injection moulding can be beneficial for simple shapes, such as rods, especially if the material is brittle and difficult to cut. A drawback for rods is that moulding may be a little slower in overall throughput and produce more waste material than extrusion," Arps adds.

Coextrusion can be used to make multi-layer shapes, such as a drug core with a rate-controlling membrane. "The drug-loaded layer

Drug Delivery Innovation Funded by the Gates Foundation

The Global Health division of the Bill and Melinda Gates Foundation is seeking solutions for health problems, such as infectious diseases, that impact the developing world. One of the challenges is identifying drug delivery forms to compensate for the lack of infrastructure in these regions. "The lack of healthcare providers means there is a need for simple delivery to avoid mistakes," explained Niya Bowers, senior program officer for Chemistry, Manufacturing, and Controls in Global Health & Integrated Development, Gates Foundation (1). "Another problem is poor access and a limited supply chain; the last mile is often carried by person, animal, or motorcycle on poor roads. Rugged, lightweight, and compact products are needed. Combination products also help so patients don't have to travel to the clinic frequently. Drug stability is also a challenge due to the lack of a cold chain in many areas."

Solutions must be both inexpensive and protect drug quality, added Bowers. The Foundation funds research programmes with various partners. Of the 60 programmes in their pipeline, 40% are complex solid oral delivery forms, not just simple tablets. For example, a long-acting oral drug for malaria prevention was developed in Dr. Robert Langer's laboratory at the Massachusetts Institute of Technology using funding from the Gates Foundation and is being further developed for other potential uses at a spin-off company called Lyndra (2). Another example is a long-duration implant for HIV prevention. At the end of 2016, Intarcia received funding from the Gates Foundation to develop an anti-HIV prophylactic therapy using its Medici Drug Delivery System, which is a matchstick-sized, osmotic mini-pump implanted under the skin (3).

According to the Gates Foundation, these and other innovations could reduce and eventually eradicate infectious diseases such as malaria. The Foundation has committed nearly €1.72 billion (US $2 billion) in grants to combat malaria and more than €1.37 billion (US $1.6 billion) to the Global Fund to Fight AIDS, Tuberculosis, and Malaria (4).

References

1. N. Bowers, "Leveraging Modern Manufacturing for Global Health—Is this Possible?" presentation at IFPAC (North Bethesda, MD, 2018).
2. MIT, "New Capsule Achieves Long-Term Drug Delivery," Press Release, 16 Nov. 2016.
3. Intarcia, "Intarcia Secures Second Close of the Series EE Equity Financing for an Additional $206M; As Part of the Financing and a New Strategic Initiative, Intarcia Now Aims Its Medici Technology Towards Preventing HIV," Press Release, 29 Dec. 2016.
4. Gates Foundation, "Malaria: Strategy Overview," www.gatesfoundation.org/What-We-Do/Global-Health/Malaria, accessed 27 Aug. 2018.

can also be the outer layer with a [unloaded] polymer used on the inside as a strength member for explantation," adds Listro. The type of extrusion equipment used can be selected depending on the formulation (i.e., the processing conditions it can handle) and the tolerance needed in the final part, with a variation of less than 10 microns possible.

Understanding the physicochemical characteristics of the API (e.g., melting point, degradation temperature, flow characteristics) and any API-excipient interactions is important in developing the formulation and optimizing the manufacturing process. Twin-screw extruders used for mixing the API and excipient can be optimized for a formula, so getting a formulation to work can be more of an engineering exercise, notes Listro. Choosing an appropriate feeder, feeding point, screw design, and temperature profile, for example, are important variables.

Sensitivity of the ingredients to processing temperatures, shear energy, and moisture are other considerations. "Some silicones can be mixed and cured at room temperature. Thermoplastic polymers are processed in the range of 100–150 °C, and the API will need to be able to handle those temperatures for a short time period," says Arps. He adds that some degradable materials may have moisture sensitivity and require processing under low humidity conditions to avoid degrading the polymer, which would affect the drug release.

3DP

While extrusion and injection moulding are traditional methods of forming polymer devices, three-dimensional printing (3DP) is an emerging manufacturing technology being used to produce medical devices and, since the 2015 approval of Aprecia Pharmaceuticals's Spritam (levetiracetam), solid-dosage drug forms as well. 3DP, also called additive manufacturing, is a category of manufacturing methods that are used to form a product by building it layer-by-layer using digital control. 3DP lends itself to customization of complex products, and it has been described as a way to allow personalized and even on-demand medicine, once requirements such as quality control and safety testing can be achieved.

3DP is also being investigated as a manufacturing method for microneedles used in transdermal patches, in which the ability to quickly change geometries could be useful for prototyping, and for making complex, delayed-release capsule shells that could be used in clinical trials (1).

Aprecia, which manufactures what is currently the only FDA-approved 3D-printed drug, is employing 3DP for cGMP manufacturing of solid-dosage drugs marketed through the conventional, FDA-approved regulatory path. Tim Tracy, CEO of Aprecia, comments that the greatest advantage of the process is "the ability to produce novel dosage forms that are not possible by traditional tablet and capsule processes. 3DP allows us to produce unique shapes, varying degrees of dispersion and disintegration, customization of dosage, and the potential for flexibility and combining multiple drugs."

The company uses its ZipDose technology to produce a tablet that combines the benefit of rapid disintegration in the mouth with taste-masking ability and high drug load; Spritam tablets, for oral suspension for treatment of seizures in adults and children with certain types of epilepsy, provide an easy-to-swallow alternative to existing, large pills. The technology could also be used to make extended-release forms.

In December 2017, Aprecia announced a partnership with Cycle Pharmaceuticals to develop and commercialize orphan drugs using ZipDose technology, and an initial product is in the development and formulation stage.

FabRx, established in 2014 by researchers from the University College London, is focused on optimizing 3DP technology for manufacturing solid-dosage drugs and identifying drugs that would be most suitable for using 3DP for personalized medicine. "3DP offers many opportunities to researchers by creating customized formulations that will be useful in clinical trials for testing new drugs, in the treatment of rare diseases (where the number of patients is low and costs are high), or in treatments where doses change frequently depending on therapeutic needs (e.g., narrow therapeutic index medicines)," says Alvaro Goyanes, director of Development at FabRx. Ensuring that this novel manufacturing process can accurately produce quality drugs is crucial, notes Goyanes, who adds: "We are working to integrate a quality control system in the printer to enable both the production and real-time release of medicines at the dispensing point. In the near future, we envision that hospitals and pharmacies will have 3D printers on-site, enabling healthcare professionals to print out tailor-made medicines on-demand."

Disruptive technology?

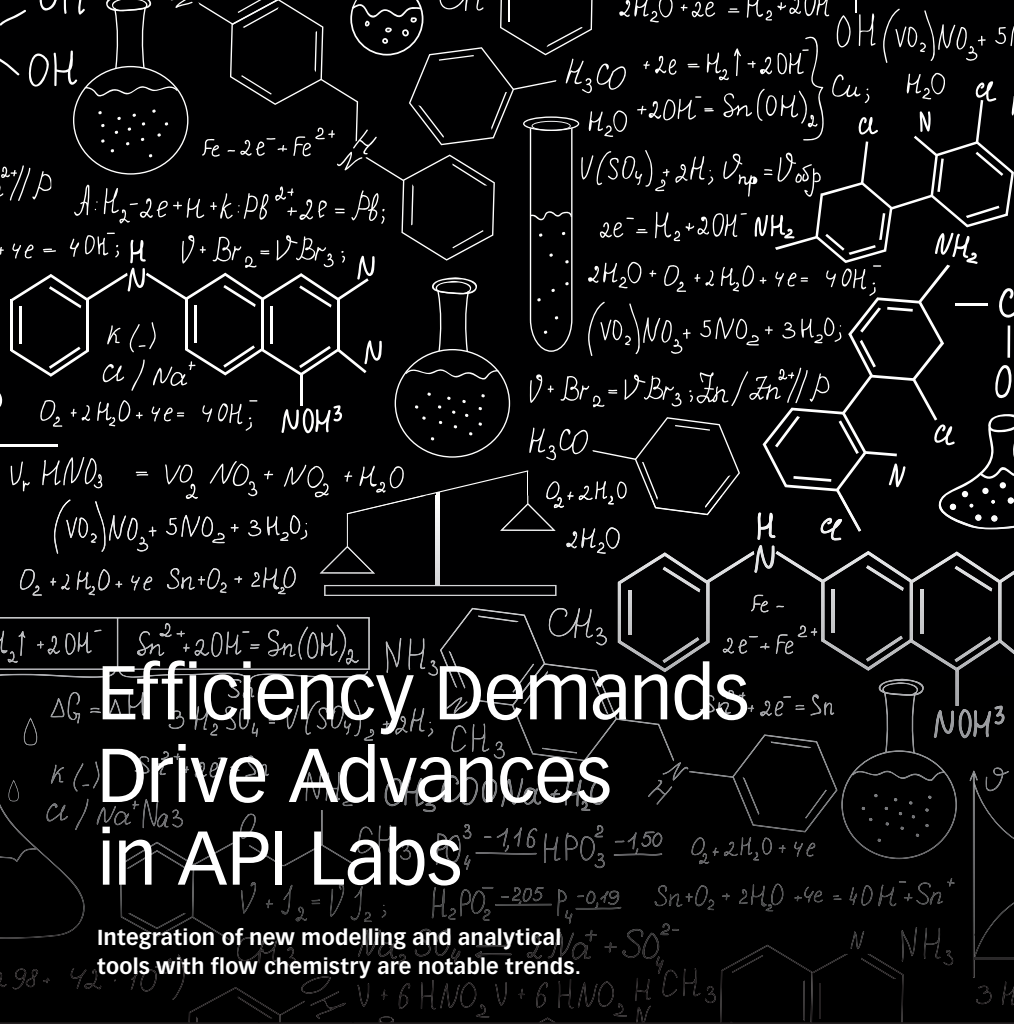
3DP could be a disruptive technology in pharmaceutical manufacturing. Once technical and regulatory issues are addressed, it could enable the development of more personalized therapies. How soon this technology advances and to what extent it might replace traditional manufacturing remain to be seen. Considering how 3DP has found a niche in other manufacturing industries, however, pharmaceutical manufacturers should monitor 3DP developments closely.

Reference

1. A. Procopio, "3D Printing for Dosage Form Design and Delivery," presentation at IFPAC (North Bethesda, MD, 2018). **PTE**

For more on 3DP

To read an interview with researchers from the University College London and FabRx on their work in 3DP, go to PharmTech.com/considering-3d-printing-solid-dosage-forms.



Efficiency Demands Drive Advances in API Labs

Integration of new modelling and analytical tools with flow chemistry are notable trends.

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

A key focus of the pharmaceutical industry today is increasing efficiency and productivity to reduce cost and time to market. These issues are being addressed across the entire development lifecycle, including in API development labs. From improvement of existing technologies to the introduction of more advanced analytical instruments and modelling software, development labs are focused on increasing speed of optimization and reducing issues during scale up.

Need for speed

Innovation in API development labs is taking place at all pharmaceutical companies. Adam Kujath, senior director of global manufacturing sciences and technology at Alcami, points out how this innovation is being driven largely by smaller pharma and biotech companies. "Speed is the most important thing for these organizations as they work to get into and through the clinic as quickly as possible. Therefore, most investments are not necessarily for exotic new technologies, but rather expansion and improvement of those that drive more efficient throughput," he comments. Examples include robotic screening equipment, parallel reactors, and more advanced in-line analytics to support process characterization.

Flow chemistry for the synthesis of APIs is an important trend in the industry, according to Rui Loureiro, director of R&D process chemistry development for Hovione. "Flow chemistry enables the implementation of chemistries that previously were not possible due to a lack of technology. As a result, chemists are gaining access to new methods for producing new and more complex molecules," he says. It can also dramatically reduce scale-up times because the same equipment can be used in the lab and for production, just for longer periods of time and/or in multiple copies.

A side benefit of the interest in flow chemistry is improvements in process analytical technology (PAT)—including nuclear magnetic resonance (NMR) spectroscopy and high-performance liquid chromatography (HPLC)—are being developed to allow their use for continuous manufacturing, according to Loureiro.

Equipment integration and miniaturization

The ability to integrate different aspects of API development laboratory initiatives is helping to speed up activities. Access to a growing selection of miniaturized probes with high resolutions allows researchers to more quickly gain a better understanding of how crystals are formed and how polymorphic forms can be controlled, according to Jerod Robertson, a senior process chemist at Hovione.

He points to smaller probes for focused-beam reflectance measurements and particle vision and measurement from Mettler Toledo as examples that allow performance of crystallization studies in smaller reactors using smaller quantities of expensive API. "Using less material is important since at the beginning of development there normally aren't significant amounts of product available, but the shape and size of the obtained crystals should be understood as in-depth as possible because these parameters can significantly impact process development down the road to reaching the commercial phase," Robertson explains.

Most notable for Alcami when it comes to equipment advances has been the integration of multiple systems, according to Kujath. "When a piece of equipment capable of performing automated, high-throughput synthesis or crystallization experiments is directly integrated with direct sampling for multiple forms of analysis on the same system, it drives efficiency, such as the Bruker D8 Discover HTS[2]. Better, more robust data sets can be obtained, making tools such as design of experiments more accessible for earlier development activities and thereby allowing Alcami to create stronger early clinical processes," he observes.

More intuitive software

Advances in software are equally important as improved equipment and technology. "Software packages are becoming more intuitive, which is important as the databases behind them grow," Kujath notes. "Scientists today build on the developments of those who came before them, and the software packages that exist today are making that information more accessible for application on a daily basis," he adds.

At Hovione, using the simple but effective Dynochem (Scale-Up Systems) and Visimix (VisiMix Ltd.) software packages for optimizing scale up and mixing processes and equipment have been great tools for chemists responsible for the scale-up of API syntheses. "The use of Dynochem has enabled Hovione to achieve faster development of unit operations such as solvent swapping, and it has also been a great tool for understanding reaction mechanisms, including those that lead to impurity formation," Loureiro says. Such understanding helps the development chemists implement effective control strategies that ensure product quality.

The use of tools such as Visimix provides chemists with a greater understanding of effects like mass transfer and mixing and how they can impact product quality, according to Robertson. This information can be used to gain insight into how reactions will run at scale or when they are changed from one piece of equipment to another.

Hovione is also leveraging software designed for *ab initio* calculations, such as Gaussian calculations. "These types of software are very important because they provide chemists with a better understanding of the possible transition states that can be formed during the different steps in an API synthesis route. This information is helpful for identification of pathways that lead to impurity formation," says Loureiro.

Better modelling for greater control

The software packages used at Hovione mainly help with modelling. The information that is obtained on process kinetics and impurity formation is used to determine the optimum control strategies, according to Robertson. The company also uses software such as SuperPro Designer (Intelligen) for batch process simulations and computational fluid dynamics software for modelling the scale up of processes when moving from the lab to large-scale production.

The algorithms used in modelling tools are becoming more accurate and predictive in part because the data behind them continue to grow, according to Kujath. Alcami has seen that they are as a result useful for further refining processes.

As importantly Kujath notes that while the new predictive synthesis applications being developed in academia are not yet widely used in industry, they hold tremendous future potential in reducing time and materials spent in early screening work. He also expects further development of applications of predictive models like solvent maps, which through principal component analysis enable scientists to make more data-driven decisions in solvent and reagent selection.

In-line and bench-top analytical advances

As the pharmaceutical industry moves toward continuous manufacturing, work is also progressing with respect to in-line process analytical technology for use in both the production plant and development labs, according to Kujath. "These new tools not only provide more rapid feedback on experimental results, but are being effectively used to establish proof of concept for scale up at Alcami," he observes.

For Hovione, advances in two technologies in particular are speeding of development work: bench-top NRM systems and ultra-high-pressure liquid chromatography (UHPLC).

Traditional NMR systems were quite large and carried high capital and consumable costs. Newer bench-top systems are much less expensive and do not carry the running costs of older machines because they do not require the use of liquid helium for cooling, according to Robertson. "Although they are much smaller, the new bench-top NMRs still provide high resolution and allow chemists to follow reactions that previously were not analyzed due to lack of immediate access to NMR instruments," he says.

Hovione has found that it is possible to more quickly gather information about impurity formation that was possible before. In addition, the bench-top NMR is used in place of gas chromatography to quantify solvents in distillations more quickly and cheaply. Loureiro also notes that the bench-top NMR system can be connected to flow reactors for continuous monitoring of product formation, providing real-time data and enabling faster process development.

While UHPLC is not new, it is not yet widely used throughout the industry. Many projects that Hovione accepts come with HPLC methods. "We often work with our clients to improve and where possible further convert them using a quality-by-design approach to UHPLC methods," comments Loureiro.

More emphasis on continuous flow

Both Kujath and Loureiro expect to see more focus on the development of continuous-flow chemical processes going forward. "New small-molecule entities as a whole are becoming more potent. Chemical synthesis already carries inherent risk with potential high energetics, flammable solvents, and other safety management challenges. Coupling that with the need to continually be more cost effective, it simply makes sense to apply this concept whenever possible," asserts Kujath.

Adds Loureiro: "We think that the continuous manufacturing of APIs still has some space to be further improved. Several people are working on the downstream steps, which still require further development before fully continuous processes can be implemented from addition of the starting raw materials to packaging of the final API." **PTE**

Developing Lipid-Based Formulations

Lipid-based formulations offer a means of addressing the physicochemical and biological challenges of poorly soluble APIs.

Adeline Siew was previously editor for *Pharmaceutical Technology Europe.*

Lipid-based formulations (LBFs) may improve oral bioavailability by exploiting the body's lipid digestion and absorption pathways, offering a proven means of addressing the physicochemical and biological challenges of poorly soluble APIs. LBFs can be complex systems, so their development requires a multifaceted approach, and experience in how to approach their development provides significant benefits. With the availability of robust delivery systems, such as the softgel dosage form, LBFs can offer formulators potential benefits, provided that the most appropriate excipients are selected.

Pharmaceutical Technology Europe spoke with Karunakar Sukuru, vice-president of Product Development, Pharmaceutical Softgel, and Vincent Plassat, lead scientist, Softgel Product Development, both from Catalent, about the importance of excipient selection and stability testing in the development of LBFs.

Challenges to LBF development

PTE: Can you discuss the challenges in the development of LBFs and the key considerations when working with these systems?

Sukuru and Plassat (Catalent): LBFs provide a versatile platform to formulate APIs with a wide range of physicochemical properties. The excipients that can be used within these formulations have a wide range of properties themselves, accommodating lipophilic compounds to be solubilized in oil as well as hydrophilic compounds that can be solubilized in high hydrophilic–lipophilic balanced (HLB) surfactants or hydrophilic solvents. The development of successful formulations requires specialized formulation expertise to perform preformulation screening and assessments due to the great versatility and dynamic nature of LBFs *in vivo*.

The first hurdle is choosing appropriate formulation excipients that not only have adequate solvent capacity to solubilize the entire dose, but which also ensure that the formulation maintains its solvent properties in the intestine after dilution and digestion. The balance between these two requirements is currently poorly understood, and there is a considerable risk of precipitation of drug during the various intermediate stages of drug transfer, for example, from the solution state to the micellar state. The extent of this precipitation is dependent upon the formulation—it is, therefore, crucial to conduct various *in-vitro* studies to challenge the formulation and help predict the likelihood of precipitation and/or guide the appropriate excipient selection.

Some of the important parameters to consider in LBFs include: screening for solubility in excipients, biorelevant media and lipid-digestion products, excipient compatibility, and finally, the risk of precipitation upon dispersion and digestion.

Another key consideration in oral formulation design is the safety and regulatory status of proposed lipid excipients. Not all lipid excipients are generally recognized as safe (GRAS), hence, specific attention to their maximum daily intake should be considered as soon as possible in the development of a LBF. This is a critical factor for new molecular entities because high doses of excipients could be required during dose escalation studies.

Stability assurance

PTE: How do you ensure the formulation is stable? And how do you test for stability?

Sukuru and Plassat (Catalent): The physicochemical stability of LBFs is just as crucial as with any other formulation. Chemical stability is handled the same as it would be with other dosage forms, with appropriate excipient selection based on a compatibility study with a mixture of API and a single or blend of excipient(s), along with analysis of the impurities formed (if any) during storage at various temperature and humidity conditions. Once the formulation is established, a formal stability study is performed on the dosage form in the proposed packaging at International Council

for Harmonization (ICH) conditions to establish the shelf life. For LBFs, the differences come in testing for physical stability. For example, when LBFs are made with excipients that could be semisolid or that have different hydrophilicity or lipophilicity characteristics, these excipients can settle over time, especially during storage at 40 °C. It is, therefore, necessary to conduct stress studies to challenge the robustness of the formulation. Cycling studies are commonly used with cycles of high and low temperature to stress the formulation. Additional tests to challenge the LBF's robustness to ensure the API does not precipitate out in *in-vivo* or *in-vitro* conditions can also be performed.

PTE: Can you outline the different excipients used in LBFs and the role they play?

Sukuru and Plassat (Catalent): There are a wide range of excipients that can be used in LBFs. They can be classified under five different categories:

- Triglycerides are vegetable oils composed of triglyceride esters of fatty acids. They are a component of many foods and do not present safety issues. Triglycerides are foundational excipients for LBFs. Their solvent power is usually limited, but after digestion, the fatty acids released form mixed micelles with bile salts that can dissolve a portion of the API and thus become carriers for the now suspended API. Examples include corn oil and sesame oil.
- Mixed glycerides and polar oils are partially hydrolyzed triglycerides that are generally much better solvents than triglycerides. These excipients help to form self-emulsifying systems but can still be sensitive to digestion. Other esters such as propylene glycol or sorbitan esters of fatty acid are currently available and may be valuable additives in cases of chemical incompatibility. An example is glycerol monocaprylocaprate.
- Water-insoluble surfactants include non-ionic polyethoxylated or polyglycerylated esters of fatty acid that are not hydrophilic enough to be soluble in water but form a good oil/water interface. They are considered dispersible in water and are therefore commonly used to create self-emulsifying systems. Examples include linoleoyl polyoxylglycerides.
- Water-soluble surfactants are the most commonly used excipients for formulation of self-emulsifying drug delivery systems (SEDDS) or self-micro-emulsifying drug delivery systems (SMEDDS). Above their critical micelle concentration, these excipients spontaneously form micellar solutions that help to solubilize the API. Examples includes polysorbate 20 and 80.
- Co-solvents are water-soluble solvents such as ethanol, propylene glycol, and polyethylene glycol. They have multiple roles in LBFs. They increase the solvent

Hard Capsules—a Flexible Dosage Form

Oral solid-dosage products offer ease of swallowing, ease of handling, consumer compliance, and attractive colour options. Hard capsules allow flexibility in formulation because they are available in various shapes and sizes and limit the need for additional excipients. Hard capsules also limit the requirement of formulating powders into a compact mass for handling. The capsule allows limited API to be filled into capsules of sizes of between 000 and 5, offering much needed flexibility in the preliminary stages of development.

Thousands of probable drug candidates are subjected to multiple screening criteria to yield a single chemical entity, which is then developed through three phases of clinical trials to bring one new drug to market. Once drug candidates have passed through preclinical stages, they must undergo lengthy clinical trials, and hard capsules offer a quick way to first-in-human (FIH) studies by allowing for the API to be filled directly into the capsules. Because no excipients are needed, the process saves three or four months worth of time—which would otherwise be used for stability testing and formulation development. It is easier to formulate an API with a wide dosage range in the capsule form than in the tablet form. Hard capsule shells also offer unique flexibility for modified-release formulations, as capsule shells can be coated with appropriate components to modify the release of the drug, thereby limiting the need to add excipients to the formulation while it is still under development.

Data suggest that more than 50% of all new chemical entities (NCEs) are potent compounds, demanding a smooth production flow where containment is necessary (1). Encapsulation with a containment solution ensures the easy formulation of powders, pellets, and granules, enabling the formulation of complex APIs that are potent and difficult to formulate in a dosage form. A sizable percentage of the currently available products and drug candidates in the development pipeline fit the technical definition of "poorly soluble." The advancements in encapsulation technology with containment have enabled researchers to formulate highly potent or low-dose APIs in capsules using liquid filling hard capsule and capsule-in-capsule technology. There is now a viable alternative for highly potent ingredients, which are difficult to formulate into traditional oral solid-dosage forms owing to their hygroscopic and toxic nature. Encapsulation as a liquid in a hard-shell capsule allows the development in an oral solid-dosage form, while capsule-in-capsule encapsulation technology allows the formulation of a combination of products in one capsule and permits the combination of a prefilled smaller capsule inside a liquid-filled larger capsule for modified-release products.

Reference

1. A. Stark, ed., "Containment Calls for Paradigm Change in Solids Production," *Process-Worldwide.com*, 9 June 2018.

To read the full article, go to www.pharmtech.com/hard-capsules-flexible-dosage-form.

—Sunil Singh, senior manager corporate marketing, and Ilesh Desai, vice-president, ACG Capsules

capacity of the formulation for drugs and aid the dispersion of systems containing a high proportion of water-soluble surfactants. However, because they lose solvent power during dilution in gastrointestinal fluids, their use is limited.

Because lipids are prone to lipid peroxidation, which generates free radicals that can adversely affect API stability, liposoluble antioxidants such as tocopherols and butylated hydroxytoluene/hydroxyanisole are sometimes also needed as additives in LBFs.

Excipients effects

PTE: Can you tell us about the variability of lipid excipients and how it can affect the formulation? What must formulators do to address this issue?

Sukuru and Plassat (Catalent): Due to their natural origin, some excipients can have a variable composition. Subsequent chemical modifications on excipients that are inherently variable, such as hydrolysis and esterification, can lead to even greater variability and challenges.

The formulator must have a good understanding of the exact excipient specifications to select the one most suitable for the formulation. The formulator must also understand and accept that there will be small variations between batches of the same product. The formulation must, therefore, be robust enough not to be sensitive to these small variations in the composition of the excipients. If the LBF cannot withstand small variations, a strategy to mitigate the impact from such variations should be put in place. **PTE**

MORE ARTICLES ON LIPIDS

For more articles on lipids, go to *www.PharmTech.com* to read the following:

- **The Importance of Lipid Screening in the Development of Lipid-Based Formulations**
  www.pharmtech.com/importance-lipid-screening-development-lipid-based-formulations
- **Bringing Together the Benefits of Lipid-Based Formulations and Modified-Release Drug Delivery**
  www.pharmtech.com/bringing-together-benefits-lipid-based-formulations-and-modified-release-drug-delivery
- **Boosting Solubility in Lipid-Based Formulations**
  www.pharmtech.com/boosting-solubility-lipid-based-formulations
- **Bioavailability Enhancement through Lipid-Based Drug Delivery**
  www.pharmtech.com/bioavailability-enhancement-through-lipid-based-drug-delivery
- **Biopharma Demand Continues to Influence CMO Actions**
  www.pharmtech.com/biopharma-demand-continues-influence-cmo-actions-0

CPhI india | P-mec

12-14 December 2018

India Expo Centre, Greater Noida, Delhi NCR

Register Today
gotocphi.com/in18

Why Visit **CPhI & P-MEC India 2018?**

1. India's pharmaceutical sector is forecasted to grow to **US $55 billion by 2020**
2. About **75% of the top 20 pharma companies are Indian owned**
3. India has a total of **24,000** pharmaceutical companies
4. According to the FDA, **India accounts for 23.7% of the 3,652 facilities approved** to produce APIs and FDFs
5. Outside of the U.S., India boasts the **largest number of U.S. Food and Drug Administration (or FDA) compliant plants**

Visit India's largest and leading pharmaceutical exhibition
gotocphi.com/in18

Organised by
UBM

Understanding Internal Release Limits

Stan Altan, Yilje Dong, Mary Ann Gorko, Niels Vaever Hartvig, Mark Johnson, Greg Larner, and Stacy Sherling

Internal release limits help ensure that a batch of drug product remains within specifications throughout its shelf life. This article explores what internal release limits are and why they are important.

The manufacture of pharmaceutical and biopharmaceutical drug products is a complex process that takes place in a highly regulated environment (1). Success requires a combination of scientific, engineering, and regulatory knowledge. One critical part of drug development is formulating the compound into a final drug product, ensuring that desirable physical and chemical properties remain stable for an acceptable period of time and meet regulatory and commercial requirements for specifications for the product (2).

One key requirement is that the drug retain its physical and chemical properties such as potency, purity, and bioavailability for a set period of time, referred to as its shelf life (3). Once a shelf life has been defined for the drug, control strategies must be instituted to provide a high level of assurance that batches of drug product released into the market remain within specifications throughout the drug's shelf life.

One critical control strategy is the use of internal release limits. This article discusses how these limits are calculated and applied to ensure drug product quality.

Internal release limits (IRLs) are one- or two-sided bounds that ensure that a batch of drug product is sufficiently likely to remain within specifications throughout its shelf life. These limits are internally derived and represent good business practice, by accommodating producer risk (i.e., the likelihood of rejecting a "good" lot that fails to meet acceptance criteria) and consumer risk (i.e., the likelihood of releasing a lot that meets specifications during manufacture but fails to meet them through product expiry date).

Internal release limits account for uncertainties that are caused by product instability and measurement variation, and are applied to a given batch's measured critical quality attributes (CQA) at time of manufacture. The decision of what constitutes "acceptably high" assurance and the details of the calculations in relation to a statistical model are considered to be an internal business practice and are not prescribed by regulatory requirements.

Submitted: 29 May 2018
Accepted: 19 June 2018

CITATION: When referring to this article, please cite it as S. Altan *et al*., "Understanding Internal Release Limits," *Pharmaceutical Technology* 42 (10) 2018.

Relationships among limits

During batch manufacture, release results are compared to various criteria, the most common of which include:

- IRLs
- Shelf-life specifications
- External release limits (also referred to as release specifications)
- Control chart or process-control limits.

Each of these limits has a different purpose and may be applied at different times. For example, a shelf-life specification is a registered limit that a CQA must meet from the time of release until expiry. An external release limit is a registered limit that is required in some, but not all, markets. CQAs must meet external release limits at the time of batch release only (i.e., not throughout expiry). IRLs, as described previously, are internal (not registered) limits that are met at the time of product release. Control chart limits are designed to monitor and control process performance.

IRLs are calculated as a buffer to protect the shelf-life specification and, as such, are set by moving in from the shelf life specification. In contrast, control chart limits (another internal limit that could be applied at release) are calculated as a range of typical release results and are set by moving out from the center of the release data. **Figure 1** demonstrates the ideal relationship between the two, using the lower specification as an example.

Internal and external release limits share a similar purpose: to provide assurance that a batch will meet the shelf life specification at expiry. Each limit is determined in part by the stability change that occurs to the CQA during expiry and the level of risk deemed acceptable.

It is possible for internal and external release limits to be different, as shown in **Figure 2**. This may be due to different levels of acceptable risk, internally and externally; additional data generated since the registration of the limits; or other factors. When the calculated IRLs are less restrictive than external release limits, then the IRLs should be set to the tightest external release limit across markets.

Determining the need for IRLs

IRLs should be established for CQAs and stability indicating tests representative of pharmaceutical products. In addition, an IRL may be recommended for stable CQAs, because the method variability on retest could cause an out-of-specification (OOS) result later on, if the initial time point is close to the specification.

Typically, CQAs would include such characteristics as:

- Product potency and/or purity
- Impurities
- Moisture or water content
- Protein concentration.

A risk assessment may be used to determine whether an IRL is necessary or IRLs can be put in place for all CQAs.

Figure 1: Illustration of the difference in calculation between internal release limits (IRLs) and control charts.

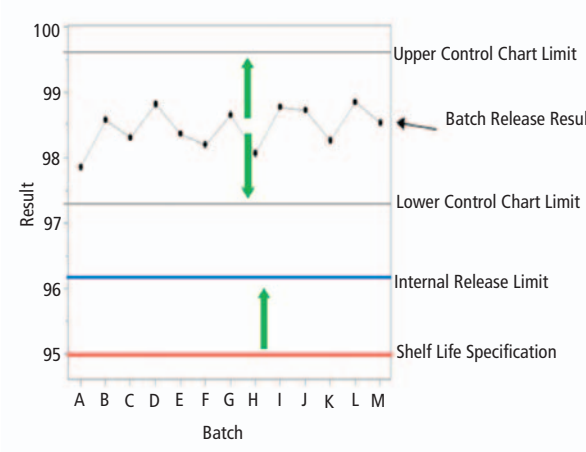
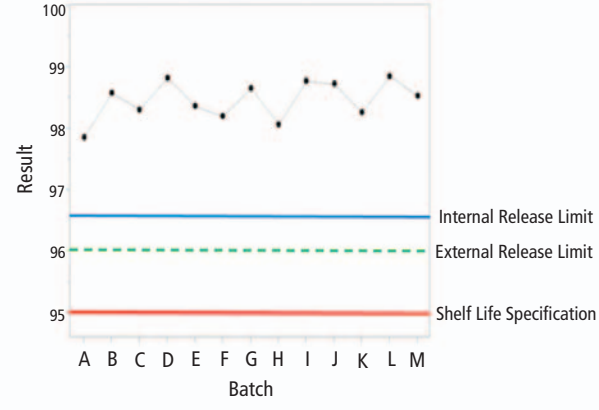


Figure 2: Illustration of an internal release limit (IRL) that is more restrictive than the external release limit.



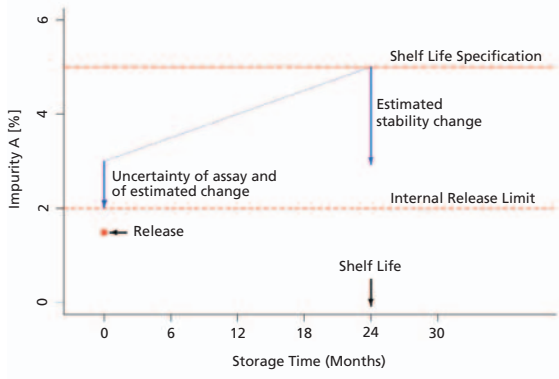
Risk assessment

Any risk assessment should consider the degradation rate and measurement variability. Generally, closer attention must be taken in proposing release limits based on methods that show high variability. A risk assessment strategy assists in identifying whether an attribute that falls outside of specifications might adversely impact patients or lead to other negative consequences such as product complaints and other negative customer interactions.

These assessments examine potential product failure modes, estimate their frequencies of occurrence, and identify the potential impact of exposure on a patient. Frequency of occurrence and severity of patient impact can be categorized based on review of available quantitative data or on qualitative ratings provided by medical or scientific experts. It may be necessary to reevaluate the frequency of occurrence as more data become available.

ALL FIGURES COURTESY OF THE AUTHORS

Figure 3: Illustration of the method for calculating an upper internal release limit from an upper shelf life limit (4). The illustration is based on an impurity that increases during stability.



When in the lifecycle should IRLs be calculated?

Typically, preliminary IRLs are calculated at the time of Stage 2 validation and are used during validation. All batches from development that are similar to the full-scale process should be included in the calculation.

Because the number of batches may be limited and formulation or analytical methods may have changed during development, the amount of data available at Stage 2 may be limited. Once IRLs have been established, their appropriateness should be reviewed periodically. The components of an IRL calculation (specification, change on stability, variability of that change, and analytical variability) may need to be updated.

For products that are at an early developmental stage in their lifecycle, IRLs may have been based on limited data. Additional stability data will become available that may improve the estimates of change and variability. Therefore, it may be necessary to reevaluate the IRLs as more stability data become available.

For more mature products, additional stability data are unlikely to alter the calculation unless a process change has occurred that affects the change on stability or the analytical variability increases or decreases. Therefore, for mature products, longer intervals (i.e., every two to three years) between IRL evaluation will suffice. If the shelf-life specification changes, the IRL must also change. Alternately, IRLs can be evaluated regularly (e.g., annually) and compared to the current limits. If a newly calculated IRL differs significantly from the current value, this can signal a change in the process or the level of analytical variability.

Calculating the IRL

The commonly used method (4) for calculating IRLs relies on the principle that a batch is released if there is sufficient statistical confidence, typically 95%, that the batch will comply with registered shelf-life limits throughout its shelf life.

The IRL is calculated from the shelf-life specification, by subtracting the estimated change during stability, uncertainty of the latter, and the assay uncertainty (**Figure 3**). A distinct feature of this method is that the decision is based only on:

- The average of the release results at the time of manufacture
- Historical stability data and analytical method precision data.

The rationale behind this approach is that the release results at time of manufacture is a reasonable approximation to the true batch mean value, and the disposition of the batch can therefore be based on this estimate. This contrasts with methods that also imply an assumption about the manufacturing process being in a state of statistical control producing a population of batches (5).

The batch is released if the release result is within the IRLs. The principle is illustrated in the example below, both for constant parameters and for parameters that follow a linear stability change over time.

CQAs that remain stable during shelf life

Consider a CQA (e.g., content, with a lower shelf-life limit [LSL]), and suppose the product is stable and also that it is reasonable to set the change during long-term stability to zero. In this case, the lower internal release limit (LRL) should only account for the expected variability and is given by **Equation 1**.

$$LRL = LSL + t_{0.95f}\sqrt{S^2 / n} \qquad \text{[Eq.1]}$$

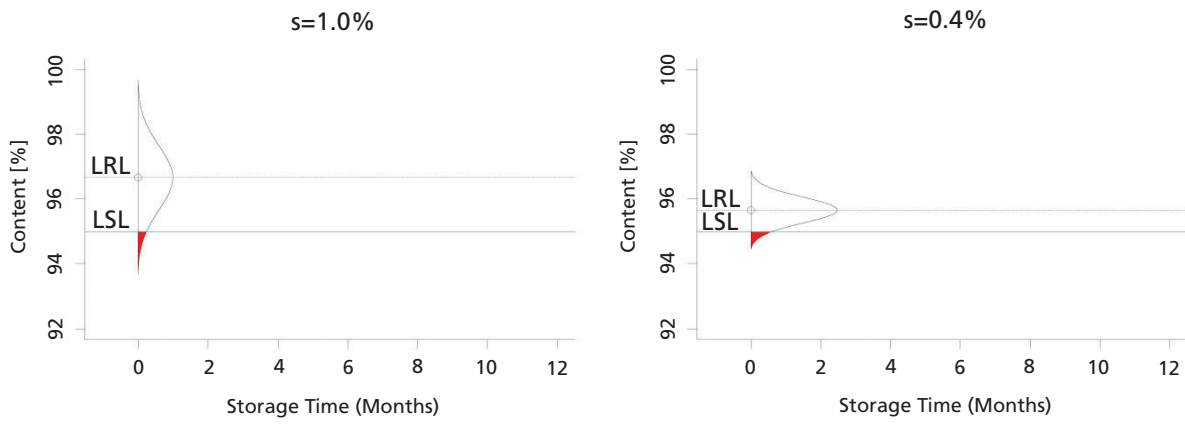
Where s^2 is the uncertainty of assay method (estimated intermediate precision),
f is the degrees of freedom of the variance estimate,
n is the number of determinations of this QA at release, and $t_{0.95,f}$ is the upper 95% quantile of a t-distribution with *f* degrees of freedom. The t-quantile is typically in the order of 1.7 to 2.0 depending on the degrees of freedom. Tables are readily available in any standard statistical methods reference book.

Suppose the LSL for content is 95.0% of target and that a batch is released based on a single content result with an intermediate precision standard deviation of 1.0% (absolute % of target) with 10 degrees of freedom. The t-quantile is $t_{0.95,10}$=1.81 and the LRL is given by the following:

$$LRL = 95.0 + 1.81\ (1.0) = 96.81$$

The principle is illustrated in **Figure 4.** Notice that the gap between the IRL and the shelf-life specification will become narrower when the analytical uncertainty is lower. This is

Figure 4: Illustration of the lower internal release limit (LRL) for a quality attribute that does not change on stability with large analytical variation (left) and smaller analytical variation (right). The risk, that a batch with release result exactly at the LRL does not comply with the shelf life limit, is 5% in both situations as illustrated by the red region. LSL is lower shelf-life limit.



a natural consequence of the method, because the decision to release a batch is based only on the release result; the more precise the result is, the closer to the shelf-life limit the release limit can be, while still providing the required confidence that the batch remains within specification at end of shelf life. An upper release limit could be constructed in a similar way, by subtracting the error term from the upper shelf-life limit.

CQAs that change during shelf life

Consider next a quality attribute that changes linearly during long-term stability, for instance high molecular weight proteins (HMWP), for which an upper specification limit (USL) is registered.

In this case, the upper internal release limit (URL) is given by **Equation 2**.

$$URL = USL - \hat{b}T_{0.95,f}\sqrt{S_b^2T^2 + \frac{S^2}{n}} \qquad \text{[Eq. 2]}$$

where:

$\hat{b}$ is the estimated stability slope (change per month),
T is the shelf life in months, and
S_b is standard error of the estimated stability slope.

The principle is illustrated in **Figure 3**. Notice that there is an extra term under the square root sign, $s_b^2T^2$ compared to the formula given in **Equation 1**. This accounts for the uncertainty in the estimated stability slope, which depends on the precision of the stability data available.

The degrees of freedom *f* are either associated with the error term (if the variance estimates are from the same stability study) or calculated using Satterthwaite's formula if the variance estimates are from independent studies (6).

Suppose the USL for an impurity is 5.0% and the estimated degradation rate is 0.10%/month (absolute) with a standard error of s_b=0.0028%/month with 17 degrees of freedom. The intermediate precision standard deviation is 0.10% (absolute) with 10 degrees of freedom, and a single result is obtained at release. The shelf life is T=24 months.

The total degradation during shelf life is estimated to be 0.10 x 24 = 2.40%. The total uncertainty under the square root sign is given by:

$$\sqrt{S_b^2T^2 + S^2} = \sqrt{0.0028^2 24^2 + 0.10^2} = \sqrt{0.67^2 + 0.10^2} = 0.12$$

The degrees of freedom can be calculated to 18.5 and t-quantile to $t_{0.95,f}$= 1.73. The upper release limit is therefore

$$URL = 5.0 - 2.40 - 1.73 \times 0.12 = 2.39\%$$

To ensure that the (unrounded) release result is less than 2.39%, an effective release limit of <= 2.3% is needed, when rounding the limit to one decimal.

CQAs with batch differences in slope

In the previous examples, a common slope *b* is assumed for all batches, which is generally a reasonable assumption, in particular for solid dosage forms and small-molecule products, where the degradation is due to simple kinetic reactions.

For some products, however, the stability slope may differ between batches (i.e., the slopes are significantly different according to the International Council for Harmonization [ICH] Q1E and there is a scientific basis for the difference). This can be the case for liquid formulations of biological products, where, for instance, the formation rate of high molecular weight proteins may depend on formulation con-

stituents or on a property such as pH, which is inevitably subject to some level of random variation. Batch differences in the slope can be included in the IRL, to the extent that they can be explained and justified as small random perturbation in the stability behaviour.

Inclusion of batch differences complicates the calculations and the interpretation of the limits, and should only be used when properly justified by data and product understanding. A single outlying batch or an outlying result in a stability study may be an outlier due to some special cause effect, and this should not be confused with random batch differences. The random effect due to differences between batches is best estimated through mixed effects modelling.

When a random batch-slope difference is justified, this can be included in the release limits by the following extension of the formula used in the method previously discussed (4), as shown in **Equation 3**.

$$URL = USL - \hat{b}T - t_{0.95,f}\sqrt{S_\beta^2 T^2 + S_\beta^2 T^2 + \frac{S^2}{n}} \qquad \text{[Eq. 3]}$$

where s_b^2 is the variance of the random slope in the batch population.

Suppose that, in addition to the figures provided in example two, that a slight variation around the common slope exists with s_b = 0.0060% /month (with 5 degrees of freedom). The total uncertainty under the square root sign is now,

$$\sqrt{S_\beta^2 T^2 + S_\beta^2 T^2 + S^2} = \sqrt{0.0060^2 24^2 + 0.0028^2 24^2 + 0.10^2}\sqrt{0.144^2 + 0.067^2 + 0.10^2} = 0.19\%$$

The degrees of freedom can be calculated to 12.8, which gives a t-quantile of 1.77, and the upper release limit (URL) is, therefore, 5.0 – 2.40 –1.77 x 0.19 = 2.27%. A tightening of the release limits from example 2 of 0.1% to <= 2.2% is needed in this case, to account for the random batch-slope variation.

When results are outside of IRL

A result outside an IRL may lead to a batch not being released to market so company quality systems may treat it like an OOS result and have standard operating procedures for mitigation. Note that, by definition, a result outside of an IRL is not an OOS result unless the IRL is set to the same value as the corresponding registrational release or shelf-life specification. The result should be confirmed through lab investigation as a typical first step. Review of the batch record and recent history would generally be next if no lab-related cause were found. A retest protocol may be employed to confirm or overcome the original result when no probable cause is found only if documented in operating procedures.

The risk implications of the final result should be estimated so that company quality authorities have the information relevant to the batch disposition decision. Probability estimates of failing before expiry both for the batch average and individuals are important inputs to that decision. The risk thresholds, however, may be different for different companies; it should be noted that failing an IRL is already breaching an established risk alert level. Releasing the batch with a reduced expiry could be considered.

Understanding risk for release limit calculations

Regulatory guidance documents (i.e., ICH Q8, Q9, Q10, and the 2011 US Food and Drug Administration (FDA) process validation guidance [7–10]) suggest a need for quantitative risk assessments including IRLs. The risk assessment exercise is intended to characterize product and process uncertainties to improve product development and manufacturing.

Out of internal release limit (ORL) cases may trigger technical and operational improvements. The negative impact of ORLs include higher investigation costs, increased doubts about product robustness and quality, and potential rejection of a batch that may stress inventory and supply and add to operational costs.

Quantitative risk assessments are critical in making decisions related to IRLs and address at minimum prediction of process capability (against IRLs), probability of OOS, sources and control of variabilities, and impacts to filing and supply.

In pharmaceutical applications, the risk of a harm is commonly defined as a combined effect of its:

- Probability of occurrence
- Severity
- Detectability.

Quantitative approaches will generate more robust data for all three elements, especially the probability of occurrence. Statistical expertise can be valuable in optimizing these data, in conjunction with scientific, engineering, and business principles.

As reflected in the formulas in this article, an IRL risk assessment should be an integrated evaluation of IRL, shelf-life, registered specifications, and product performance including at least stability, process, and analytical components. To achieve the desired benefits, IRLs must be set at appropriate levels in order to control both producer's risk and consumer's risk.

Bayesian modelling provides a comprehensive framework for assessing a producer's and a consumer's risk. It also permits inclusion of prior knowledge in making predictions and accounts for parameter uncertainties. The details of the Bayesian approach are outside the scope of this article, but essentially the approach involves a mixed-effects model with parameters for process mean, batch-to-batch variability, and changes over time.

In summary, a more systematic quantitative risk assessment carried out throughout the product lifecycle will lead to deeper product knowledge, collectively strengthening the two enablers of pharmaceutical quality system: knowledge transfer and quality risk management. Note that the concept and associated benefits are applicable to scenarios besides IRLs. Therefore, this is an area that is worthy of more effort and investment by the pharmaceutical industry.

References

1. J. Peterson and S. Altan, "Overview of Drug Development and Statistical Tools for Manufacturing and Testing,"in *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries,* Zhang,L. editor, (Springer, Switzerland, 2016).
2. ICH, *Q6B, Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*, CPMP/ICH/365/96, (ICH, March 1999).
3. ICH *Topic Q1E, Evaluation of Stability Data,* CPMP/ICH/420/02, (ICH, March 2003).
4. P. Allen, G. Dukes, M. Gerger, *Pharmaceutical Research* 8 (9), pp 1210-1213 (1991).
5. G. Wei, C.G. Greg, *J. Biopharmaceutical Statistics,* 8(1), pp 103-114 (1998).
6. F.E. Satterthwaite, *Biometrics Bulletin*, 2 (6), pp. 110-114 (1946).
7. ICH, *Q8, Pharmaceutical Development*, CPMP/ICH/167068/04. (ICH, June 2009).
8. FDA/ICH, *Q9 Quality Risk Management* (CDER and CBER, June 2006).
9. ICH, *Q10, Pharmaceutical Quality Systems*, CPMP/ICH/214732/04 (ICH, July 2008)
10. FDA, *Process Validation: General Principles and Practices, Guidance for Industry* (CDER and CBER, January 2011). **PTE**

Mary Ann Gorko* is technical manager of statistics at AstraZeneca, maryann.gorko@astrazeneca.com; **Stan Altan** is senior director at Janssen Pharmaceutical R&D; **Yilje Dong** is an independent consultant; **Niels Vaever Hartvig** is principal big data analyst at Novo Nordisk A/S; **Mark Johnson** is senior principal statistician at AbbVie's research department; **Gregory Larner** is manager of statistics at Pfizer; and **Stacy Sherling** is research scientist at Eli Lilly.

*To whom all correspondence should be addressed.

Optimizing Containment in OSD Manufacturing

Engineering controls and safe practices protect both operator and product in tablet and capsule production.

Jennifer Markarian

When handling highly potent materials in oral-solid dosage (OSD) manufacturing, appropriately designed equipment and safe practices are crucial for protecting the operator from exposure and for protecting the drug product from potential cross-contamination. Containment of airborne particles (i.e., dust) is important when producing capsules and especially when making tablets. *Pharmaceutical Technology Europe* spoke with Jörg Stadelmann, head of Technical Sales at Bosch Packaging Technology, about some best practices in this area.

Designing containment

PTE: What are the primary considerations for designing containment in OSD manufacturing facilities? Are there different considerations for capsule filling vs. tabletting?

Stadelmann (Bosch): Containment in OSD facilities is all about maintaining the required occupational exposure limit (OEL) during production, cleaning, and maintenance. First of all, a safe product transfer into the machine is essential, as well as the transfer of the finished product from the machine to the following peripheral equipment.

During production, safe sampling and troubleshooting are important. Sampling can be done, for instance, by integrating split valves with a washing cap or with a suction point on the active valve to minimize the so-called 'ring of concern,' which is the ring on the split valve between active and passive containment parts of the machine. The use of endless hose ejection systems, glove ports, rapid transfer ports (RTP), and H13/H14 high-efficiency particulate air filter systems are further options that are important not only for sampling but for the complete containment process.

To uphold the required OEL during cleaning between and at the end of batches, the machine can be accessed via gloves, while the remaining product can be pre-cleaned with an integrated suction hose. Fine mist from the spray nozzles binds airborne particles. Manual or fully automated washing-in-place (WIP) processes can be used.

As far as maintenance activities are concerned, it is important to seal the drive section room, for example through bellows, double, or air-flushed seals, as well as negative pressure in the production room.

The more a machine is automated, the less operator intervention is required, which naturally reduces the risk of exposure to highly potent products. With some of our fully automated capsule filling machines, intervention is not required at all, apart from very rare interventions. Bosch has also developed a 'closing force detection' to ensure that only completely closed capsules are transferred into the good capsule ejection area, so that the contents of open capsules will not contaminate this area.

In general, the main considerations for containment capsule filling and tablet pressing are identical. However, tablets will create additional dust before coating due to additional transportation and handling processes. Hence, the processes following tablet compression must be designed carefully to avoid contamination of the environment.

PTE: What types of engineering controls are available?

Stadelmann (Bosch): Engineering controls include monitoring of the negative pressure in the cabin and the overpressure of the inflatable seals. Redundant systems can be designed in many different ways; two examples are a combination of inflatable and static seals and establishing negative pressure in the production cabin by an exhaust system and vacuum pump. In the event of a system failure, warnings should be issued. Before production starts, the production cabin must be checked for leaks, and a glove testing unit performs pressure decay tests of the gloves before the batch starts. In any case, a room contamination control process

must be established, which includes cleaning procedures, swabbing, personnel protective equipment (PPE), and personal monitoring.

Best practices

PTE: What are some best practices for handling dust created during manufacturing with highly potent materials?

Stadelmann (Bosch): My main credo would be to avoid or at least minimize dust as much as possible. A 'no cap, no fill' function on the dosing stations definitely helps. Otherwise, additional suction points in the machine chamber and integrated suction hoses for pre-cleaning after batch completion are a good option. One of the most important factors of containment machine design is negative pressure in the production chamber. At Bosch, we have created a sophisticated zone concept with pressure barriers during production.

Hygiene and cleaning ability are also important factors, which can be influenced by the choice of surface material and cleaning media. Wetting (i.e., creating fine mist in the machine chamber to bind airborne particles before opening the equipment) is another possibility to reduce dust development, as well as surface pre-cleaning by WIP. And, most importantly, the use of suitable peripheral equipment (e.g., dedusters) can help a lot. It is extremely important to always check the entire system for adequate product handling.

PTE: What are some best practices for containment during sampling?

Stadelmann (Bosch): Sampling is a crucial step that requires systematic monitoring by the technical staff. For sampling there are both manual and automated samplers.

With our Bosch GKF capsule filling machines, we use an integrated in-process control (IPC). Samples are taken automatically, weighed, and transported to a sample container—of course, all contained. The weight results are recorded in the batch report.

There are several possible systems that can be used for containment during sampling. For instance, an endless hose system offers the possibility of crimping or cutting off during production. Other options are a contamination-free removal of the complete sampling system, rinsing the complete system at the end of production, or attaching a split-butterfly system.

PTE: What are some best practices for cleaning and maintenance of equipment in containment? Can you describe best practices for manual cleaning and explain when automated, wash-in-place systems should be used?

Stadelmann (Bosch): After the end of a batch, the first step is preparing the machine for cleaning. Glove ports allow the operator to access the machine through the closed machine doors. The safe transfer of size parts out of the production chamber can be done via RTP, while the remaining product is pre-cleaned with an integrated suction hose. Fine mist from the spray nozzles binds airborne particles.

If products with an OEL < 1 µg/m^3 are manufactured, a WIP process is mandatory. It should therefore also be considered to wash the interfaces, pipe work, and peripheral equipment. Apart from occupational safety, it is paramount that product safety is considered and cross-contamination from one product to another is avoided. For this reason, validated cleaning procedures must be performed, monitored, and documented. **PTE**

MARTIN BARRAUD/OJO IMAGES/GETTY IMAGES

Using Nondestructive *in-situ* Measurements to Ensure Lyophilized Product Stability

Non-destructive surface area measurement can improve stability testing.

Jeff Kenvin
is chief scientific officer at Micromeritics.

Lyophilization, or freeze drying, is a vital process for the pharmaceutical industry and is used widely to extend the shelf-life of injectables. Many biological molecules, including a significant number of important commercial therapies, are labile in solution but can be stabilized through the removal of water.

Stability is of the utmost importance because lyophilized products, typically small cakes of material, must maintain integrity throughout their intended shelf life. The cakes' physical properties, such as surface area, directly influence stability and thus, clinical efficacy, and may consequently be critical quality attributes (CQAs) for the product. Beyond this, such properties are routinely measured because of their impact on process efficiency and the behaviour of the product during reconstitution. This article examines surface area measurement, used to determine stability, and highlights technology designed to enable reproducible, relevant *in-situ* measurement.

The relevance of surface area

Stability is the primary concern for a lyophilized product, with reconstitution behavior an important but secondary issue. For ease of administration, manufacturers aim for a cake that can be reconstituted in approximately 10 to 30 minutes, using minimal volumes of solvent. Complete dissolution of the drug is critical to its clinical efficacy, because in-line filtration will remove any undissolved drug.

With respect to process optimization, lyophilization is a lengthy, time-consuming process, associated with low energy efficiency. There is considerable pressure on biopharmaceutical manufacturers to boost drying efficiency, particularly for the primary drying step, and to reduce lyophilization cycle times, within the constraint of consistently and reliably reaching an acceptable moisture level.

The surface area that the cake develops is primarily defined by the conditions applied during freezing, with rate and temperature influencing the size of ice crystals formed. Sublimation in the primary drying stage removes most of the water, leaving behind a honeycombed structure with physical characteristics such as surface area determined by the size of the ice crystals. However, secondary drying, the removal of bound or adsorbed water at more elevated temperature, can also affect the structure and surface area of the finished cake, depending on the conditions applied.

The surface area that develops affects both the lyophilization process itself and the performance of the finished cake, and helps determine:

- Progress of the sublimation front through the evolving cake and the efficiency of both primary and secondary drying
- Drug stability, for example, by altering the probability of active molecules exposed to the cake-air interface
- The rate and ease of reconstitution, by defining the contact area between solvent and the dried formulation.

These competing factors make surface area optimization a unique challenge for each lyophilized formulation and create an ongoing requirement for more reliable measurement method.

Traditional methods

Surface area is usually determined by gas adsorption measurements, as described in *United States Pharmacopeia (USP)* Chapter <846> (1). In simple terms, this involves measuring the amount of gas adsorbed by the sample as a function of pressure, at a controlled temperature. These measurements enable the generation of an isotherm, from which surface area is determined using classical Brunauer, Emmett and Teller (BET) theory (2). **Figure 1** shows a standardized apparatus for such measurements.

An adsorption measurement usually begins by degassing or outgassing of the sample, to remove adsorbed gases and ensure reproducible measurement. This is typically achieved through the application of a vacuum, at ambient or slightly elevated temperature.

The sample tube is then isolated from the manifold and submerged in a cold bath containing liquid nitrogen (LN2). Charging the manifold to a certain pressure admits a quantity of gas that can be calculated from the gas law, and the manifold is then opened up to the sample to allow gas adsorption. Once pressure has equilibrated, the amount of gas adsorbed can be calculated by determining the difference between the two values, again through application of the gas law. Further measurements are made by repeating this procedure at progressively higher pressures to generate a complete quantity of gas adsorbed versus pressure isotherm.

For lyophilized cakes, the crucial limitation of traditional apparatus is the sample cell design and the associated requirement for sampling. Standard sample tubes have an opening of 7–10 mm and may either be straight walled or a have a triangular flattened base to aid stability. All such tubes necessitate sampling of the cake, which typically involves its (partial) destruction. This introduces concerns as to how representative the data are, particularly when assessed within the context of why measurements are being made. Any sampling alters the cake's morphology and compromises structural integrity, potentially changing surface area in an unknown and uncontrolled way.

A switch to alternative sample tubes is complicated by the requirement to maintain a precisely controlled cold volume. Maintaining a constant liquid nitrogen level during measurement is critical for defining temperature regions in the apparatus. These regions are used in the gas law calculations, and consequently the accuracy of the resulting data. All modern gas adsorption systems address this issue, but some solutions are inextricably associated with the geometry of standard sample tubes, providing little or no flexibility to change designs.

Measuring the entire cake, *in-situ*, within the vial, eliminates any requirement for sampling, maximizing the relevance of the resulting information. This approach offers reassurance that data are obtained under precisely the conditions of interest with respect to stability and reconstitution behaviour and reduces the variability associated with sampling and cake damage. From a practical perspective, *in-situ* measurement is also a simpler option that requires less manual effort for each measurement.

To load the sample, the top is taken off the vial, which is then placed directly in the sample tube (see **Figure 2**). The lyophilization process seals the cake under closely controlled conditions precluding the requirement for initial degassing; krypton is the preferred adsorptive, as per *USP* <846>, because the surface area of lyophilized cakes tends to be low.

With these tubes, the liquid level of nitrogen is kept constant using an isothermal jacket made specifically to accommodate their larger diameter. This porous jacket is approximately 2–3 mm thick and acts as a wick for the liquid nitrogen in the flask reservoir, holding it against the sample tube to maintain a constant temperature profile for the duration of the analysis. This design is well established for smaller sample tubes and has been proven to lead to highly reproducible measurement. Measurement is otherwise directly analogous to the standard technique except for the determination of sample mass, which is carried out post- rather than pre-measurement.

By providing access to more relevant surface area information, new accessories for *in-situ* gas adsorption measurements support the more efficient application of lyophilization. Measurements that correlate robustly with progress of the sublimation front during the critical primary drying step aid efforts toward knowledge-based process optimization and more secure scale-up. *in-situ* testing of the finished product, on the other hand, provides detailed insight into stability and reconstitution behaviour that is inaccessible via surface area and particle sizing techniques that require sampling.

Figure 1: Charging of the manifold occurs on the left, and sample dosing and pressure equilibration on the right.

Gas adsorption apparatus for determining the surface area of lyophilized cakes

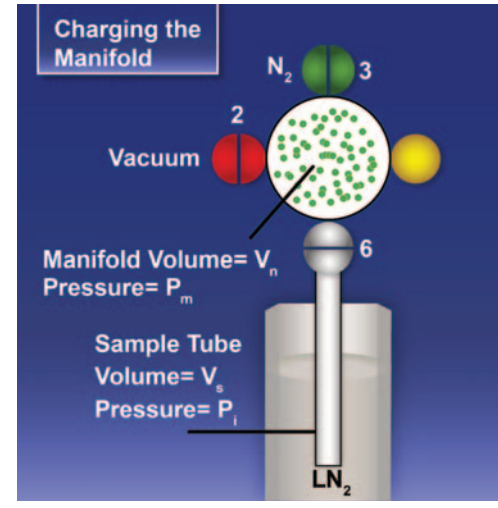
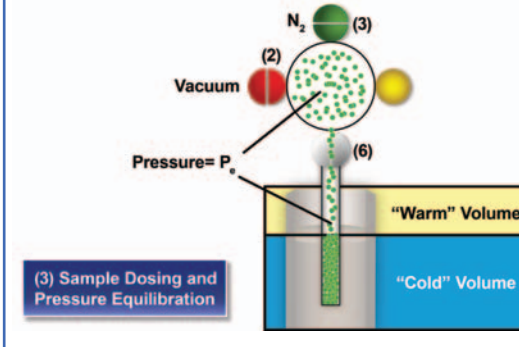


Figure 2: New accessories accommodating industry standard lyophilization vials enable *in-situ* gas adsorption measurements.



References

1. USP, General Chapter <846>, Specific Surface Area, *USP-NF.*
2. S. Brunauer, P.H. Emmett, E. Teller, *J.Am. Chem. Soc.,* 60 (1938) 309-319

PTE

Figures courtesy of the author

US FDA Clarifies Worldwide Inspection Policies

The US Food and Drug Administration is revising its inspection process and seeks harmonization of standards for US and foreign regulatory oversight to ensure the safety of medicines.

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

In the name of enhancing transparency in agency decisions and compliance actions, US Food and Drug Administration (FDA) published updated information on how it selects and schedules pharmaceutical plant inspections around the world and the process for disclosing the findings of those oversight actions. The increasingly global nature of the biopharmaceutical supply chain has prompted FDA to revise its inspection process and to seek harmonization in standards for US and foreign regulatory oversight to further ensure the safety and quality of medicines in the United States and around the world.

This approach was highlighted in a 5 Sept. 2018 statement by FDA Commissioner Scott Gottlieb outlining a series of actions FDA is taking to ensure drug quality by all producers (1). Gottlieb noted that FDA has moved to modernize its field inspection programme through a recent reorganization of its Office of Regional Affairs to better align staff expertise with inspection priorities and to expand oversight of foreign manufacturers.

It's no coincidence that the FDA commissioner is emphasizing the agency's more extensive scrutiny of foreign manufacturers in the wake of uncovering potentially harmful impurities in a widely used API produced in China. FDA and other regulatory authorities have launched massive recalls of valsartan, a common generic-drug treatment for high blood pressure, after multiple drug manufacturers detected a possible cancer-causing chemical known as N-nitrosodimethylamine in the Chinese API (2). Continued FDA testing of these drugs has uncovered an additional impurity—N-Nitrosodiethylamine (NDEA)—in valsartan drug products (3). The problem evidently arose when Zhejiang Huahai Pharmaceutical made a change in its manufacturing process four years ago.

Focus on risk

One response from FDA is to emphasize how its pharmaceutical inspection programme is designed to focus on more problematic production sites, including the rising number of overseas firms providing pharmaceuticals for the US market. In 2017, FDA conducted 1453 surveillance inspections, including 762 on foreign soil, to ensure that firms were following good manufacturing practices (GMPs) and maintaining high quality standards.

To this end, FDA has implemented a risk-based programme for scheduling both foreign and domestic GMP surveillance inspections, as outlined in an updated manual of policies and procedures document from the Center for Drug Evaluation and Research (CDER) (4). This inspection model is structured so that inspection frequency for all facilities relates to operations that pose the greatest potential risk for problems—regardless of where the facility is located. Priority factors considered in scheduling inspection visits include the facility's compliance history, recall trends, time since last inspection, inherent risk of product being produced, and processing complexity. These criteria are similar to those initially proposed by CDER in 2005 and then codified in legislation in 2012. CDER notes that its Office of Surveillance (OS) in the Office of Pharmaceutical Quality maintains oversight of more than 5000 drug manufacturing facilities around the world, including 3000 outside the US. The agency taps risk information on these sites from the OS database to produce an annual Site Surveillance Inspection List that sets priorities for surveillance inspections.

FDA also is expanding its capacity for monitoring foreign manufacturers through expanded collaboration with European and other capable regulators. An FDA Mutual Recognition Agreement (MRA) with the European Union has been established to recognize drug inspections conducted by participating parties (5).

contin. on page 33

Lot Release Testing Analytics for Small-Molecule Drugs

Experts weigh in on up-to-date analytical procedures for the lot release testing of small-molecule pharmaceuticals.

Amber Lowry

Successful lot release testing for small-molecule drugs is dependent on efficient analytical tools and practices. *Pharmaceutical Technology Europe* explores the analytics of this testing process with Natalia Belikova, PhD, Analytical Services director, and Gayla Velez, general manager, both at SGS Life Sciences in Lincolnshire, IL; and Mark Shapiro, director, Analytical Research & Development, and Daniel M. Bowles, PhD, senior director, Chemical Development, both at Cambrex in High Point, NC.

Methodology advancements

PTE: What are some common analytical methods used for the lot release testing of small-molecule pharmaceuticals? Have there been any recent advances to these methods?

Belikova and Velez (SGS): First, we have to distinguish whether we are talking about small molecules as active pharmaceutical ingredients (APIs) or small molecules as finished drug products (tablets, capsules, injectables, etc.).

Most common panels for the testing of APIs will include basic tests such as loss on drying (LOD), residue on ignition (ROI), water content, identification, assay/purity, residual solvents, heavy metals, and microbial tests. Pharmaceutical manufacturing companies have to be absolutely sure that they are dealing with APIs with sufficient quality. If a contaminated or adulterated batch of API is used in production, it can result in a big financial loss, production delays, and a loss of reputation.

There has not been much advancement in traditional basic wet chemistry tests, which are very conservative and have not changed for the past several decades. Recently, heavy metals testing has moved from non-specific wet chemistry colour reaction to inductively coupled plasma (ICP) technology that distinguishes between specific elemental impurities, and can quantify them at very low levels down to parts per billion depending on the element. That change was officially accepted by the United States and European pharmacopoeias. Many assays are traditionally done by titration or using high-performance liquid chromatography (HPLC), and there is a trend of moving from titration to chromatographic techniques as HPLC is more specific. Additionally, there is a trend of moving from traditional HPLC to high-throughput ultra-high performance liquid chromatography (UHPLC), although that is still not common in compendial methods.

"If a contaminated or adulterated batch of API is used in production, it can result in a big financial loss, production delays, and a loss of reputation."
— Belikova and Velez, SGS

Another methodology that is used to confirm polymorphic structure (ID test) for small molecules uses X-ray powder diffraction. This allows an analyst to distinguish between small-molecule batches with the same molecular structure but different crystallinity.

For the small molecules in drug product form, the most common test panel will include assay, related substances, water test (for lyophilized products), container-integrity test (for individually packaged products), dissolution (if applicable) and particulate matter (for injectable products).

Shapiro and Bowles (Cambrex): As a manufacturer of small-molecule APIs, all the batches of products we make undergo rigorous analytical protocols to ensure their quality. Depending on the type of molecule, we would generally use either HPLC or capillary gas chromatography (GC). Each method gives us the option to use various detection modes: for HPLC, there are ultraviolet, charged

aerosol detection (CAD), a mass spectrometer or a triple quadrupole mass spectrometer (TQMS); and for GC, there are flame ionization detector (FID), electron capture detector (ECD), thermal conductivity detector (TCD), or again, a mass spectrometer.

We would also use other techniques such as inductively coupled plasma-mass spectrometry (ICP-MS) to ensure there were no elemental metal or inorganic impurities, as well as infra-red spectroscopy and nuclear magnetic resonance (NMR). Additionally, we would test water content using Karl Fischer (KF) titration, and undertake any appropriate *United States Pharmacopeia* (*USP*) tests, as well as analyzing particle size distribution, while also using X-ray powder diffraction to confirm that we have produced the correct polymorph.

In terms of advances, developments in HPLC in terms of porous shell columns and shorter columns, as well as the introduction of UHPLC across our sites, have shortened method times, and increased the efficiency of the analysis we undertake. The greater sensitivity that is also possible with modern mass spectrometers, as well as the increased use of CAD for non-UV active components, has also improved the ability and speed of analytical departments to both develop methods and undertake quality control (QC) analysis.

Procedure walk-through

PTE: Can you walk us through your small-molecule lot release testing procedures?

Shapiro and Bowles (Cambrex): For any molecule we manufacture, there will be a predefined procedure that contains all the information pertinent to its release, including specifications, methods, and any outsourced testing necessary. Once a batch is made, a sample is submitted to the QC team along with a material release form which tracks the data associated with the sample throughout the analytical process. An analyst is assigned the sample who will ensure the testing is carried out in accordance with its needs, and when completed the data are reviewed and verified to ensure compliance with all specifications. A certificate of analysis is then generated by the quality analysis (QA) department which then releases the material to the customer.

Belikova and Velez (SGS): As a contract lab, we rely on our individual clients' needs, and usually they will provide us with a list of tests and specifications. If the small molecule is known and has a compendial monograph for it, we will follow procedures described in the monograph, but if the small molecule is new and not yet published in a compendium, our lab will offer to develop and validate methods for release testing.

> **"Clear and effective standard operating procedures…ensure proper compliance stance at all stages."**
>
> *— Shapiro and Bowles, Cambrex*

All results generated in the laboratory have a thorough QC data review. Our quality assurance (QA) department also independently verifies all data packages prior to releasing the results, and our final 'product' is the certificate of analysis (CoA) that lists all tests performed and the results of each test.

New technology

PTE: What are some products/instruments that have been recently incorporated into your small-molecule lot release testing procedures? How are these products improving testing quality and analytical capabilities?

Belikova and Velez (SGS): For the past five years our laboratory in Lincolnshire, Illinois, US has extensively used Pinnacle PCX, a post-column derivatization system from Pickering Laboratories that allows us to perform analysis of amino acids for individual raw materials and small peptides. This instrument replaced thin layer chromatography (TLC) tests used in the past to monitor ninhydrin positive substances. HPLC technology is more specific than TLC, has better sensitivity, is faster, and costs less. Additionally, our laboratory has an X-ray powder diffractogram D2-phaser from Bruker that is used extensively for the identification of polymorphic form of small molecules. It also allows us to evaluate the purity of an API (qualitatively) and confirm that the polymorphic structure of API does not change when an API is incorporated into the final drug product during the manufacturing process. This methodology is very useful when clients ask us to evaluate if extensive storage (under International Council for Harmonization conditions or accelerated studies) affects the polymorphic form of an API as well.

We also use Acquity H-Class UPLC systems from Waters for method development/validation and release testing of various client products. The use of UHPLC technology results in much shorter runs/higher throughput, better resolution between peaks, and higher sensitivity than traditional HPLC.

Other analytical equipment that we extensively utilize for routine small-molecule testing are: differential scanning calorimeter (DSC) for melting point (ID test); thermogravimetric analyzer (TGA) for ID and water test; elemental analyzer (CHNS/O) to confirm carbon/hydrogen/nitrogen/sulfur composition; and a Malvern Mastersizer 2000 to evaluate particle size distribution.

Shapiro and Bowles (Cambrex): The use of a TQMS alongside HPLC allows the sensitive and specific analysis of potential genotoxic impurities (PGIs) to sub-1 ppm level. ICP-MS allows us to test for elemental impurities as per the new *USP* <233> in-house, and we have an autosampler on this instrument to allow us to undertake efficient method development and validation. Our use of coulometric oven KF reagents removes the dependence on the solubility parameter with the traditional direct KF. This can be critical in early-phase molecules where a small change in production parameters can result in large changes in solubility, resulting in the inability to perform direct KF in the qualified solvent.

Best practices

PTE: What are some best practices for conducting small-molecule testing?

Shapiro and Bowles (Cambrex): The pharmaceutical industry is highly regulated, and so as analysts we must adhere to these regulations by using appropriate, qualified, and verified or validated methods to ensure product and patient safety at all times. At Cambrex, we have clear and effective standard operating procedures laid out to ensure we can maintain a proper compliance stance at all stages, in line with good manufacturing, distribution, and laboratory practices.

Internally, these include the development and writing of clear, safe procedures that can be easily and effectively executed by all QC staff, and we encourage open communication between disciplines (manufacturing, QC, and QA) throughout the process of method development. Our testing procedures are passed from the analytical R&D team to the QC department through an intermediary validation stage to provide enhanced method robustness. During the QC stage of lot release, we parse the testing across a number of colleagues to enhance the throughput and efficiency of the process.

Belikova and Velez (SGS): Our Lincolnshire facility, IL has recently been expanded to accommodate the increasing demand in both chemistry and microbiology/sterility testing. If a client sends us a sample for both (chemistry and microbiology/sterility) release testing, then we often ask clients to send samples in multiple vials, so that each department can work with its own sample to run tests concurrently. Otherwise, the microbiology/sterility department will work with a sample first under aseptic conditions and then all chemistry tests will be performed.

For hygroscopic materials, our standard practice is to perform a water test first (in a low humidity-controlled environment), so the sample is not compromised with possible moisture uptake. For the tests that require a relatively long test procedure (for example, loss on drying for constant weight or residue on ignition to constant weight), we coordinate between different analysts on different shifts so we have workflow continuation and can deliver results to the clients in a timely manner.

Highly toxic, potent compounds and controlled substances require special handling and safe disposal, which SGS offers to its clients as a service. **PTE**

Quality/Regulations — *contin. from page 30*

The aim is to avoid duplicate inspections of facilities that demonstrate good compliance with standards and rules in order to focus resources on more high-risk and non-compliant operations.

Disclosing results

In addition to targeting inspections to more problematic firms, Gottlieb discusses how FDA is making inspection results more visible to the public. The aim is to be more transparent about inspection outcomes and compliance issues, particularly where the agency uncovers violative conditions that may warrant further regulatory action. FDA recently updated its inspections classifications database to provide more recent information on the outcomes of GMP surveillance visits (6). This supports the EU MRA through the addition of inspection reports from European and other recognized regulatory authorities. Access to more current inspection reports aims to enable FDA and other regulators to issue import alerts, warning letters, and recalls more efficiently to prevent repeat violations.

FDA also is working to speed up the process for communicating inspection findings to facility owners to facilitate fast resolution of any quality failings. Agency officials now aim to provide inspection classification information to companies within 90 days of the close of a surveillance inspection, which is much faster than in the past. FDA similarly seeks to notify firms seeking approval of new drugs and generics when issues are identified during premarket inspections that could block application approval. While the agency recognizes that the majority of firms in the US and overseas meet quality standards, the aim is to prevent problems that can delay efforts to provide quality products efficiently to patients.

References

1. FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Global Efforts to Help Assure Product Quality and Transparency at Foreign Drug Manufacturing Facilities," Press Release, 5 Sept. 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm619435.htm.
2. FDA, FDA Updates on Valsartan Recalls, FDA.gov, www.fda.gov/drugs/drugsafety/ucm613916.htm-Valsartan.
3. FDA, "FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products," Press Release, 13 Sept. 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620499.htm
4. FDA, *MAPP 5014.1 Understanding CDER's Risk-Based Site Selection Model* (CDER, OPQ, 26 Sept. 2018), www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM619302.pdf .
5. FDA, Mutual Recognition Agreement, FDA.gov, www.fda.gov/InternationalPrograms/Agreements/ucm598735.htm.
6. FDA, Inspection Classification Database, FDA.gov, www.fda.gov/ICECI/Inspections/ucm222557.htm.

PTE

Protecting Solid-Dose Shelf-Life

Barrier materials, scavengers, and good seal integrity maximize shelf-life of oral solid-dosage drug packaging.

Hallie Forcinio
is *Pharmaceutical Technology Europe's* Packaging editor, editorhal@cs.com.

Tactics to protect or extend the shelf-life of solid dosage forms fall into two main categories: passive barrier materials and active packaging. The former prevents transmission of shelf-life-sapping influences such as oxygen and water vapour. The latter actively scavenges, or captures, deleterious substances. Seal integrity plays a role as well. Weak spots can occur in the packaging wall, in the sealing surfaces between containers and closures, or in the sealed seams of blister packs.

Changes in solid-dose products, the advent of new drug delivery systems, and the increase in generic-drug manufacturing are spurring interest in active and passive shelf-life-protecting technologies. "Branded drugs continue to be released with more complex characteristics to facilitate solubility and bioavailability, including timed release, delayed release, quick release, or combinations that inherently impact hygroscopicity and stability," reports Mark Florez, product manager, Business Development & Marketing at Clariant North America.

Oliver Stauffer, chief executive officer at PTI Packaging Technologies and Inspection, a supplier of seal integrity testing equipment, agrees, noting: "More complex formulations, delivering hormones, for example, are potentially more susceptible to oxidation and other influences and more at risk."

There's also a need for longer shelf-life. Stuart Brown, business development manager at Sanner Group, a pharmaceutical packaging specialist, explains, "The shelf-life of solid-dosage forms was usually set to about two years. We are currently witnessing the growing demand of many pharmaceutical companies to extend it to a minimum of three years, preferably even longer. Accordingly, requirements are also changing regarding packaging."

As a result, demand is rising not only for improved barrier materials, but also in more powerful desiccants for moisture protection and scavengers for gases, such as oxygen, carbon dioxide, and ethanol. "[Scavengers for] volatile organic compounds, such as formaldehyde, are also of growing interest," says Craig Voellmicke, vice-president of Business Development for CSP Technologies, a supplier of active packaging technologies.

Better barrier

Barrier properties can be boosted by material choice, thickness, and structure (i.e., coating or multiple layers). An alternative to high-barrier materials, such as polychlorotrifluoroethylene (PCTFE) and cold-formed foil, the Flexapharm SBC240 polyvinyl chloride/polyethylene lamination from Tekni-Plex provides a substantial barrier to water vapour and oxygen by applying a 240 g/m^2 coating weight of a polyvinylidene chloride variant. Coating weights can be customized, but multiple standard grades (120-, 150-, 180- , 210-, and 240-g/m^2 coating weights) cover a multitude of barrier needs. "This technology offers a great degree of customization and flexibility compared to alternative laminated structures," says Melissa Green, senior director Global Marketing & Strategy, Tekni-Films, a Tekni-Plex business.

She adds, "To date, Flexapharm SBC240 has the best oxygen barrier of any thermoformable blister material available in the market, while also providing the same moisture barrier as a 6-mil [-thick] PCTFE. Another added benefit of all SBC structures is that oxygen barrier performance does not vary with changes in relative humidity. The combination of moisture and oxygen barrier properties makes it uniquely suited to protect drugs for companies wishing to maximize their shelf-life in a thermoformed blister, instead of packaging in blister packs that would be double in size if packaged in a cold-formed foil blister. In addition, the clarity of the SBC240 gives patients insight into whether …

PharmTech.com
ADVANCING DEVELOPMENT AND MANUFACTURING

Pharma Marketplace
Your Connection to Global Pharmacuetical Suppliers

NEW

CHECK OUT *PHARMACEUTICAL TECHNOLOGY'S* ALL NEW MARKET RESOURCE!

Pharma Marketplace is your online resource to connect with pharma manufacturing suppliers around the world.

Find global suppliers and resources for:

- Analytical Instruments
- Chemicals, Excipients, Ingredients & API
- Contract Services
- Facility Design and Operations
- Laboratory Instruments, Equipment & Supplies
- Manufacturing, Processing Equipment & Supplies
- Aseptic/Sterile Processing
- Drug Delivery Technology
- Packaging Equipment & Accessories
- Information Technology
- Compliance & Validation

www.pharmtech.com/marketplace

CONTACT US TODAY!

Figure 1: Sanner Group's AdCap capsules can be customized in blue instead of the usual white to differentiate the desiccant capsule from product. A grid structure in the capsule wall enhances moisture adsorption.

they've taken their prescribed dose, improving the compliance to the drug therapy."

The SBC240 coated lamination can represent a materials savings throughout the packaging process. It doesn't need stiffening ribs, which are sometimes necessary to ensure PCTFE blisters lie flat, and it is formable into smaller blister wells than cold-formed foil. So, a smaller blister card can be specified, or the number of doses per card can be increased. The lamination also favourably impacts production efficiency because it offers a wider processing window than PCTFE—as much as 20 °F.

Active packaging

Options for desiccants, oxygen absorbers, and other scavenging technologies continue to expand. Sachets, canisters, and capsules are becoming smaller and more powerful, but increasingly, the scavenger is integrated into packaging materials.

One new product, Clariant's EQius humidity stabilizer, maintains a specific relative humidity (RH) inside a drug package. It can be calibrated to different RH levels (e.g., to maintain a drug product within a 20% RH range throughout its shelf-life). Equilibrium levels range from 10–30% RH, and the technology is available in capsule, canister, packet, stopper, and bag forms. Although standard desiccants maintain dry conditions inside the package, there's a possibility of the package environment becoming over dry, which can be detrimental. "Gelatin capsules can have critical stability attributes at both high and low humidity thresholds," explains Florez. "Excessively high humidity can cause API degradation, while overly dry conditions can cause brittleness and friability of the gelatin capsule."

Sanner Group has expanded its AdCap capsules portfolio. One, filled with activated carbon, ensures optimum odour adsorption. The other holds a mixture of silica gel and activated carbon for both odour and moisture adsorption. Capsules generally handle faster on filling machines due to their shape and fineness, and properties can be customized.

A grid structure enables 360-degree moisture adsorption (see **Figure 1**). Brown explains, "The unique grid structure in the capsule wall combines the advantages of conventional capsules and canisters. Even if the capsule ends up on the cardboard side within the container after filling, moisture adsorption is ensured without losing effectiveness. This leads to up to 30% higher moisture adsorption compared to conventional capsules and, consequently, prolongs the shelf-life of pharmaceuticals. In addition, the tactile grid structure prevents confusion with drugs, and thus accidental ingestion, ensuring higher patient safety."

Another tactic to overcome issues with accidental ingestion is integration of the desiccant/scavenger into the packaging. An integrated system also eliminates the need for dispensing equipment and the related step on the packaging line, as well the chance for premature removal by the consumer.

Activ-Seal tamper-evident screw closures from CSP Technologies permanently integrate a molded desiccant or scavenger into the bottle neck. The desiccant/scavenger component is press-fit into the cap, which also contains an induction seal. The technology is compatible with standard bottles and capping systems and requires no changes to packaging lines.

Seal integrity

Another shelf-life-sustaining option for bottles, induction sealing, prevents oxygen and moisture from entering the container through its mouth (see **Figure 2**). Mark Plantier, vice-president of Marketing at Enercon Industries, a supplier of induction-sealing equipment, notes: "An unsealed container opening is the biggest threat to product freshness … [the induction seal] helps preserve product integrity while extending shelf-life. Additionally, a desiccant can be used to absorb moisture trapped in the headspace or that may transgress through the walls of the container."

A tactic to overcome issues with accidental ingestion is integration of the desiccant or scavenger into the packaging.

The cap, induction foil, and container quality all influence seal integrity. "The interaction between the cap and container threads is very important," says Plantier. "A properly torqued cap provides the pressure required for induction sealing. Additionally, a consistent land area on the mouth of the container is required for successful sealing."

The choice of sealing head also impacts seal integrity. Plantier reports: "Enercon offers application-specific sealing heads depending on line speeds and cap size and style. For example, with most child-resistant caps, the induction foil is seated well below the cap, and a tunnel sealing head is more efficient."

To maximize seal quality, Enercon has developed a cap inspection system that detects high caps, missing foils, and stalled bottles. Today's induction cap sealers are easier to integrate and operate and can be washdown-compatible. Typical features and options include automated reject, quick-connect systems, infeed bottle stop, password-protected supervisory settings, diagnostic help screens, uploadable event logs, recipe menus, intuitive setup screens, and multiple language support.

Because seal defects can allow ingress of oxygen, water vapour,

Figure 1 is courtesy of Sanner Group

and other undesirable influences, quality control plays an important role in ensuring seal integrity. Today's vacuum-based leak testers can detect leaks in the single-digit micron range on blisters or induction-sealed bottles.

In the coming decade, the growth of new delivery systems will impact protective packaging.

For blister packages, PTI offers the VeriPac UBV leak tester. It combines an image processing system and sequence of vacuum cycles to test blister cards and identify defects. The operator simply places the card in the unit; no card-specific tooling is needed. The non-destructive test means no loss of product unless a flaw is detected, and even then, it may be possible to perform a deeper investigation. The UBV tester replaces the traditional blue dye test, which is a destructive test that relies on subjective observations and can be time-consuming and error-prone. "With the blue dye test, every cavity needs to be inspected, and it's possible to overlook a defect as large as a thumbtack hole," says Stauffer. "The products with the greatest level of risk are packaged in cold-form blister packs, which require each cavity to be individually opened and carefully inspected. Even if the pack is flawless, the test destroys it. This not only means loss of product, but higher disposal costs because the packs must be disposed of in a controlled manner."

For rigid containers and pouches, PTI's VeriPac 465 vacuum leak tester uses patent-pending hardware and sequencing of pneumatics to provide better control and measure vacuum decay. "By focusing on inert gas laws and the physics of what happens in the test chamber, the Veripac 456 vacuum leak tester results in more stable measurement and detection of smaller leaks. The flexible system can be paired with various test chambers to allow testing of pouches as well as rigid containers," says Stauffer.

What's next?

In the coming decade, the growth of new delivery systems, such as quick-dissolve tablets or strips and sublingual dosage forms, will impact protective packaging. Active packaging technologies will be needed to protect drug products exposed to varied storage conditions and climates, particularly Zone III and Zone IV. "The ability to manage headspace at time of packaging as well as ingress/egress over time are key," says Voellmicke.

Demands for even longer shelf-life will continue to grow. Brown predicts, "We will see even higher requirements in the area of barrier properties … This will necessarily also increase the requirements concerning material properties, above all in plastic packaging."

Green agrees: "We see potential for active barrier or 'smart' materials that indicate expiration or that the drug has been exposed to unhealthy heat and humidity. However, the industry is somewhat risk-averse and doesn't always adopt new innovations quickly. The real opportunity for shelf-life extension/protection may really be simply utilizing the current packaging platforms to the fullest, such as fully embracing the blister versus the bottle. Unit-dose packaging, where a single dose is encapsulated in its own 'dome of protection' may really be the best way to ensure our solid dosage forms are protected adequately until consumed by the patient. The opening and closing of a bottle continuously exposes the remaining doses to moisture and oxygen. This may not offer enough protection to ensure that the first dose is as efficacious as the last in the bottle."

Figure 2: An induction seal prevents oxygen and moisture from entering the container through its mouth.

Stauffer predicts product chemistry will impact the importance of packaging in protecting and extending shelf life. He says, "New chemistries may be less susceptible to oxidation." He believes some injectable treatments will be converted to oral doses. "With parenteral products, there's always the risk of microbial ingress, especially in humid climates," he explains.

Florez also says conversions from biopharma injectable to solid dosage forms will occur. "This is challenging due to the nature of biopharmaceuticals, but once accomplished would impact the protective packaging space," he concludes. **PTE**

Considerations for shelf-life-protecting packaging

- Product sensitivities (moisture, oxygen, light, other)
- Potential routes of ingress
- Critical leak size
- Desired shelf-life
- Barrier properties of the packaging
- Package size and product count
- Climate/ICH zones likely to be experienced
- Effect of shelf-life protection on consumers
- Impact on overall package design
- Impact on operations from equipment needs to production efficiency
- Defect monitoring.

Figure is courtesy of Enercon Industries.

Sartan Recalls Beg the Question: Is Compendial Impurity Testing Enough?

Experts blame the recalls, not on cGMP failures, but on inadequate risk assessment of processes that can generate toxic impurities.

Agnes Shanley

It is not unusual to hear of current good manufacturing practice (cGMP) and quality failings in API and finished drug manufacturing, especially as more functions are outsourced. Between October 2016 and September 2017, out of 3343 citations for pharmaceutical quality systems failures, roughly 11% were likely due to problems with supplier quality management, according to Phil Johnson, senior principal for quality and compliance services at IQVIA (1).

But the root causes for some quality failures can be extremely difficult to sort out. This is becoming particularly evident in the valsartan recalls, which began in July 2018 after traces of the toxic nitrosamine, N-nitrosodimethylamine (NDMA), were found in some APIs that are used to manufacture generic sartans, the angiotensin inhibitor blockers [ARBs]) prescribed to some patients to treat high blood pressure.

By 27 August, 2018, valsartan from 16 different suppliers had been yanked from pharmacy shelves (2). NDMA, classified as a "probable human carcinogen," was found in API made by Zhejiang Huahai, a manufacturer in China. But subsequently, traces of another nitrosamine contaminant, nitrosodiethylamine (NDEA), were discovered in a batch of another ARB, losartan, made in India by Hetero Labs, and in lots of API made by Zhejiang Huahai and of generic valsartan distributed by Torrent Pharmaceuticals.

NDMA's toxic effects in animals have been known since the 1950s (3), and it was the poison of choice in two murders in 1978 (4). Over the past few decades, growing evidence of nitrosamines' potential impact on human health has helped drive public area smoking bans and intensive process changes in the food industry (5,6).

While investigations into the root cause of the contamination continue, this article touches on some questions that the case has brought up so far. Of particular concern is the way that the industry assesses process synthesis risks, especially for small-molecule APIs whose processes may generate trace levels of genotoxic impurities. Most of these compounds are manufactured overseas. Compendial testing requirements may not be enough to convince manufacturers to monitor and test for trace levels of genotoxic contaminants. As offshoring and outsourcing continue, the recall suggests that developing different approaches will be crucial.

Process improvement efforts

It is believed that NDMA contamination resulted from changes that Zhejiang Huahai made to its manufacturing process in 2011 and 2012, using a method that was patented in 2014 to reduce waste and improve product yield. Zhejiang Huahai had submitted documentation for the process change to regulators, and no objections were found. "The US Food and Drug Admin. (FDA) and the European Directorate for the Quality of Medicines and Healthcare (EDQM) approved the changed process, but may have missed the potential for formation of genotoxic impurities," says Philippe André, a cGMP auditor with Qualandre, based in Zhejiang, China, who inspected the Zhejiang Huahai facility.

"In the end, we can only find what we are looking for."

—Anders Fluglsang, Fluglsang Pharma

What began as a single case has snowballed into a major risk-assessment puzzle. The European Medicines Agency (EMA) is considering not only valsartan and losartan, but candesartan, irbesartan, and olmesartan in its efforts to find root cause (7). Both FDA and the General European Official Medicines Control Laboratories Network (GEON) published methods that can be used to test product for the impurities in August and September (8,9).

FDA and EMA also found cGMP deficiencies at the company's facility.

FDA placed the company's products under Import Alert on 28 September (10), when EMA also revoked its right to sell the products in Europe (11).

In an FDA 483 published on 21 September, based on inspections in July and August (12), FDA found fault with the company's change-control system and its "failure to evaluate all potential risks from the 2011 manufacturing process change."The company had hired a lab to conduct a small-scale assessment without pilot-scale testing or a formal risk assessment, the inspectors wrote. In addition, the 483 found that the company did not have a quality agreement in place with that lab.

Inspectors also found fault with Zhejiang Huahai's inconsistent classification of risks in different process-change documents. Where the initial change request classified the process change as critical, drug master file (DMF) amendments sent in 2013 classified the changes as minor, inspectors wrote. Among other problems, FDA inspectors also singled out inadequate validation, cleaning procedures, analytical methods, sampling and testing, and equipment maintenance.

However, observers see some of these observations as focusing more on procedural details rather than fundamental risk assessment problems. Many of the problems noted during FDA's site inspection may not have led to the presence of nitrosamines in valsartan, says André.

"If Zhejiang Huahai did not identify the need to develop a control strategy to reduce the new risks introduced with the optimized process, neither did regulators when they approved the process change," he says, "and the manufacturer's failure in this regard was just part of an industry-wide failure led by the regulators."

Focusing on genotoxic impurities

In response to the valsartan recall, André's company is now conducting audits that zero in on the potential for any process to generate genotoxic impurities. So far, audits have found three problematic synthetic drug substances, says André. One of them is levocarnitine, synthesized from a probable carcinogen, epichlorohydrin. Depending on how it is synthesized, the compound may not only contain epichlorohydrin, but also traces of cyanide.

The yield of synthesis is not great, André says, so it is difficult to predict whether a residue of unreacted epichlorohydrin might be carried over in the final product. Nevertheless, he asks, "Which impurities does the US Pharmacopoeia require testing for? Chlorides, sulfates, sodium and potassium, none of which is toxic at such levels." He wonders how many manufacturers of this compound are even aware of the potential risk.

Even the Chinese manufacturing process for acetaminophen (a.k.a. paracetamol) is a point of concern, says André, since one of the early intermediates is the probable carcinogen, 1-chloro-4-nitrobenzene. "We have audited most of the major Chinese manufacturing plants of acetaminophen, and found no evaluation of and no testing for 1-chloro-4-nitrobenzene at any of them," he says.

"The manufacturer's failure [to develop a control strategy to reduce new risks introduced with the optimized process] was just part of an industry-wide failure led by the regulators."
—Philippe André, Qualandré

André sees a need for manufacturers and regulators to pay much closer attention to potential risks in the manufacturing process. "In the valsartan case, the focus was on control of the related substances of synthesis and other impurities above the reporting threshold (0.05% in the case of valsartan), rather than on the safety of the chemical synthesis processes.

Missing the red flags

Zhejiang Huahai's improved process replaced tributyltin azide with the more toxic compound, sodium azide, says André. As a result, the yield of tetrazole formation was much better. However, sodium nitrite was used to destroy the excess sodium azide that remained after the synthesis step. Sodium nitrite is often used as a decontaminating agent of sodium azide in acidic conditions, André says. However, under these conditions, it forms nitrous acid, which could react with the residue of dimethylamine in dimethylformamide, the solvent that is used in the tetrazole-forming reaction, to generate NDMA, says André.

"The possible formation of nitrosamines from nitrites and secondary amines in acidic conditions was already well-known to the food industry," says André. "The use of sodium nitrite should have been a red flag prompting a check of possible presence of secondary amines, but it was not," he says.

"So we arrive at the million-dollar question: Are regulatory agencies and pharmacopoeias doing a good enough job, if a sponsor can comply with [most] regulations and yet send a product on the market which contains carcinogens," asks Anders Fuglsang, founder of Fuglsang Pharma."We can't test for everything, but I'm not entirely happy with that statement as a patient or consumer," he says. Fuglsang hopes that there will be an independent analysis of the root cause of the nitrosamine contamination, performed by independent experts outside of regulatory agencies or pharmacopoeias. In the end, he says, "we can only find what we are looking for." But the sartan API contamination case suggests a need to focus more closely on assessing potential risks during process synthesis review.

The need to see a bigger picture

Preventing situations like this from occurring in the future will be complex, says Fuglsang, and require getting all the different players involved to see the bigger picture, from pharmacopoeias and regulators, to finished drug manufacturers, API manufacturers, and national testing labs. "At this point," he says, "that may be wishful thinking."

contin. on page 42

SCANRAIL1/
SHUTTERSTOCK.COM

Process Stability, Performance, and Capability; What is the Difference?

This article applies the basics of stability, performance, and capability to modern process performance and capability indices.

Chris Burgess, PhD, is an analytical scientist at Burgess Analytical Consultancy Limited, 'Rose Rae,' The Lendings, Startforth, Barnard Castle, Co Durham, DL12 9AB, UK; Tel: +44 1833 637 446; chris@burgessconsultancy.com; www.burgessconsultancy.com.

Performance metrics for processes are an area of much regulatory interest currently. There isn't always a readily available clear definition of what is needed, however, and guidance from regulators is not always consistent. This column goes back to the basics that were first set out by Shewhart (1) nearly 90 years ago and relates them to some modern process performance and capability indices. Definitions are important in providing a consistent nomenclature, and the global International Organization for Standardization (ISO) standard 3534-2:2006 (2) will be used.

Process variation

All process measurement results are subject to variations that come from a variety of sources as was seen in the previous Statistical Solutions column (3). However, there are only two types as defined by Shewhart, namely common cause variation and special cause variation.

Common cause variation is the inherent noise in a process over time due to random effects and hence predictable within statistically derived limits. By definition, a process that contains only common cause variation is said to be in statistical control.

Special cause variation occurs because of specific circumstances that are not always present manifesting themselves by, for example, a shift or drift in the process mean or excessive noise. If a process contains special cause variation, it is unstable from a statistical point of view, and the overall variation observed contains both common and special cause components. Control charts are designed to detect the presence of special causes of variation. The normal distribution is characterized by two parameters: a measure of location (the arithmetic mean or average) and a measure of dispersion (the standard deviation). An unstable process means that both of these parameters could be or are changing in an uncontrolled manner (**Figure 1A**) (4).

The task is to bring these two parameters into a state of statistical control. This would entail ensuring that the mean and the standard deviations were not varying significantly. This ideal situation is illustrated in **Figure 1B**. This process would then be said to be under statistical control (i.e., no special cause variation and stable common cause variation). In this state, the process is amenable to the tools of statistical process control (SPC). However, a stable process may not be statistically capable of meeting the specification limits. **Figure 1C** illustrates this, showing that the red process, albeit stable, is incapable. The desired state is to arrive at the blue capable state.

Capability is assessed using a family of quality metrics or indices called process performance and capability indices.

Quality metrics for process performance and capability

There are a variety of performance indices for processes in regular use. However, in this column, only four will be discussed, P_p, P_{pk}, C_p, and C_{pk}. The definition and meaning of these four will be defined later. Of these four, only two have any practical relevance, $P_{pk,}$ and C_{pk}. The other two are of theoretical interest as they do not occur in practice other than by chance.

Process performance. P_p, a process performance index, relates to the output performance of a process, irrespective if it is in control or not, with the specification assuming that the long-term mean will be on the target for the product (an unbiased process).

The index is defined as a ratio of the difference between the upper and lower specification limits (called the specified tolerance in ISO) and the 99.73% probability of a value lying within ±3 standard deviations from the target (called the reference interval in ISO). Hence, it can be said that this index would represent what the customer actually receives from the overall process (see **Equation 1**).

$$P_p = \frac{U - L}{6S_t} \qquad \text{[Eq. 1.1]}$$

The overall standard deviation, S_t, is calculated from the usual formula for a sample standard deviation.

$$S_t = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(X_i - \bar{X})^2} \qquad \text{[Eq. 1.2]}$$

Where $\bar{X}$ is the mean of the N data points.

Values for P_p of 1.33 or more would indicate a highly capable process. A value of less than 1 would indicate an incapable process that would lead to out-of-specification (OOS) results.

As it is highly improbable that processes are unbiased, a practical process performance index would need to take this bias into account when assessing process performance. This is done by calculating the upper and lower process performance indices P_{pkU} and P_{pkL} using not the target but the actual observed mean to calculate them from:

$$P_{pkU} = \frac{U - \bar{X}}{3S_t} \text{ and } P_{pkL} = \frac{\bar{X} - U}{3S_t} \qquad \text{[Eq. 1.3]}$$

Hence the process performance index, P_{pk} is given by the smaller of the two values above.

$$P_{pk} = \min\left[\frac{U - \bar{X}}{3S_t}, \frac{\bar{X} - L}{3S_t}\right] \qquad \text{[Eq. 1.4]}$$

Process capability. Process capability refers to the performance of the process when it is operating under statistical control. Two capability indices are usually computed: C_p and C_{pk} in a similar way as was described with P_p and P_{pk}. However, C_p measures the potential capability in the process, if the process was centred, while C_{pk} measures the actual capability in a process, which is off-centre or biased. If a process is centred, then C_p=C_{pk}.

Figure 1: Process stability and capability (4).

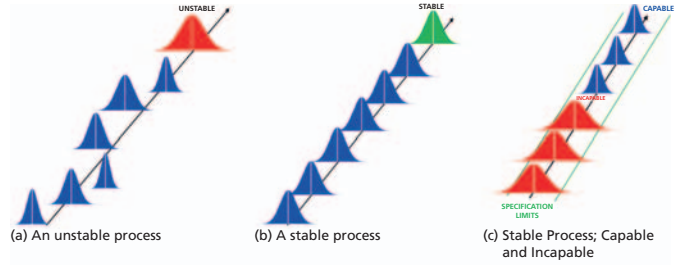
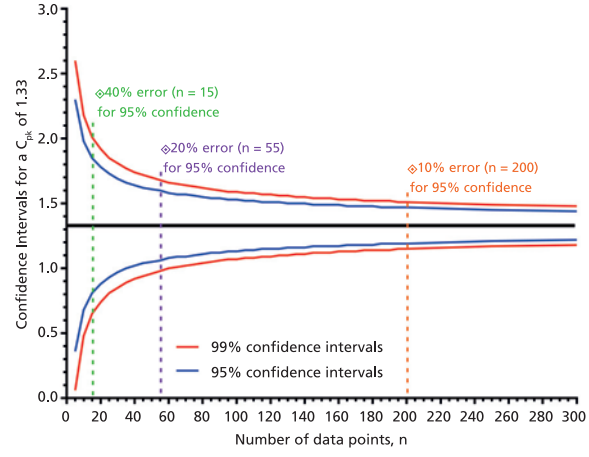


Figure 2: Confidence intervals as a function of sample size for C_{pk} of 1.33.



$$C_{pk} = \min\left[\frac{U - \bar{X}}{3S_w}, \frac{\bar{X} - L}{3S_w}\right] \qquad \text{[Eq. 1.5]}$$

The critical thing to note is that while the formulae for P_{pk} and C_{pk} look very similar, the standard deviation used to calculate the reference interval for C_{pk} is not S_t but S_w.

S_w is the within batch standard deviation (called the within sub-group standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula:

$$S_w \approx \frac{\bar{R}}{d_2} \qquad \text{[Eq. 1.6]}$$

where $\bar{R}$ is the mean range of the subgroups and d_2 is a constant based on the subgroup size and may be found in many Statistical Process Control books

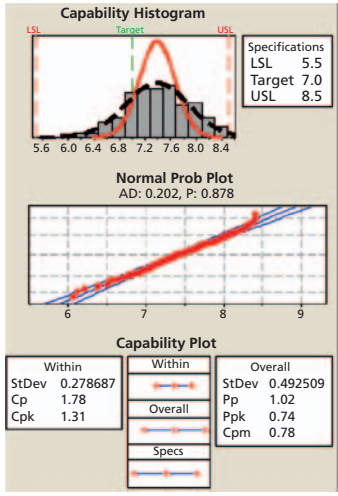
Typical values for C_p and C_{pk} are 0.5 to 1 for incapable processes, 1 to 2 for capable processes and >2 for highly capable processes.

A word of caution is necessary in interpreting C_{pk} values. C_{pk} analysis requires a normal underlying distribution and a demonstrated state of statistical process control. When reporting a C_{pk} value, a 95% or 99% confidence interval should always be reported because this takes into account the sample size used in the calculation (5,6). Sadly, this is usually missing.

The confidence interval is extremely important because it is not always recognized that, for reasonably small confidence intervals around C_{pk} values, the number of data points needs to be large. **Figure 2** shows that to have a 95% confidence interval in C_{pk} of 1.33 ±10% requires in excess of 200 data points. One commonly used approximation formula (5) for the confidence interval is:

FIGURES COURTESY OF THE AUTHOR

Figure 3: Example of process performance and capability plots (Minitab 17).



$$C_{pk} = C_{pk} \pm Z_{\alpha/2}\sqrt{\frac{1}{9n} + \frac{C^2_{pk}}{2n-2}} \qquad \text{[Eq. 1.7]}$$

Hence the use of C_{pk} values for comparison of performance needs to be interpreted with great care when n is small.

Conclusion

It has been shown how to differentiate between process performance and process capability. Equations, however, are not normally as clear as an example. **Figure 3** shows data from 157 batches of a product with a target of 7.0 and upper and lower specification limits ± 1.5. The data are nicely normally distributed as can be seen from the normal probability plot, but the long term mean of 7.4 is biased high. However, the process capability C_{pk} is excellent at 1.31 and even with the bias would be unlikely to produce OOS results due to common cause variation (red curve). Unfortunately, the process suffers from considerable special cause variation, the dashed black curve, with P_{pk} being an unacceptable 0.74 because the overall batch standard deviation (S_t) is 0.49, whereas the within batch standard deviation (S_w) used to calculate C_{pk} is much smaller at 0.28. Note that if we could remove the mean bias, P_p would be a more acceptable 1.02. However, it would require a root cause investigation and process change(s) to remove some of the special cause variation(s) to approach a truly capable process.

References

1. W A Shewart, *Economic Control of Quality of Manufactured Product* (Van Nostrand, 1931).
2. ISO 3534-2:2006; Statistics—Vocabulary and symbols—Part 2: Applied statistics
3. C. Burgess, *Pharmaceutical Technology* 42 (5) 2018.
4. Redrawn & adapted from *QMS – Process Validation Guidance GHTF/SG3/N99-10:2004* (Edition 2) Annex A, Statistical methods and tools for process validation, www.imdrf.org/documents/doc-ghtf-sg3.asp.
5. ASTM E2281-15, Standard Practice for Process and Measurement Capability Indices.
6. S. Klotz and N.L. Johnson, *Process Capability Indices* (Chapman & Hall/CRC, 1993). **PTE**

Supply Chain Safety — *contin. from page 39*

André sees the root cause study as an opportunity for the industry to look more deeply into the way it approaches risk assessment. This will be especially important for API syntheses that may result in residual levels of potentially genotoxic impurities. "I hope we will all draw the right lessons from this [recall] debacle," says André. "Despite its mistakes and deficiencies, Zhejiang Huahai basically did what the regulators expected from them at the time. Stoning the company would be a distraction from the critical deficiency in the regulatory supervision of drug substances," he says.

References

1. P. Johnson, "Quality In, Quality Out: Regulatory Drivers of Supplier Quality Management in the Pharm and Biopharma Industries," Xtalks Webcast (18 September, 2018).
2. FDA, "Valsartan Products Under Recall," *fda.gov*, 28 August, 2018, www.fda.gov/downloads/Drugs/DrugSafety/UCM615703.pdf
3. P. Magee and J. Barnes, "*British Journal of Cancer*, 10 (1) 114-122 (1956),
4. C. Purdy, "A Common Blood Pressure Medicine is Being Recalled Because it Was Mixed With NDMA," www.qz.com/1330936/the-fda-is-recalling-a-common-blood-pressure-drug-because-it-was-mixed-with-ndma/
5. A. Tricker et al, *Carcinogenesis* 12(2); 257-261 (1991), www.ncbi.nlm.nih.gov/pubmed/1995191
6. M. Jagerstad, *Mutation Research* 574(1-2), 156-172 (August 2005)
7. EMA, "Valsartan: Review of Impurities Extended to Other Sartan Medicines," Press Release, 21 September, 2018.
8. FDA, "FDA Announces Preliminary GC/MS Headspace Method for Determining NDMA in valsartan" Press Release, 16 August, 2018.
9. EDQM, "OMCLs Release Three Methods for Determination of NDMA in Sartans," Press Release, 21 September, 2018.
10. FDA Press Release, "FDA Places Zhejiang-Huahai on Import Alert," *fda.gov*, 28 September, 2018, www.fda.gov/Drugs/DrugSafety/ucm613916.htm
11. EMA, Press Release, "EU Inspection Finds Zhejiang Huahai Site Non-Compliant," *ema.europa.eu*, 28 September, 2018, www.ema.europa.eu/en/news/eu-inspection-finds-zhejiang-huahai-site-non-compliant-manufacture-valsartan
12. FDA, Form 483, *fda.gov*, www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM621162.pdf **PTE**

Outsourcing Development: Small-Scale to Commercial

Industry experts discuss the formulation and development issues that should be considered when addressing scale-up from small-scale batches to commercial production.

Susan Haigney

An API's physiochemical properties and its pharmacokinetic profile, as well as patient considerations, should dictate drug product formulation, according to experts at Catalent. Budget and timeline constraints, however, sometimes create difficulties. "The positive effects of formulation approaches on solubility, permeability, and ultimately bioavailability should be weighed against complexity, cost, and risk-to-launch of the chosen technology," say experts at Catalent. "It is unrealistic to expect any formulation group to tackle all these considerations without the experience from many multiple product launches or the ability to leverage the expertise across a large and diverse formulation team."

According to Joe Masi, senior director MS&T at Cambrex, pharmaceutical companies turn to contract development and manufacturing organizations (CDMOs) to "resolve capacity shortages, tighten development timelines, reduce processing costs, and/or lack of internal development capability, etc." Pharmaceutical companies are requesting end-to-end services more and more, according to Masi. "This includes API, formulation development, analytical methods development, manufacturing, and packaging development. In addition, paediatric formulation and fixed-dose combination products (two or more active ingredients in one product), as well as modified- and controlled-release complex formulation, continue to gain popularity and are often outsourced."

When it comes to outsourcing formulation development, however, challenges may arise when scaling up from small-scale batch to commercial production. Dr. Baerbel Hinneburg, director Technology and Process Transfer at Vetter Pharma-Fertigung GmbH & Co. KG, states that "concrete planning of execution with attention to detail is critical."

Pharmaceutical Technology Europe spoke with Masi, Hinneburg, and experts at Catalent about the formulation and development issues that should be considered when addressing scale-up from small-scale batches to commercial production.

Moving from clinical to commerical phases

PTE: What formulation challenges occur when moving from clinical to commercial phases?

Hinneburg (Vetter): From a processing and technical point of view, one example is a change in material and equipment that may occur when moving from clinical to commercial manufacturing, such as the use of larger compounding equipment or a change from disposable to non-disposable material. One must be aware of the impact a change in material could have on the relevant attributes derived from the drug product profile. This awareness avoids further lab trials that need to be undertaken to determine the appropriate operational parameters that help maintain the quality and functionality of the drug product produced with the new process.

Masi (Cambrex): Usually, batch size and equipment used throughout development phases are small due to API availability, manufacturing cost, and the scale needed to meet clinical and registration requirements. However, some manufacturing process parameters may need to be changed when scaling up or using large-sized equipment for commercial production.

Common challenges could occur during different manufacturing steps. A few examples are listed below:

Blending step: Material flow (i.e., the flowability of granules) is one common challenge during manufacturing. Funnel flow is non-uniform, and the materials adhere to the walls of the hopper, resulting in blend uniformity issues during the blend. To overcome the issue, change the geometry of mixers, blenders, and hoppers to improve flow of materials through the hopper. Another way is using vibratory mechanisms to ensure a mass flow or having a paddle stirrer in the hopper.

Compression step: Sticking and capping issues are commonly observed during compression. When different compression machines are used, they may not directly generate expected results. Modification of a tabletting process can sometimes reduce or eliminate film formation or sticking during compression without making any drug formulation changes. Modifications include changes to pre-compression force, compression force, and tabletting turret dwell time/speed. These modifications may be helpful in delaying the sticking behaviour.

Coating step: When using a large-sized coater, some of the parameters from the small coater may not work and coating uniformity may suffer. Coating variability usually increases at a faster pace with higher pan speeds. Therefore, the first consideration is to reduce coating pace to obtain better coating uniformity. The spray distribution across the tablet bed may be another cause of the coating uniformity issue. However, with functional coatings it is important that each nozzle is spraying the same amount of coating suspension. Each nozzle must have an even spray and be calibrated to ensure it functions properly.

In early formulation and clinical phases of development, there are options to modify the qualitative formulation to overcome these challenges. However, because it is often difficult to make major changes at later phase without regulatory involvement, engage with an experienced CDMO from the earlier clinical development phase. They can help to develop and manufacture quality products with minimal to no clinical or regulatory impact.

Catalent: The main challenge of a formulation proven as safe and effective for the therapeutic action tested in patients is to ensure that as we move from the beginning of the quality by design (QbD) process to commercial process validation, there are no changes in correlated critical material attributes (CMAs) (APIs, excipients, synthesis route, suppliers, etc.) and that none of the critical process parameters (CPPs) (associated with scale up to commercial batches) will affect the critical quality attributes (CQA) of the product that ensured efficacy and safety in clinical-phase stages. If any change is necessary to apply as part of the process, a risk assessment and mitigation should be implemented to assure the desired quality, considering the safety and efficacy of the pharmaceutical form.

Critical quality attributes and critical process parameters

PTE: What steps should be taken for successful scale-up from small-scale batches to commercial production?

Hinneburg (Vetter): To prepare a robust and reproducible commercial production process we perform a QbD approach. This approach involves a combination of gap and risk analysis to identify and evaluate any factors that could potentially impact CQA and any not obvious scale-up process steps that become CPPs. A comprehensive process design to accommodate both known and newly identified CPPs, combined with a process qualification to verify a constant product quality and define a control strategy, is essential.

Masi (Cambrex): First, define the target product profile (TPP), which describes the use, safety, and efficacy of the product. Prior knowledge and in-depth understanding of formulation, excipients, and process is advantageous when defining the TPP and will reduce the number of experiments and analytical testing required and, consequently, the manufacturing and testing costs.

The next step is to identify the CQAs of the final product. CQAs should be studied thoroughly and controlled to meet the TPP. To achieve the desirable CQAs, it is necessary to identify and control CPPs. CPPs identified throughout the development and scale-up process include raw material and API controls (particle size distribution, polymorphs, and impurities), process controls, and design spaces around individual or multiple unit operations (granulation, compression, coating, packaging). These CPPs are monitored throughout development and updated upon the collection of new information.

Successful scale up can be achieved by a QbD approach, which includes design of experiments (DoE), risk assessment, and process analytical technology (PAT).

Catalent: Most frequently, there will be changes between the equipment used in small-scale batches to ones in the commercial setting. With the difference in the equipment, the CQAs (e.g., dissolution) of the drug product could be affected, and this may depend on the complexity of the formulation. It is important to understand the correlations between the equipment scale, CPPs, and CQAs as this knowledge will help to fine tune the CPPs in the commercial-scale production that will produce drug product with the desired CQAs. These relationships can be studied by appropriate DoE at small-scale.

Analytical methods and validation

PTE: How do analytical methods change from clinical development to commercial production?

Catalent: Often, analytical methods do not change dramatically from clinical development to commercial production, but the understanding of the method and information changes. Early-phase methods are developed for speed and to minimize cost, and the assay/purity methods are commonly adapted from the method developed by the API manufacturer (for ease of tracking API impurities). Dissolution methods may simply be discriminating rather than profile generating, and things such as extraction procedures may need to be optimized. Once a drug has moved from clinical to commercial, a commercial quality control laboratory performs a method evaluation and transfer to confirm that the method can be performed, and the same results can be obtained using similar instrumentation. If there are any nuances to the method (understanding its variability, the level of validation performed, the experience on different equipment or by different analysts), then changes are usually minor adjustments and the method is updated. Changes in the analytical methods could support certain adjustments during a

validated-state maintenance process if they merit it. Historical data generated by the method can be used to adjust or refine the acceptance criteria as the programme progresses from clinical to commercial batch production. It is key to use these data to assess critical method parameters that must be controlled carefully as part of the overall analytical control strategy—as the molecule moves to commercial testing and release. Statistical tools are valuable to set acceptance appropriately for commercial products—while also considering practicality, so as to not fail a batch unnecessarily.

PTE: When moving from clinical-scale production to commercial production, what validation steps must be performed?

Masi (Cambrex): The successful transfer of a product from clinical- to commercial-scale production is based on a thorough understanding of the manufacturing process, the inherent variability in the process, and strategies to mitigate or control these sources of variability. This knowledge is gained through scientifically based process development work and documented in reports that are used as the source documentation to create the commercial validation plan.

The validation plan and process risk assessments are used to justify and implement the validation strategy, number of validations batches to be executed, sampling plans, and testing criteria.

The validation batches are executed under protocol by trained personnel using qualified equipment. Enhanced physical and analytical testing may be done to assure process robustness and control. A validation summary report including physical and analytical batch data, statistical data treatment, and summary of batch outcomes is approved by discipline subject matter experts and the quality unit prior to commercial batch release to distribution.

Catalent: A total of three consecutive, successful (commercial-scale) batches need to be manufactured within 10 times the size of the registered batch size. Validation demonstrates that a specific process will produce batches that meet specification and that normal variation would not predict an out-of-specification result. Emphasis is given to those elements that have been established, through QbD, as having a significant impact upon product quality, accompanied by increased testing of samples from throughout the process. It is not good practice to use validation batches for experimentation beyond that which has already been demonstrated, as the costs of validation batches are typically very high.

Tech transfer best practices

PTE: What are some best practices for successful tech transfer?

Hinneburg (Vetter): In our experience, a dedicated transfer team that includes a wide breadth of experts is crucial. This team is responsible for the process design required to perform a QbD-driven tech transfer. Roles and responsibilities must be agreed upon, and a system that enables adequate communication and feedback should be established. Open communication and exchange of all information gained during development is a key element. The license holder should also check early in the process that all partners and suppliers can provide adequate quality and documentation systems that help ascertain regulatory requirements are being met.

Masi (Cambrex): The main goal of tech transfer is to transfer the product and process with minimal or no changes, which will minimize regulatory challenges and smooth the path to regulatory approval.

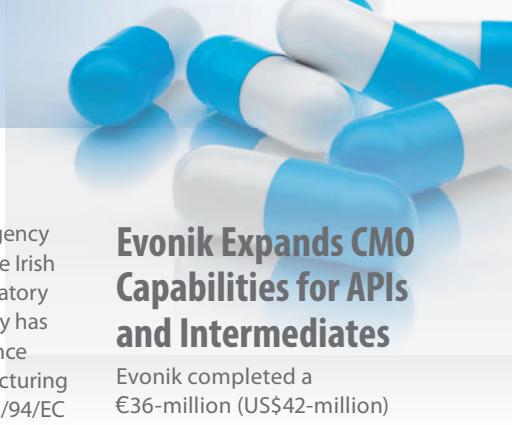
The success of a technology transfer depends on several things: the quality of the finished product, open communication between two parties, feasibility of scale-up to desired levels, and compatibility of equipment at the transferred site. Therefore, it is advisable to consult with the technical and regulatory experts from the transferred site regarding the feasibility of the process with minimal impact on finished product.

Important actions to take for a successful tech transfer include:

- Obtain detailed technology transfer documents such as product development reports, batch records, protocols, and documents containing CPPs, CQAs, and TPPs from the transferring site. Better communication between transferring and transferred site is a key for successful tech transfer.
- Understand formulation, manufacturing process, key equipment, function of each and every excipient, specifications, and critical manufacturing process parameters, etc. for the tech transfer product.
- Perform a gap analysis between sites (transferring and transferred site) by evaluating the equipment and supporting the information by comparing differences in the make, model, type, and capabilities of equipment available between transferring and transferred site.
- Identify the regulatory strategy; SUPAC guidelines describe equipment in detail and classifies changes in three levels: Level I, Level II, and Level III changes. CBE30, PAS, and annual reportable are common strategies for tech transfer, which can save companies significant time and money.
- Perform feasibility batches and capture the critical process parameters and optimize the process before registration/validation batches.
- Gather stability data including bulk hold data on finished product to gain more confidence on the quality of the product from transferred site.
- Generate a comparison report to compare equipment and manufacturing process parameters between transferring and transferred site and to perform a risk assessment.

Catalent: First, understand and capture the historical technical details or lessons learned from previous manufacturer(s) via discussions or detailed development reports.

Second, understand customers' timelines for milestones and plan critical activities (e.g., raw materials, specifications, analytical method transfer/validation, and ancillary equipment parts) accordingly. PTE



Rentschler Fill Solutions Starts GMP Operations in Austria

Rentschler Fill Solutions GmbH, a contract development and manufacturing organization (CDMO) for aseptic fill/finish services, obtained a certificate of GMP compliance and a pharmaceutical manufacturing license for the European market from the Austrian Agency for Health and Food Safety (AGES) on 20 Aug. 2018, the company announced in an 1 Oct. 2018 press release.

The company, located in Rankweil, Austria, offers CDMO services from GMP-compliant aseptic filling and freeze-drying to analytics. The facility is designed for the flexible handling of small- to medium-sized batches of up to 60,000 vials and provides lyophilization capacity of 15 m^2. Single-use equipment guarantees maximum product safety. The facility is designed to enable future expansion without interrupting ongoing operations.

Together with its strategic partners, Rentschler Biopharma SE and Leukocare AG, Rentschler Fill Solutions offers end-to-end services from formulation development through drug substance production to aseptic fill/finish.

APC and Bavarian Nordic Build 500-L Single-Use Biologics Pilot Plant

The Applied Process Company (APC) and Bavarian Nordic have completed a €2-million (US$2.3-million) joint investment and have partnered to build a new 500-L pilot-scale single-use biologics facility at APC's headquarters in Cherrywood, Dublin, Ireland, APC announced on 27 Sept. 2018.

The new facility fully integrates process analytical technology (PAT) and process modelling and control capabilities. The pilot plant will initially employ a single-use bioreactor system and process-tailored bags to support upstream processing. After pilot-scale development, the manufacturing process will be transferred into GMP assets within Bavarian Nordic.

Downstream processing elements will initially include unit operations for cell lysis, clarification, and purification to address current project requirements, with the ability to add further equipment as needed. Both upstream and downstream processing are supported by APC's biologics analytical laboratories, currently focusing on viral titer and impurity analysis.

Manufacturing License Granted to Alvotech for Biopharma Facility

Specialist biopharmaceutical company, Alvotech, has announced receipt of a manufacturing license from the Icelandic Medicines Agency, applying to its biopharmaceutical facility based in Reykjavik, Iceland.

Founded in 2013, Alvotech is focused on the development and manufacture of high-quality biosimilar products. The Icelandic facility, which is 13,000 m^2 in size, is located within the science park of the University of Iceland and dedicated to developing and manufacturing the company's broad biosimilar portfolio.

Through this manufacturing license, granted by the Icelandic Medicines Agency in consultation with the Irish Health Products Regulatory Authority, the company has confirmed its compliance with the good manufacturing practice directive 2003/94/EC guidelines and principles.

Novo Nordisk to Restructure R&D

Novo Nordisk announced plans in a 18 Sept. 2018 press release to restructure its R&D organization to accelerate the expansion diversification of its pipeline across chronic diseases.

To enable this increased investment in transformational biological and technological innovation, approximately 400 employees will be laid off from R&D roles in Denmark and China.

According to the company, it will establish four transformational research units in 2018 to pursue new treatment modalities and platform technologies. The biotech-like units will be based in Denmark, the United States, and the United Kingdom and will operate as satellites of Novo Nordisk's central R&D function, driving innovation in priority fields such as translational cardio-metabolic research and stem cell research, the company reports.

Novo Nordisk will also significantly increase its investment in automation and digital capabilities, including machine learning and artificial intelligence (AI), in an effort "to drive a faster and more efficient path towards lead molecule selection and development." The integration of laboratory infrastructure and IT systems will also be prioritized to increase the efficiency of the R&D organization.

Evonik Expands CMO Capabilities for APIs and Intermediates

Evonik completed a €36-million (US$42-million) expansion of its contract manufacturing capabilities in the United States and Europe, the company announced in a 19 Sept. 2018 press release. A series of advanced technologies, including high-potency API (HPAPI), fermentation, polyethylene glycol monomethyl ethers (mPEGs), and continuous processing have been introduced or enhanced at multiple Evonik production sites over the past year.

At its facility in Hanau, Germany, Evonik has commissioned a new modular cGMP continuous processing plant, a pilot plant for the custom synthesis of highly pure PEGs and mPEGs for pharmaceutical applications, and a cGMP suite for the small-scale production of HPAPI and ultra-HPAPI.

At its facilities in Tippecanoe, Indiana, US, and Hanau, Germany, Evonik has increased its asset footprint and added additional capacities to support the small-, medium-, or large-scale production of HPAPI. Evonik is now able to run several HPAPI projects in parallel down to an occupational exposure level of 5 ng/m^3.

At its facility in Slovakia, the company has invested in a new, flexible pilot plant for downstream processing. It is the sixth plant in a worldwide network to support microbial fermentation projects from strain development through to commercial manufacturing.

Intelligent Dose Design

Catalent Pharma Solutions offers its partners end-to-end solutions, from early drug product development, formulation and delivery technologies, to manufacturing and clinical supply services.

Each molecule has unique characteristics, and Catalent offers partners its formulation and development experience, and a wide range of tools and technologies to create innovative, intelligent dose forms to overcome challenges, while making better products for patients.

Catalent's multi-award-winning OptiForm® Solution Suite platform can assist in the development of innovative dose forms that can improve a drug's clinical efficacy and commercial success. OptiForm Solution Suite is fast, flexible and fact-based, combining the broadest selection of enabling technologies to ensure the right decisions are made at each stage of development.

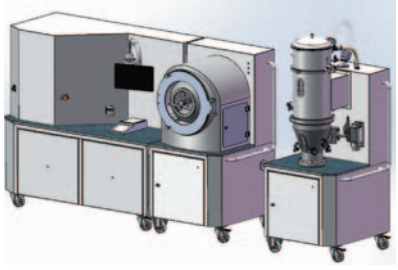
Leveraging its early phase development global centres of excellence in the UK and US, and its network of manufacturing sites, Catalent can accelerate better products to the clinic and through to commercial supply.

Catalent Pharma Solutions

www.catalent.com

solutions@catalent.com

Midilab RC



Midilab RC by DIOSNA is a highly flexible laboratory processor that is built in modular design. The device is designed for plug-and-play operation and the modular design offers a rapid change (RC) between the fluid bed module and the tablet coater module. Each module as well as the basic unit are moveable and can be connected without using any tools. For both modules different material bowl sizes are available, whereby the fluid bed module can handle batch sizes from 600 g to 9 kg and the tablet coater module can handle 2 kg to 16 kg batches. For better process monitoring both modules are equipped with inspection glass. Another highlight is the swivelling and tilting operator terminal with stainless steel housing which allows flexible adjustment for the operator. The installation is possible in line, at a corner as well as through the wall.

DIOSNA Dierks & Söhne GmbH

www.diosna.com

info@diosna.de

Capsugel® Colorista™ Capsule – Unleash your creativity

Capsule Delivery Solutions, part of Lonza Pharma & Biotech, launches the new Capsugel® Colorista™, a high-quality capsule based on an all-colorants™ formulation.

Colorista™ capsules meet the demand of pharmaceutical developers who look for solutions that cut down on development time while giving them flexibility to progress with technical development before the final commercial color decision is taken.

This new capsule further expands the Lonza Capsugel® pre-clinical and clinical capsule offering, and contains a broad selection of colorants suitable for use in major markets, allowing pharmaceutical customers to have access to a wide array of colors. Colorista™ capsules are available in both Vcaps® Plus (HPMC) and Coni-Snap® gelatin, and are available in different sizes to enable the encapsulation of a wide range of doses and formulations.

To learn more on Colorista™, visit www.capsugel.com/biopharmaceutical-products/colorista-capsules.

Lonza Pharma & Biotech

www.capsugel.com/biopharmaceutical-products/colorista-capsules

solutions.emea@lonza.com

LCMS-9030 Q-TOF

Shimadzu has introduced the new LCMS-9030 quadrupole time-of-flight liquid chromatograph mass spectrometer. The LCMS-9030 is a research grade mass spectrometer designed to deliver high-resolution, accurate-mass detection with incredibly fast data acquisition rates, allowing scientists to identify and quantify more compounds with greater confidence. It provides a new solution for analyzing even the most complex samples and integrates the world's fastest and most sensitive quadrupole technology with TOF architecture.

Shimadzu Europa GmbH

www.shimadzu.eu

shimadzu@shimadzu.eu

SHIMADZU
Excellence in Science

SMA MicroParticle ICS™

VAI is pleased to announce the addition of the SMA MicroParticle ICS line of non-viable particle counters to our contamination control portfolio. The units utilize the latest innovation in particle counting technology and have several features not found in other Particle Counters.

- *Multi-Processing*—can simultaneously process, perform tasks, and log data without interrupting sampling
- *Real-Time Meter*—displays particles counted per second, per channel, for pinpointing sources of contamination
- *Annotations*—allows users to add notes to data records during sampling
- *Advanced Power Management*—have advanced power management features, including the industry's first sleep mode, and over 10 hours of battery life
- *Sampling*—can store up to 45,000 comprehensive data records for each sample
- *Reporting*—produces reports that comply to ISO 14644-1, EU GMP Annex 1, and Federal Standard 209E

Available in three models: HandHeld, Table Top, and Wall Mount. Remote models are also available for integration into facility monitoring systems.

Veltek Associates, Inc.

www.sterile.com

vai@sterile.com

vai
VELTEK ASSOCIATES, INC.

Contract Microbiology & Toxicology Testing Services

As a GMP/GLP, compliant laboratory with over 50 years of experience, Wickham Laboratories Ltd is a trusted name in the pharmaceutical and medical device industries, providing rapid turnaround while maintaining only the highest standard of quality at all stages.

We provide a wide range of microbiology and toxicology services for medical devices & pharmaceutical industries, including:

- Antimicrobial/preservative efficacy
- Bacterial endotoxin (LAL) and Monocyte activation test (MAT)
- Bioburden determination
- Biological indicator enumeration
- Cytotoxicity enumeration
- Environmental monitoring
- *In-vitro* diagnostic assays such as ELISA, BCA and Western blot
- Rapid microbial identification (MALDI-ToF)
- Microbial ingress
- Microbial limits including TAMC/TYMC and absence of specified pathogens
- Potency bioassays and abnormal toxicity on biological products
- Rabbit pyrogen (RPT)
- Stability storage and testing
- Sterility testing
- USP Plastics class I-VI tests.

Whether assisting a start-up company demonstrating proof of concept, or working with a global medical device manufacturer, our expert technicians recognise the importance of delivering an exceptional service by taking the time with every client to fully understand their induvial requirements.

We are routinely inspected by the MHRA, FDA and Home Office, and offer the opportunity for clients to conduct audits on a regular basis.

Wickham Laboratories Ltd

www.wickhamlabs.co.uk

mail@wickhamlabs.co.uk

Wickham Laboratories
Contract Analytical Services

standards." This same document states, "Management, with the support of the quality unit, should establish and maintain a working environment that minimizes the risk of non-compliant records and erroneous records and data. An essential element of the quality culture is the transparent and open reporting of deviations, errors, omissions, and aberrant results at all levels of the organization, irrespective of hierarchy." Based on the language used in data integrity guidance documents, it is clear that regulatory authorities consider quality culture an important element in establishing the veracity and integrity of the data being generated by companies that support the products they manufacture.

The trouble with quality culture is determining how to measure it. PDA has developed a culture assessment tool that links organizational attributes to specific behaviours (7). Attributes were defined as elements of a quality system such as, but not limited to, deviations reporting, change control, CAPA, complaints, and environmental monitoring programmes or systems. Behaviours were defined as intangibles such as, but not limited to, robust communication and transparency, rewards and recognition, employee engagement, and cross functional vision. The theory was if quality attributes equaled quality behaviours, which then equaled quality culture, then if the quality attributes of a company could be measured, they would reflect the maturity of the quality culture of an organization. The PDA tool involves several steps that include training employees on the use of the tool, an onsite assessment, an all-staff survey, and finally analysis and action on the results. There are, of course, other tools available to measure the culture of an organization. The real point is whatever tool your company uses to measure culture, it will be an important element in determining your data integrity risks and remediating them before an inspection. Auditing a company to determine if their culture is conducive to generating data that meets the attributable, legible, contemporaneous, original, and accurate (ALCOA) concepts is on the horizon and may become a part of routine audits performed by regulators or industry auditors when evaluating the suitability of a manufacturer, potential partner, or service provider.

References

1. FDA, *Data Integrity and Compliance with CGMP Guidance for Industry Draft Guidance* (CDER, April 2016).
2. MHRA, A *GxP Data Integrity Definitions and Guidance for Industry*, Draft version for consultation (MHRA, July 2016).
3. MHRA, *GMP Data Integrity Definitions and Guidance for Industry* (MHRA, March 2015).
4. WHO, *Annex 5, Guidance on Good Data and Record Management Practices* (WHO, June 2016).
5. PIC/S, *Draft Guidance: Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments* (PIC/S, August 2016).
6. PDA, *Elements of a Code of Conduct for Data Integrity* (PDA, 2015).
7. S. Schniepp, "Assessing and Improving Quality Culture: Tool & Resources," presentation at 3rd PDA Europe Annual Meeting, 27 June 2018. **PTE**

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.

Ad Index

The Link Between Data Integrity and Quality Culture

Susan Schniepp, executive vice-president of Post-Approval Pharma and Distinguished fellow, Regulatory Compliance Associates, takes a look at the regulations around data integrity and how they relate to the concept of quality culture.

Q. I have been hearing that regulatory authorities are beginning to audit companies regarding their 'quality' culture with relationship to data integrity issues. Can you give me a little background on this issue?

A. The regulatory authorities have always been interested in the culture of an organization. Recently, however, the specific culture of an organization is being connected to the veracity and accuracy of the data generated to support the quality of manufactured products. The theory is the more mature an organization is the more reliable the product support data are. To understand this concept thoroughly, we should start with a brief review of the US Food and Drug Administration's (FDA's) quality metrics initiative.

When FDA posted the first draft guidance, *Request for Quality Metrics*, the metrics chosen were lot acceptance rate, product quality complaint rate, invalidated out-of-specification (OOS) rate, and annual product review or product quality review on time rate. The guidance also contained three optional metrics intended to measure quality culture: measuring senior management engagement, corrective actions and preventive actions (CAPA) effectiveness, and process capability/performance. Although the optional metrics intended to measure quality culture were removed from the current version of the guideline, it is the first indication that regulators felt there was a correlation between culture and data integrity.

At the same time the issue of quality metrics was being discussed, there was a resurgence of data integrity problems in the industry evidenced by the number of citations that reference this issue. Between 2005 and 2016, approximately 225 FDA warning letters were issued with observations for data integrity. These observations included repeat human error deviations, insufficient training, system failures, inappropriate qualification or configuration of systems, poor procedures or not following procedures, and intentional acts of falsification. The increase in data integrity observations prompted regulatory authorities to address the issue by releasing a series of guidelines that reemphasize the importance of data integrity. FDA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, the World Health Organization (WHO), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) have all released documents to reeducate the industry on data integrity concepts and expectations (1–5). In addition to the regulatory guidelines, the Parenteral Drug Association (PDA) released a free document titled *Elements of a Code of Conduct for Data Integrity* to help address the problem (6).

One common theme permeating through these documents is that of quality culture. Regulators have linked the reliability of data to the existence of a quality culture as exemplified by statements taken directly from the guidances. The PIC/S guidance on *Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments* (5) states, "Management should aim to create a work environment (i.e., quality culture) that is transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes. Organizational reporting structure should permit the information flow between personnel at all levels" (5).

The trouble with quality culture is determining how to measure it.

The MHRA guidance (2) titled *'GXP' Data Integrity Guidance and Definitions* discusses organizational culture, stating, "The organization needs to take responsibility for the systems used and the data they generate. The organizational culture should ensure data [are] complete, consistent, and accurate in all its forms (i.e., paper and electronic)" … "The impact of organizational culture, the behaviour driven by performance indicators, objectives, and senior management behaviour on the success of data governance measures should not be underestimated. The data governance policy (or equivalent) should be endorsed at the highest levels of the organization."

WHO deals with the concept of quality culture in their document *Guidance on Good Data and Record Management Practices* (4) by stating, "adoption of a quality culture within the company that encourages personnel to be transparent about failures so that management has an accurate understanding of risks and can then provide the necessary resources to achieve expectations and meet data quality

Contin. on page 49

SHIMADZU
Excellence in Science

50th ANNIVERSARY Shimadzu Europa

CHANGES **EVERYTHING**

Shimadzu's LCMS-8060 makes a real difference to working better and faster. The LCMS-triple-quadrupole combines all UF technologies and pushes the limits of LC-MS/MS quantitation for applications requiring highest sensitivity and robustness.

World's highest sensitivity
based on the new UF Qarray technology, delivering new limits of MRM sensitivity and impacting full-scan sensitivity

Unmatched speed
due to data acquisition with scan speed of 30,000 u/sec and polarity switching time of 5 msec

Outstanding durability
achieving peak area response RSD of 3.5 %*, thus showing high robustness

UFMS
ULTRA FAST MASS SPECTROMETRY

*2,400 samples of femtogram levels of alprazolam spiked into protein-precipitated human plasma extracts over a 6 day period (over 400 samples were injected each day).

www.shimadzu.eu/lcms-8060

COME & VISIT US AT
AAPS PHARMSCI 360
BOOTH 1727

Catalent®

better treatments by design.™

EARLY PHASE DOSE DESIGN OPTIMIZATION | OVERCOMING COMPLIANCE CHALLENGES IN PATIENTS | IMPROVED PATIENT ACCEPTANCE & ADHERENCE | BETTER OUTCOMES FOR PATIENTS & INNOVATORS

To be successful, new treatments require superior real world outcomes. Through our proprietary Better Treatments by Design™ process, Catalent works with you to determine and address innovator, prescriber, and patient needs at the right point in the development process. With our experience developing thousands of molecules and commercializing hundreds of products, combined with access to the broadest suite of delivery technologies, we can develop the right dose form for your treatment. Contact us today and give your candidate its best chance of success from clinical development to commercial supply.

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™
US + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 catalent.com