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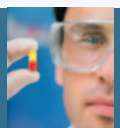

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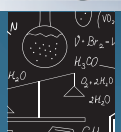

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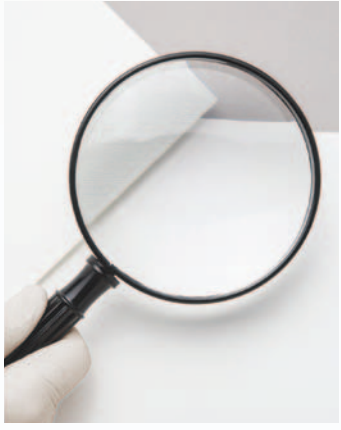

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AAPS Traces the Path to ICH M10

Binodh DeSilva

Efforts strive to harmonize bioanalytical method validation for non-clinical and clinical studies.

The importance of pharmacokinetics characterization in evaluating the safety and efficacy of drugs has given rise to a need for guidance in ensuring the accuracy and reproducibility of the underlying bioanalytical data.

For more than 25 years, bioanalytical scientists and practitioners have actively participated in defining bioanalysis procedures and standards—most notably through the joint American Association of Pharmaceutical Scientists (AAPS)/FDA 'Crystal City' workshops.

During this time, various guidelines were issued on bioanalytical method validation (BMV) by FDA; the European Medicines Agency; Japanese Ministry of Health, Labour, and Welfare; Brazil's Agencia Nacional de Vigilancia Sanitaria; and the China Food and Drug Administration. Although all regulatory guidance/guideline documents are similar in their requirement for producing accurate and reproducible standards, having multiple guidelines has resulted in variations in the substance or the interpretation of the standards, which in turn has bred ambiguity and perceived disharmony. As a result, when drug manufacturers submit their applications for drug approval globally, they struggle to address these differences in their bioanalytical application, causing delays in approval.

The opportunity for the International Council for Harmonization (ICH) to take up this issue emerged in 2016. In the absence of a harmonized guideline for BMV, members of AAPS, the European Bioanalysis Forum (EBF), and the Japan Bioanalysis Forum (JBF) formed a three-region team in March 2016 and drafted a proposal for bioanalytical harmonization, which they then submitted to the European Federation of Pharmaceutical Industries and Associations (EFPIA) to be submitted to the ICH assembly in June 2016. A proposal was also raised and endorsed by the ICH assembly. Subsequently, an Informal Working Group was formed to draft a business plan (1) and a concept paper (2). Following the finalization of these two documents, the ICH Assembly endorsed BMV as a multidisciplinary new topic for harmonization (ICH M10) in October 2016.

With the initiation of the multi-step ICH process, the three-region team proactively sought ways to understand the process; determine how each region/group would be represented in the Expert Working Group (EWG); and identify next steps. The team recognized the importance of bringing industry together to provide current perspectives to the EWG, rather than waiting until after the draft ICH document is released for comment. This was particularly important for companies that supported regulated studies but did not have representation in ICH.

The team facilitated open workshops with AAPS in the United States and Europe in September 2017 that attracted a global audience. Sessions were built around areas of expected consensus as well as current concerns that required harmonization. The US workshop focused on strategic discussion, and the EU workshop focused on sharing and discussing survey data on current industry practices/experience. With these sister workshops and sustained collaboration between AAPS, EBF, and JBF, we can continue to contribute to the objectives of the ICH harmonization process, which is to improve efficiency of the drug development process without compromising safety and efficacy evaluations.

Editor's Note: This article is excerpted from a May 2018 *AAPS Newsmagazine* article. The following individuals contributed to this report: F. Vazvaei, Roche Innovation Center New York; L. Amaravadi, Shire Plc; L. King, Pfizer Inc.; P. Timmerman, European Bioanalysis Forum; Y. Ohtsu, Astellas Pharma Inc.; and E. Fluhler, Glenmark Pharmaceuticals.

References

1. ICH, Final Endorsed Business Plan, M10: Bioanalytical Method Validation, Oct. 7, 2016, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M10/ICH_M10_Bussiness_plan_final_7Oct2016.pdf.
2. ICH, Final Endorsed Concept Paper, M10: Bioanalytical Method Validation, Oct. 7, 2016, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M10/ICH_M10_Concept_paper_final_7Oct2016.pdf **PT**

Binodh DeSilva, PhD, is AAPS past-president.

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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.

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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, FDA, or industrial standards.

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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.

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FDA Clarifies Worldwide Inspection Policies

Jill Wechsler

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

In the name of enhancing transparency in agency decisions and compliance actions, 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 Sept. 5, 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 program 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.

FDA is expanding its capacity for monitoring foreign manufacturers through expanded collaboration with European and other capable regulators.

Focus on risk

One response from FDA is to emphasize how its pharmaceutical inspection program 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 program 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). The aim is to avoid

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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, Sept. 5, 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm619435.htm.
2. FDA, FDA Updates on Valsartan Recalls, FDA.gov, www.fda.gov/drugs/drugsafety/ucm613916.htmValsartan.
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, Sept. 13, 2018, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620499.htm
4. FDA, *MAPP 5014.1 Understanding CDER's Risk-Based Site Selection Model* (CDER, OPQ, Sept. 26, 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. **PT**

New Dose Forms Focus on the Patient

Jennifer Markarian

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

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 FDA in 2016. The product is being commercialized by Titan in the United States 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 condi-

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tions 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 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 molding 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 molding creates tight dimensional tolerances (controlled within a few microns) and good surface finishes, says Arps. "In addition to complex shapes, such as stents, injection molding can be beneficial for simple shapes, such as rods, especially if the material is brittle and difficult to

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 programs with various partners. Of the 60 programs 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 $2 billion in grants to combat malaria and more than $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, Nov. 16, 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, Dec. 29, 2016.
4. Gates Foundation, "Malaria: Strategy Overview," www.gatesfoundation.org/What-We-Do/Global-Health/Malaria, accessed Aug. 27, 2018.

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cut. A drawback for rods is that molding 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 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.

Once technical and regulatory issues are addressed, 3DP could enable the development of more personalized therapies.

3DP

While extrusion and injection molding 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 com-

Producing Monofilaments for 3DP

One method of three-dimensional printing (3DP), called fused filament fabrication or fused deposition modeling (FDM), uses a continuous filament of thermoplastic polymer, which is heated to its melting point and then layered to form the final shape. Foster Delivery Science produces monofilaments of custom formulations for use in 3DP for pharma applications. The API and excipient are mixed in a twin-screw extruder, and then drawn into a monofilament, which is wound on a spool. Implementing methods to control tension are key to producing a tight tolerance product, and feedback control systems can be used to control dimensions by automatically adjust process parameters, explains Tony Listro, vice-president of Technical Business Development at Foster Delivery Science.

Leistritz, which manufactures twin-screw extrusion systems for pharmaceutical and polymer applications, installed a filament production system in its process laboratory that can be used to develop new filaments and formulations. According to the company, formulations can be modified "on the fly" for rapid sampling of filaments with different formulation percentages, and a sample can be produced every 10 minutes (1).

Reference

1. Leistritz, "Leistritz Extrusion Expands NJ laboratory: Installs ZSE-3D Filament System Installed for Pharmaceutical, Nutraceutical, and Medical Device Development," Press Release, Aug. 27, 2018.

mercialize 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). **PT**

For more on 3DP

Visit PharmTech.com to read the following:

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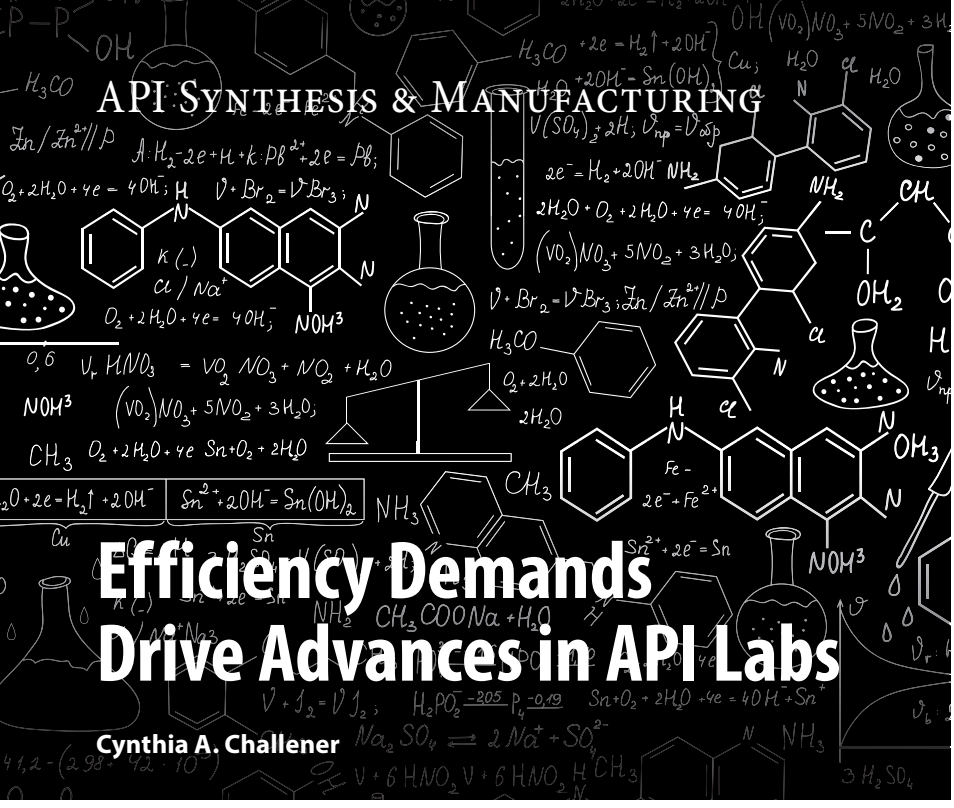

Efficiency Demands Drive Advances in API Labs

Cynthia A. Challener

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

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 modeling 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

Not only advances in equipment technology, but 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.

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

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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 modeling for greater control

The software packages used at Hovione mainly help with modeling. 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 modeling the scale up of processes when moving from the lab to large-scale production.

The algorithms used in modeling 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." **PT**

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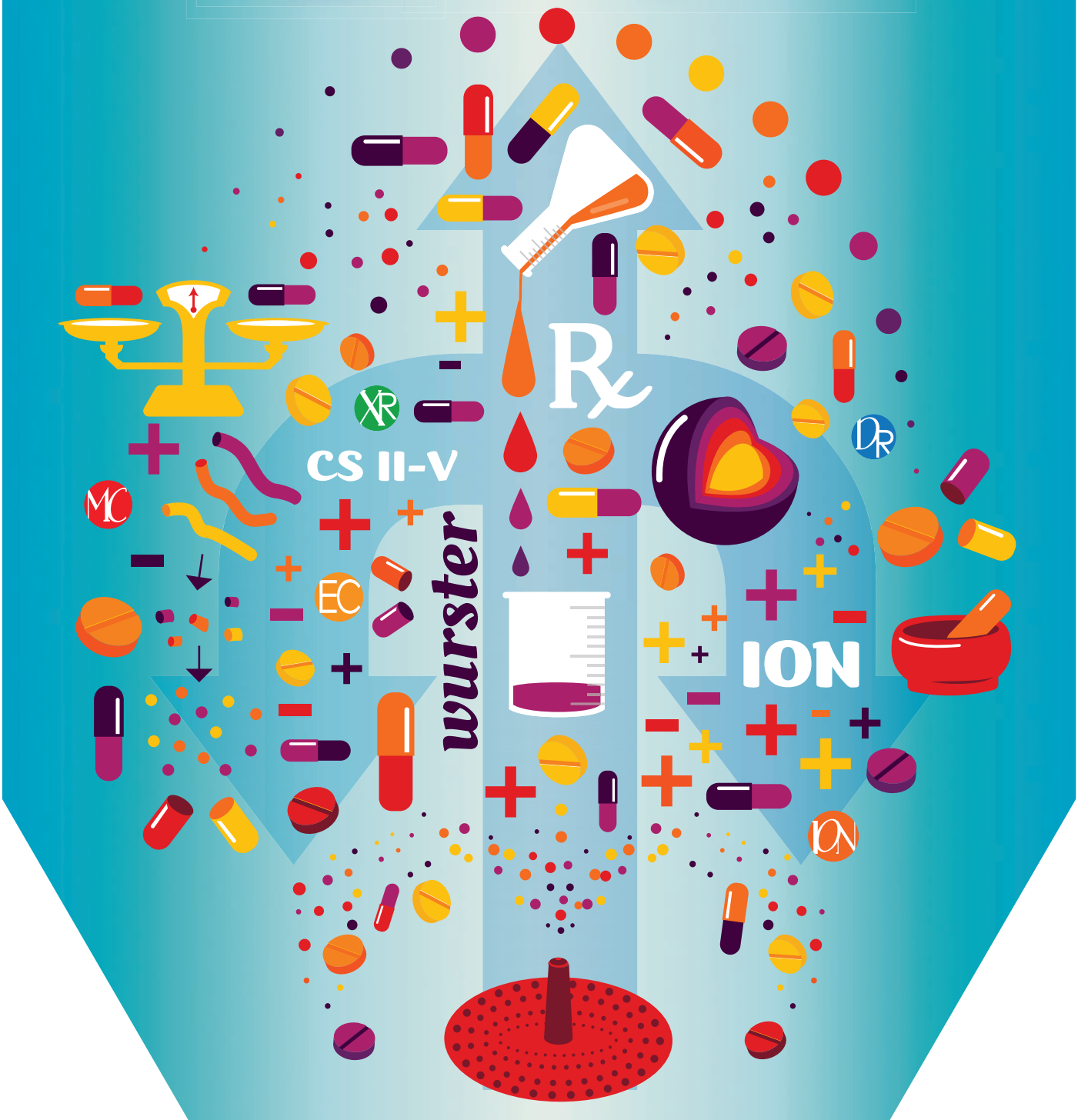

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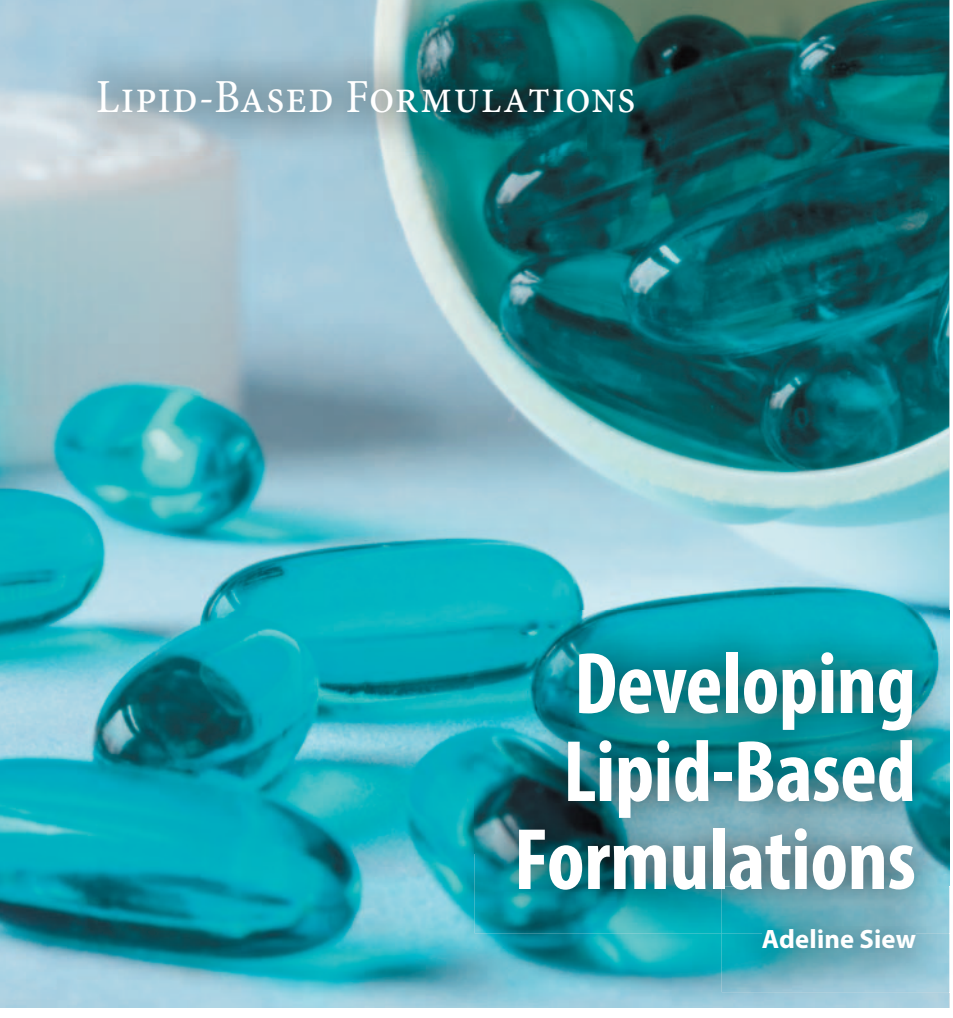

Developing Lipid-Based Formulations

Adeline Siew

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

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 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

PharmTech: 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*.

"[A] key consideration in oral formulation design is the safety and regulatory status of proposed lipid excipients."
—Sukuru and Plassat, Catalent

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 excipi-

Adeline Siew was previously editor for *Pharmaceutical Technology*.

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ents 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.

"It is necessary to conduct stress studies to challenge the robustness of the formulation."

—Sukuru and Plassat, Catalent

Stability assurance

PharmTech: 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.

PharmTech: 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.

Hard Capsules—a Flexible Dosage Form

Oral solid-dosage products offer ease of swallowing, ease of handling, consumer compliance, and attractive color 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,* June 9, 2018.

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

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

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 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

PharmTech: 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. **PT**

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.

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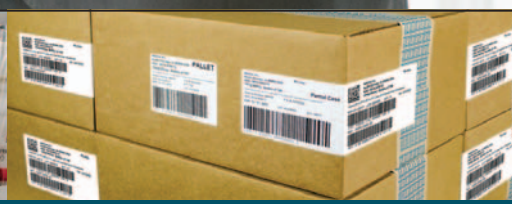

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Figure 1: Illustration of the difference in calculation between internal release limits (IRLs) and control charts.

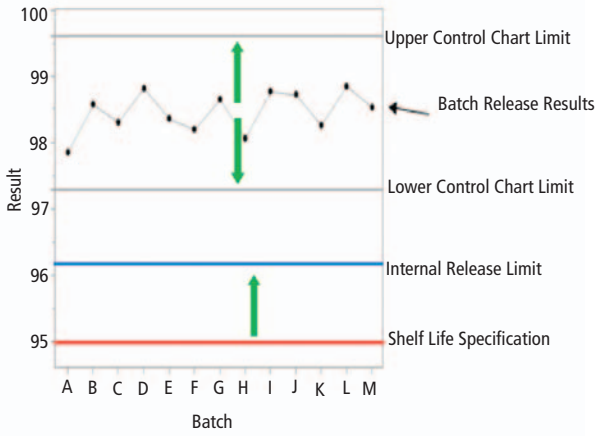
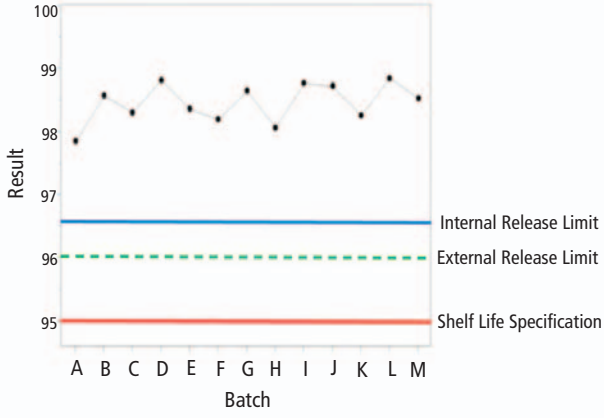


Figure 2: Illustration of an internal release limit that is more restrictive than the external release limit.



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.

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.

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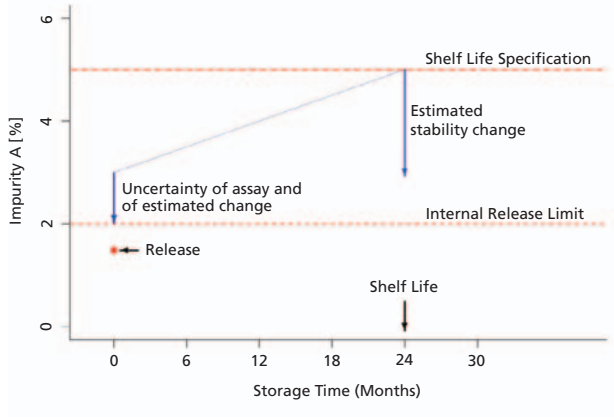
Figure 3: Illustration of the method for calculating an upper internal release limit from an upper shelf life limit (4). The illustration is based on an impurity that increases during stability.



It may be necessary to reevaluate the frequency of occurrence as more data become available.

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:

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

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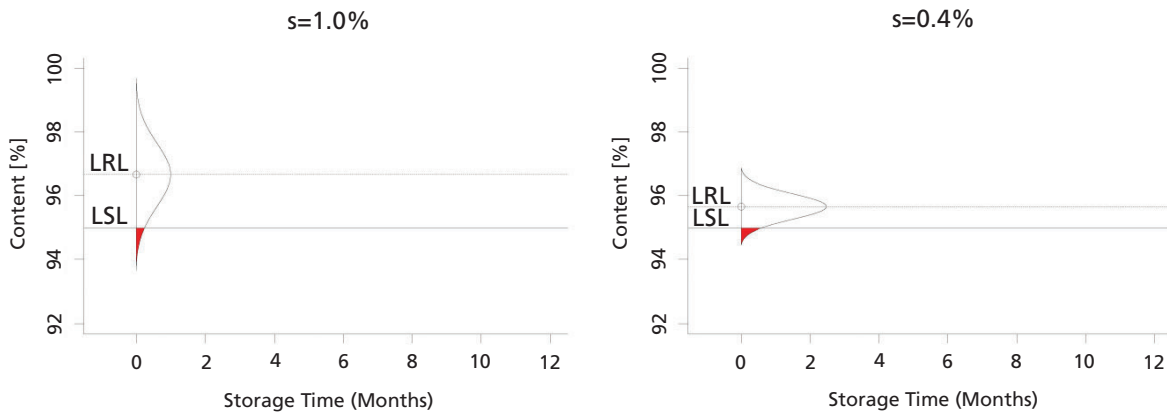
Figure 4: Illustration of the lower internal release limit (LRL) for a quality attribute that does not change on stability with large analytical variation (left) and smaller analytical variation (right). The risk, that a batch with release result exactly at the LRL does not comply with the shelf life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



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 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

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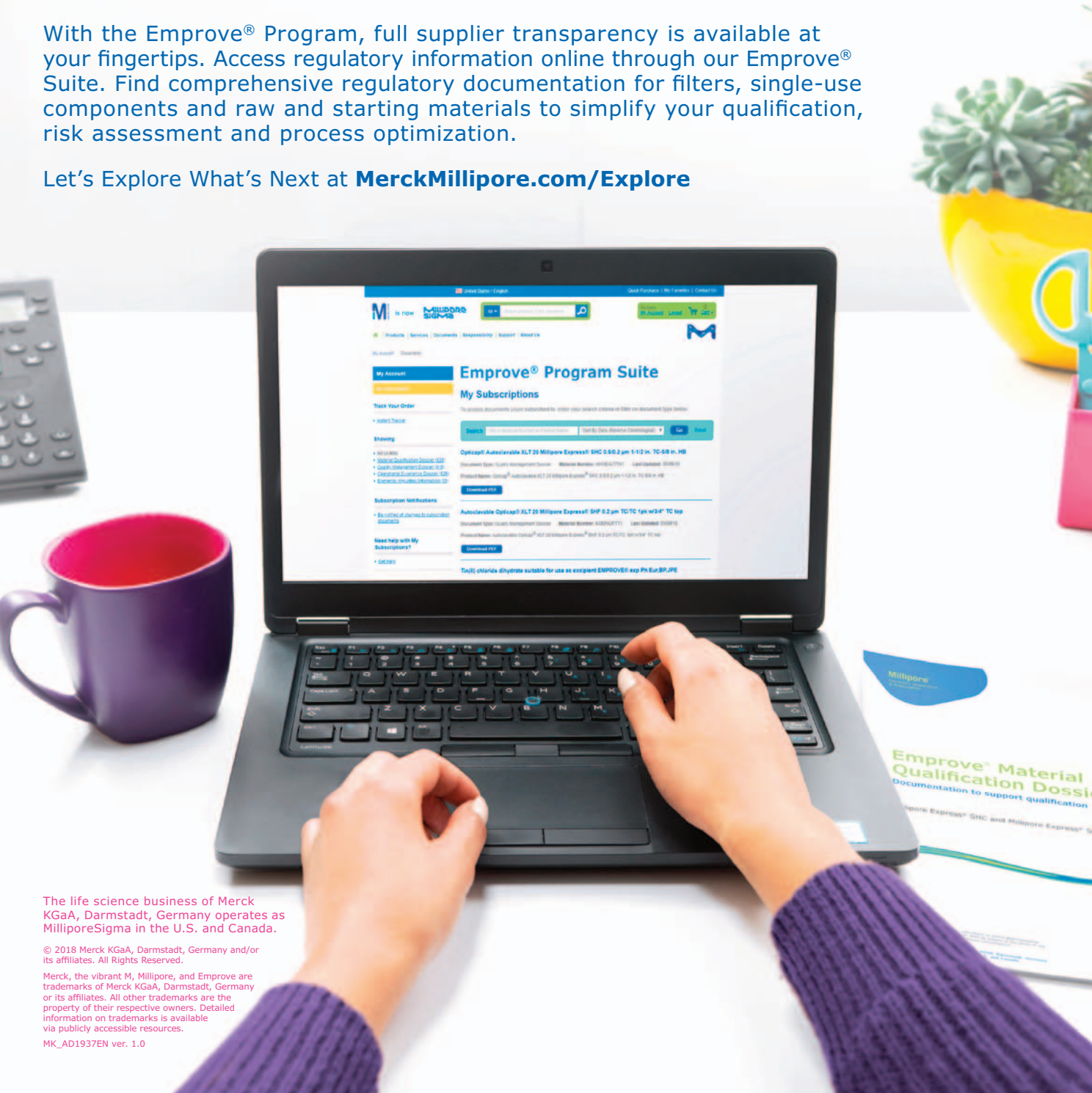

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according to the International Council for Harmonization [ICH] Q1E and there is a scientific basis for the difference). This can be the case for liquid formulations of biological products, where, for instance, the formation rate of high molecular weight proteins may depend on formulation constituents 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 behavior.

Inclusion of batch differences complicates calculations

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 modeling.

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**.

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

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 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

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 modeling provides a comprehensive framework for assessing a producer's and a consumer's risk. It also per-

mits 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.

Deeper product knowledge

In summary, a more systematic quantitative risk assessment carried out throughout the product lifecycle will lead to deeper product knowledge. This approach will collectively strengthen the two enablers of pharmaceutical quality systems: 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*, (ICH, March 1999).
3. ICH, *Q1E Evaluation of Stability Data,* (ICH, March 2003).
4. P. Allen, G. Dukes, M. Gerger, "Determination of Release Limits: A General Methodology," *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*, (ICH, June 2009).
8. FDA, *ICH Q9 Quality Risk Management,* (CDER and CBER, June 2006).
9. ICH, *Q10 Pharmaceutical Quality Systems*, (ICH, July 2008).
10. FDA, *Process Validation: General Principles and Practices, Guidance for Industry*, (CDER and CBER, January 2011). **PT**

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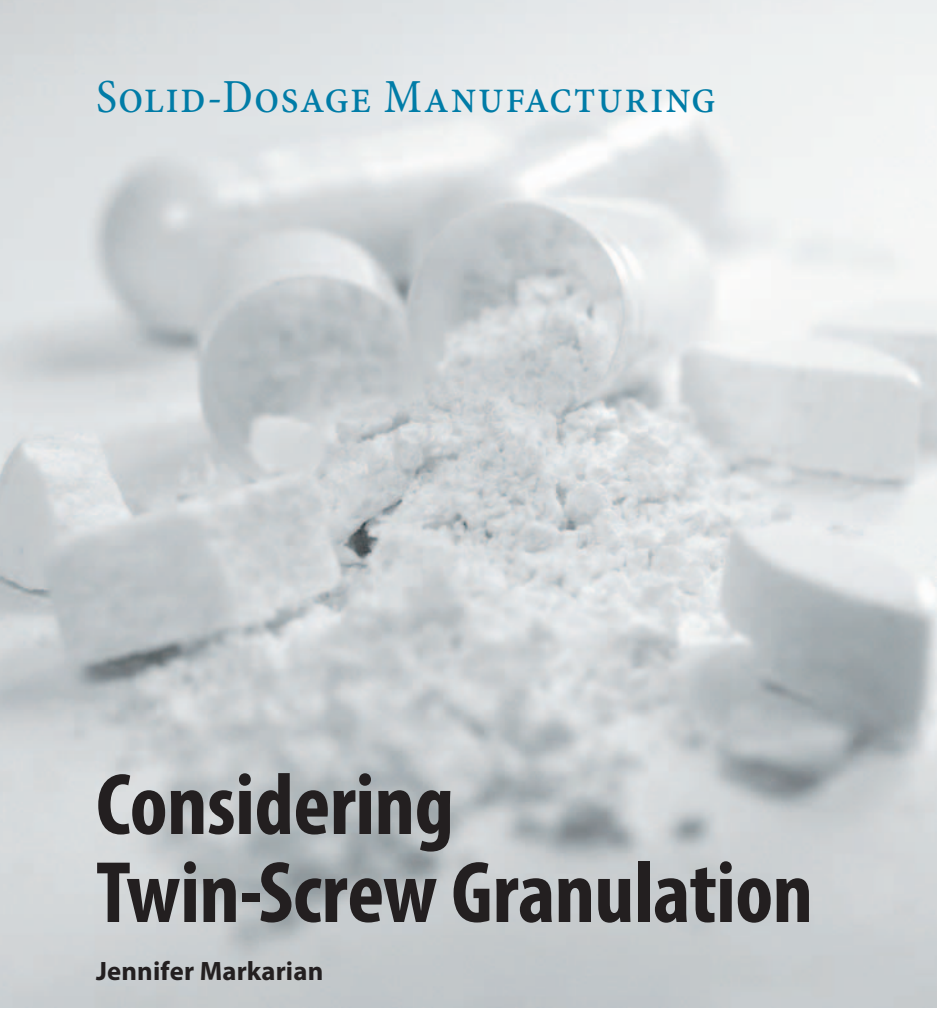

Considering Twin-Screw Granulation

Jennifer Markarian

A twin-screw extruder can be used as a continuous wet granulator.

Twin-screw extruders, which have found commercial use in making amorphous solid-dispersions for improving drug solubility and in loading drugs into polymers that can be shaped into drug-delivery devices, are also emerging as equipment for continuous wet granulation. The same machine can be used for wet granulation as for hot-melt extrusion, but the hot-melt extrusion process requires external barrel heating to raise the temperature above the melting point (T_m) or glass transition temperature (T_g) of the polymeric excipient, while granulation takes place at lower temperatures, below the excipients' T_m or T_g.

Twin-screw granulation

The ongoing development and commercialization of continuous manufacturing for oral solid-dosage (OSD) pharmaceuticals is creating a growing opportunity for continuous granulation processes, and twin-screw granulation (TSG) is already being used in commercial continuous manufacturing. Some continuous systems, such as GEA's ConsiGma and Glatt's MODCON, for example, use TSG. Twin-screw extruders are available in models designed for pharma processing from manufacturers including Coperion, CW Brabender, Leistritz, Steer, Thermo Fisher Scientific, and others.

The primary benefit of TSG is that the extruders are intended for continuous manufacturing, notes Dirk Leister, technical marketing manager, process and pharma extruders for Thermo Fisher Scientific. "Extruders are time-based production—the same equipment can be used for different amounts of material. One can potentially use the same extruder for R&D as for production, by simply running longer. Or, the process can be scaled up to a larger extruder for higher throughput." Thermo Fisher's Pharma 11 (11-mm diameter) and Pharma 16 (16-mm diameter) twin-screw extruders are designed for both R&D and production. These extruders can be set up for both granulation and hot-melt extrusion, using conversion kits for the necessary hardware modification. Thermo Fisher recently introduced the Thermo Scientific Pharma 24 TSG, a 24-mm diameter twin-screw extruder dedicated for twin-screw granulation with a throughput rate of up to 70 kg/h. The extruder can be either integrated into a continuous production line or used as a standalone instrument for project development or small-scale production using either wet or dry granulation (1). The extruder has a 40:1 ratio of length to diameter that offers flexible adaptation for processing length, screw setup, and introduction of ingredients into the process. Minimal downtime is needed for cleaning, and online monitoring facilitates detection and segregation of out-of-specification product.

In addition to flexibility of scale, continuous processes offer the potential for improved process control compared to batch processes and for on-line, real-time monitoring. The twin-screw extruder is considered a small-volume continuous mixer, and it creates a more uniform mixing history for more homogeneous distribution of drug, excipient, and binder (2).

"Consistency is a big advantage," notes Michael Thompson, professor in the department of Chemical Engineering at McMaster University in Ontario, Canada. "TSG can reduce lot-to-lot variation of the granulated product and reduces reliance on a specific seasoned operator in order to get the correct product quality by knowing when to stop the batch mixer." TSG may need less binder or less water to produce equivalent granules to batch systems, which could reduce production cost.

How the primary variables in the TSG process affect product properties is relatively well understood at this point, although each formulation would need to be optimized. "Just about any formulation based on known pharmaceutical ingredients can be made into granules so long as the formulator has a working

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knowledge of the different techniques to 'wet out' the powders," says Thompson. "I would always recommend to a company to study the binder-to-powder needs in each new formulation as if starting from scratch, but the initial machine setup and operating conditions can be treated as relatively generic." Scaling up from a small laboratory machine to larger production equipment poses more challenges, however. "One can't truly know a process until it has run for several hours, with the machine heated up by mechanical rotation and the feeders having gone through several fill cycles to fully learn the bulk density of the process's ingredients," cautions Thompson. "A product made from a 20-minute lab trial doesn't necessarily translate to a continuously operated production process."

PAT

Process analytical technology (PAT) is a crucial part of understanding and controlling a continuous process, and in-line measurements are used in advanced process control strategies and in quality-by-design studies. Innopharma Technology's Eyecon2, for example, is a direct optical imaging system that captures images of the granule particles and analyzes them in real-time. "In continuous processing, the particle analyzer can be used to monitor particle size after a twin-screw, a continuous drier, or a mill," says Chris O'Callaghan, senior product manager at Innopharma.

In a continuous system, data are needed for both feed-forward and feed-back control to maintain key parameters and attributes as close to an ideal setpoint as possible, despite some variation in the inputs and outputs of each process stage. "While feed-back control is critical in ensuring that deviations do not continue to grow unchecked, feed-forward control can enable compensation of upstream variations in subsequent processing steps to ensure that variations introduced in early stages can be partially or fully corrected in the final output material," explains O'Callaghan.

"By measuring particles after granulation, deviations in the measured size can be used to alter parameters of the twin-screw (e.g., liquid addition and screw speed) to correct for the variation in particle size, while the speed of a downstream milling step may be temporarily increased or decreased to more finely or coarsely mill the granulate currently entering, thereby maintaining a more consistent output particle size."

More work is needed to further develop different types of PAT for TSG, says Thompson. In the McMaster University laboratory, researchers are looking at ultrasonic acoustic sensors to see what information about properties exiting the twin-screw granulator, such as granule size and moisture content, can be measured. Eventually, the researchers hope to also identify technology that can monitor incoming powders, which can also have a significant effect on end properties. For example, the size of a binder particle is known to affect granule size in hot-melt granulation, but a supplier of binder material might not measure or report binder particle size or changes in grinding because they wouldn't affect chemical properties, notes Thompson. It would be difficult to track a problem with off-spec granules back to the feed materials, and a formulator might mistakenly assume something inside the extruder had gone wrong.

Sensors that are already built into extruders can also be used as PAT signals. The torque of the extruder drive motor, for example, should stay constant during steady-state processing, and can be used in process control, notes Leister.

Handling poorly flowing material

TSG has been found to be a useful unit operation for high drug load formulations that inherently have poor flow properties. These formulations would not be suitable for traditional dry granulation, explained Steve Pafiakis, senior research scientist at Bristol-Myers Squibb, in a presentation at the Leistritz Pharmaceutical-Nutraceutical Extrusion Seminar (3). Pafiakis is researching TSG for his doctoral thesis at the New Jersey Institute of Technology in close collaboration with the Polymer Processing Institute (PPI). For the formulations Pafiakis is studying, challenges include high drug loading, low bulk density, and cohesive blends that result in extremely poor flowing input material. These material properties have been shown to affect the manufacturability of the TSG process by causing build-up inside the extruder. To mitigate these effects, several screw configurations were evaluated to investigate whether the formulation could be successfully processed over an extended period of time, which is a requirement for any continuous manufacturing process. An initial screw design imposed high shear and lead to barrel fouling, but a less shear-intensive screw configuration, along with barrel cooling near the kneading zones was found to be acceptable. Pafiakis explained that understanding the fundamental mechanism for TSG—that frictional energy dissipation (FED) is the driver for granule growth in the extruder and the heat generated is from the relentless rubbing of particles in the compacted state in the kneading section—was important. This set-up controlled the heat generated by FED and led to the desired granule attributes.

Learning from other industries

The food and polymer industries successfully transitioned from batch to continuous processing using twin-screw extruders 50 years ago, and use of TSG is expected to continue to evolve in the pharma industry, say experts (2).

References

1. Thermo Scientific, "New Twin-screw Granulator Helps Maximize Throughput in Continuous Drug Manufacturing," Press Release, June 25, 2018.
2. N. Kittikunakorn, et al., "Processes, Challenges, and the Future of Twin-Screw Granulation for Manufacturing Oral Tablets and Capsules," *AAPS News Magazine*, March 2018.
3. S. Pafiakis, "Twin Screw Granulation: A Case Study for Enabling an Adaptive Study Plan," presentation at the Leistritz Pharmaceutical-Nutraceutical Extrusion Seminar (Clinton, NJ, 2018). **PT**

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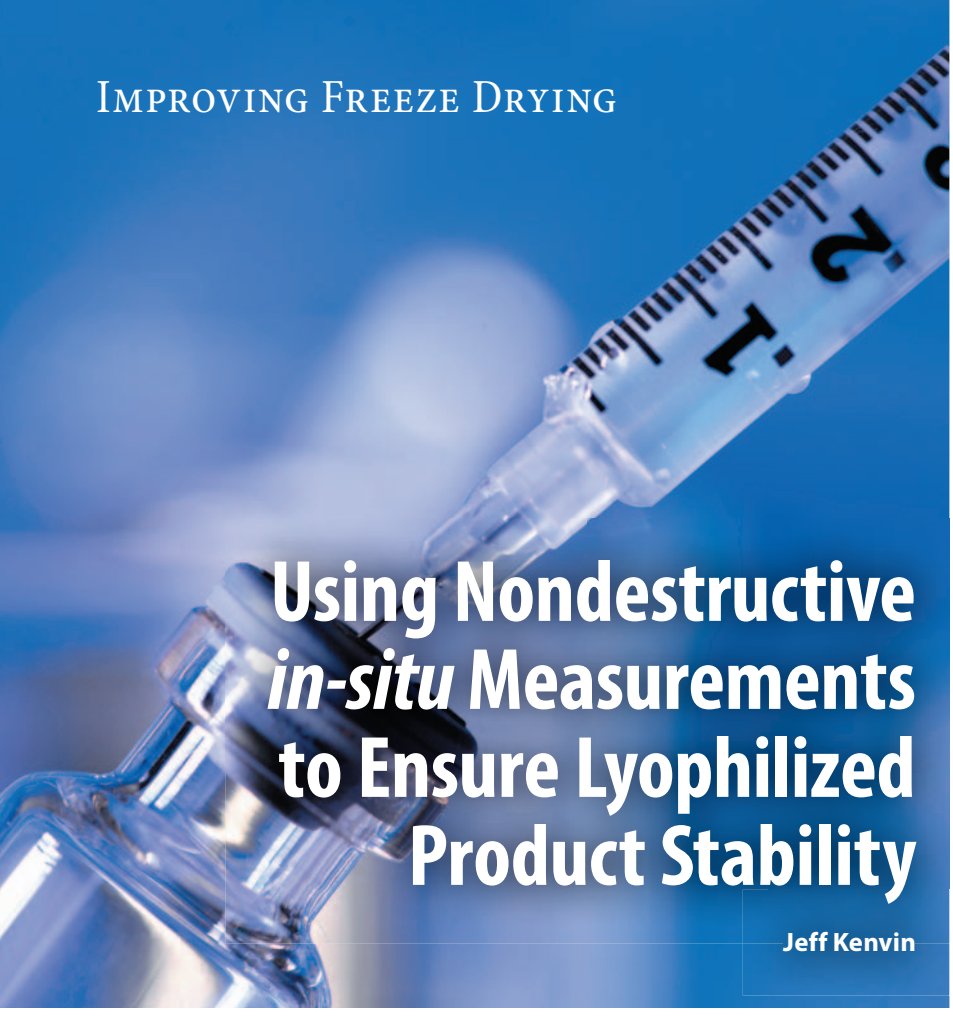

Using Nondestructive *in-situ* Measurements to Ensure Lyophilized Product Stability

Jeff Kenvin

Non-destructive surface area measurement can improve stability testing.

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 behavior 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

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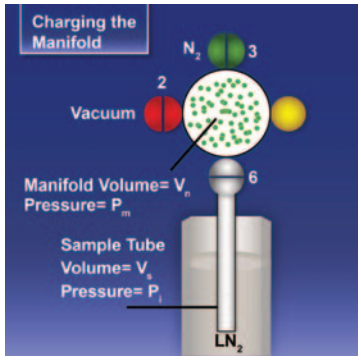
Figure 1: Gas adsorption apparatus for determining the surface area of lyophilized cakes. Charging of the manifold occurs on the left, and sample dosing and pressure equilibration on the right.



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 (LN_2). 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.

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ALL FIGURES COURTESY OF THE AUTHOR

Lot Release Testing Analytics for Small-Molecule Drugs

Amber Lowry

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

Successful lot release testing for small-molecule drugs is dependent on efficient analytical tools and practices. This article 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

PharmTech: 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 color 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 pharmacopeias. 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 appli-

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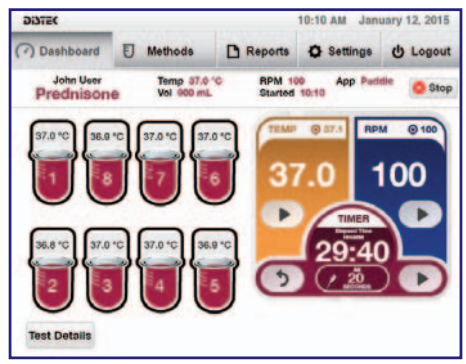

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cable), and particulate matter (for injectable products).

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 infrared 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

PharmTech: 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.

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

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.

All results generated in the laboratory have a thorough QC data review. Our quality assurance 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

PharmTech: 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, IL 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

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

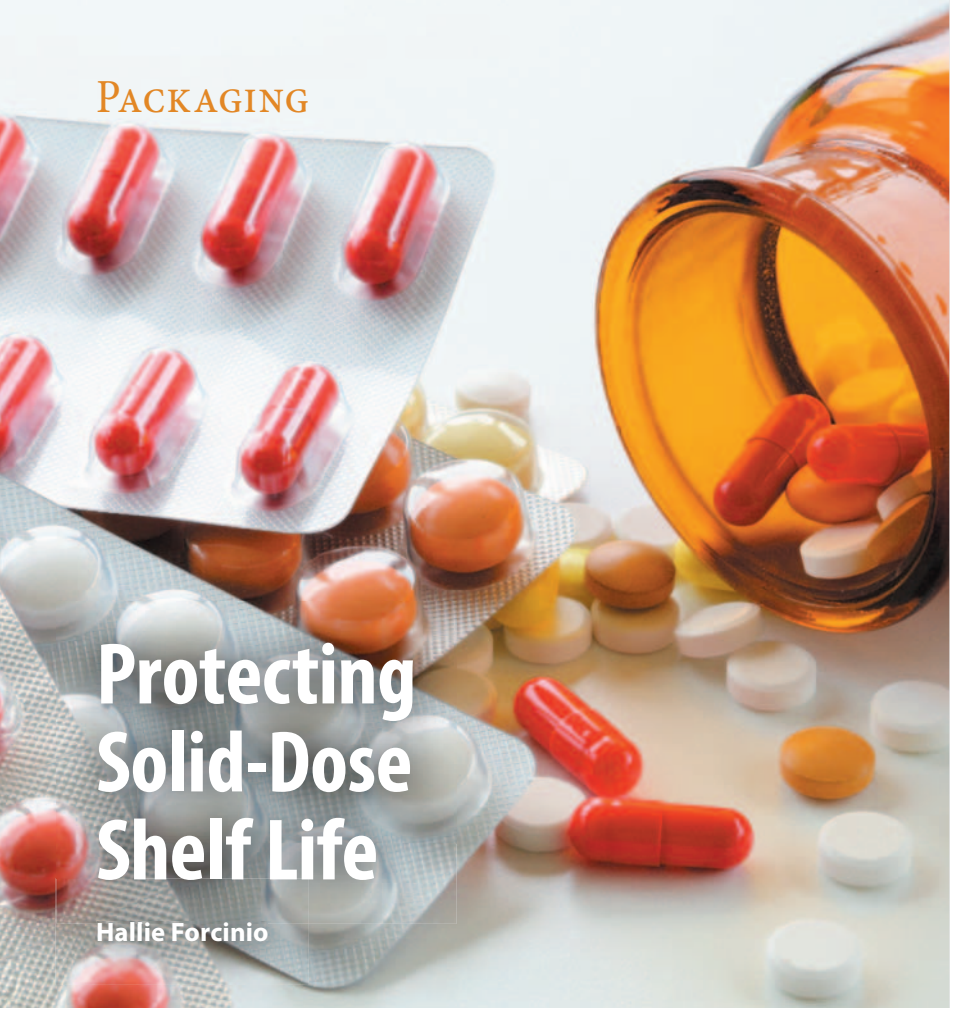
Shapiro and Bowles (Cambrex): The pharmaceutical industry is highly regulated, and so as analysts we must adhere to these regulations by using appropriate, qualified, and verified or validated methods to ensure product and patient safety at all times. At Cambrex, we have clear and effective standard 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 facility in Lincolnshire, 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. **PT**



Protecting Solid-Dose Shelf Life

Hallie Forcinio

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

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 vapor. 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 vapor 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

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

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into whether … 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 favorably 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 odor adsorption. The other holds a mixture of silica gel and activated carbon for both odor 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. 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. 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."

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 vapor, 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.

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.

contin. on page 57

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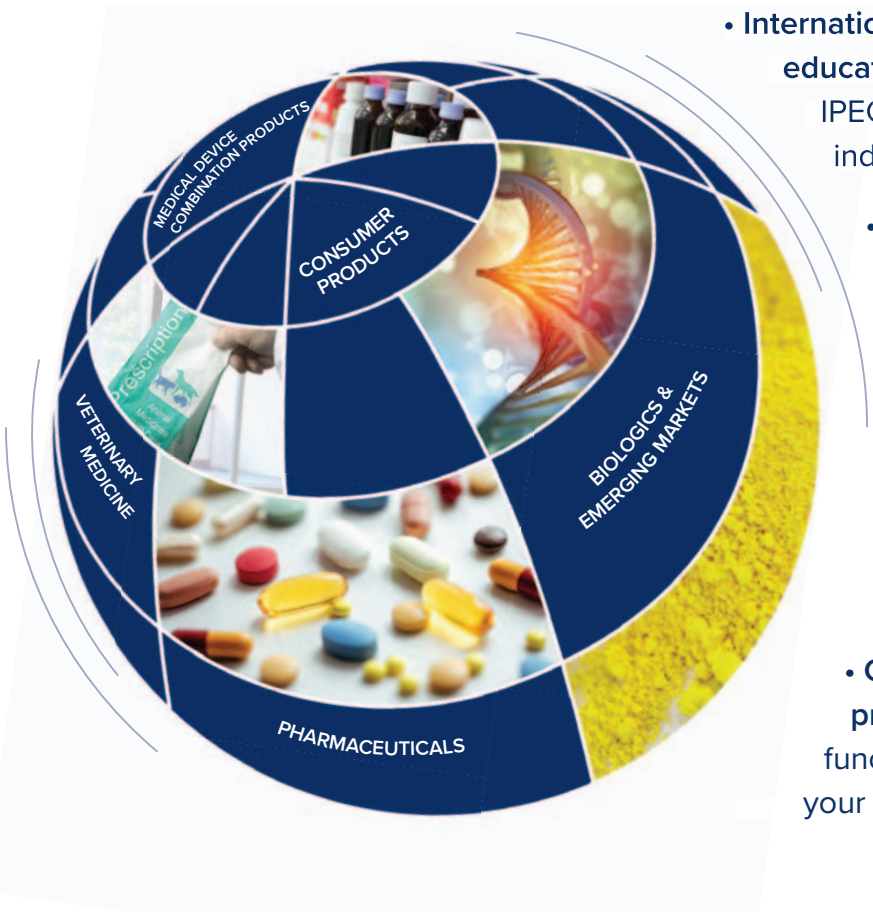

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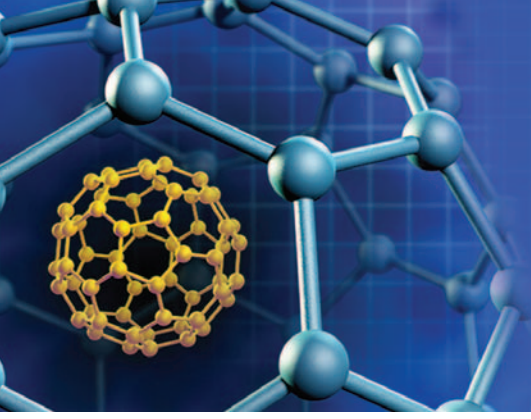

Insoluble APIs Scaring You? Don't be Afraid of Nanoparticles!

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Nanotechnology, the manipulation of materials at the nanometer length scale, sounds like daunting sci-fi, but in practice provides the pharmaceutical product developer with a host of options to protect a labile drug molecule, improve the bioavailability of a drug, target a drug to specific tissues or cells, or simply offer a reformulation option to manage the lifecycle of an existing product. This webcast will explore the most common nanotechnologies practices for pharmaceutical formulation development, the pros and cons of each approach, which types of molecules can incorporated and how, specific manufacturing equipment, characterization, and regulatory considerations.

KEY LEARNING OBJECTIVES

During the webcast, formulation expert Andrew Loxley, will discuss the implementation of nanotechnology in the development of a complex drug product for poorly soluble molecules and large molecules such as proteins, peptides, and nucleic acids. Topics will include:

- Nanoparticles in drug delivery—specific advantages and routes of administration
- Physical properties of nanoparticle systems
- Regulatory aspects of nanoparticle systems
- Equipment and processes for making different types of nanoparticles, and the pros and cons
- Incorporating the active pharmaceutical ingredient in nanoparticles
- Sterile nanoparticulate products
- Characterization tools
- Case studies on a topical organic molecule sun-block and novel vaginal HIV-vaccine

WHO SHOULD ATTEND

- Formulators, researchers, scientists, biotechnology experts, and product development managers from:
  - Branded and generic drug pharmaceutical companies
  - Biotechnology companies
  - Academia

contin. from page 54

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."

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. **PT**

A Q&A

Providing End-to-End Service to Enhance Client Satisfaction with Manufacturing Innovation

David King
Aseptic Filling Team Leader
Samsung BioLogics

An experienced team and a facility built for expansion has made Samsung BioLogics a leader in the CDMO market.

The pharmaceutical product pipeline is increasingly complex and requires specialized facilities, equipment, and operational expertise. Thus, pharmaceutical and biopharmaceutical innovators are leveraging the experience of contract manufacturing organizations. *Pharmaceutical Technology* recently spoke with David King, aseptic filling team leader at Samsung BioLogics, about the company's end-to-end service, focusing particularly on drug product manufacturing.

Pharmaceutical Technology: Please describe Samsung BioLogics.

King: Samsung BioLogics was established in April 2011 and is headquartered in Incheon, South Korea. We provide a one-stop service for contracted biopharmaceutical production: cell line development, process development, toxicology and clinical material, and commercial manufacturing of both drug substance and drug product. The facility is over seven years old and has achieved some remarkable achievements within a short time period. First, the construction of three plants having a total bioreactor capacity of 362,000 liters and this capacity has made Samsung Biologics the largest CDMO service provider in the world. Second, the facility has a track record for successful global regulatory approvals. To date, there have been 18 global approvals in Plant 1 and 2 including 4 global approvals for drug product. This all has been completed without critical observations.

Pharmaceutical Technology: How did Samsung BioLogics build a strong quality system in such a short time?

King: The success of our quality management system is based on several factors. First are the employees. A majority of employees have a science-related degree. This includes the recently graduated Korean nationals who have successfully passed an entrance exam into the company. In addition, about 5% of the staff are global employees with years of in-depth experience in the regulated pharmaceutical industry. The second factor is design. Samsung BioLogics defines success as being the best CDMO in the global market. The quality management system has been designed with this goal at its core. Examples include the dedicated quality control group that monitors every step of the manufacturing process to ensure the highest quality. We also have a quality control group on the production floor that maintains a presence and a partnership with the operations group. The third factor is business culture. Samsung BioLogics has a high employee retention rate because the

employees value the company as a great place to work. The employees work hard to produce the highest quality products and complete client projects within tight timelines. This business culture is driven by dedicated support from upper management, including our CEO, where they acknowledge employees, teams and accomplishments through presentations, awards, and incentives. In the center of this business culture is a passion to produce quality products under a quality management system.

Pharmaceutical Technology: Please talk more about Samsung's drug product manufacturing. What do you believe are Samsung's strengths within it?

David King: Samsung BioLogics has drug product manufacturing in both Plants 1 and 2. Our aseptic filling lines include industry advances like non-destructive fill volume checks, automated loading and unloading to our freeze dryers, and in-line vial headspace analysis. Our facilities are designed to do traditional stationary tank formulation with filling transfers using a piston pump operation. Or, we can use single-use sterile disposable systems where the tank, through the filling needles, is disposable and pumping is conducted with Is this human-machine interference (HMI)-driven peristaltic pumps.

As far as Samsung's strength within drug product manufacturing, aseptic filling or drug product manufacturing is complex. To produce quality sterile products, numerous things have to come together. If just one of these items does not happen, then the batch comes into question and could be lost. This means that every employee working to make the product needs to do their job right the first time. This is truer than ever, as regulations like the recent EU GMP Annex 1 revision, have been tightened to ensure patient safety and product quality.

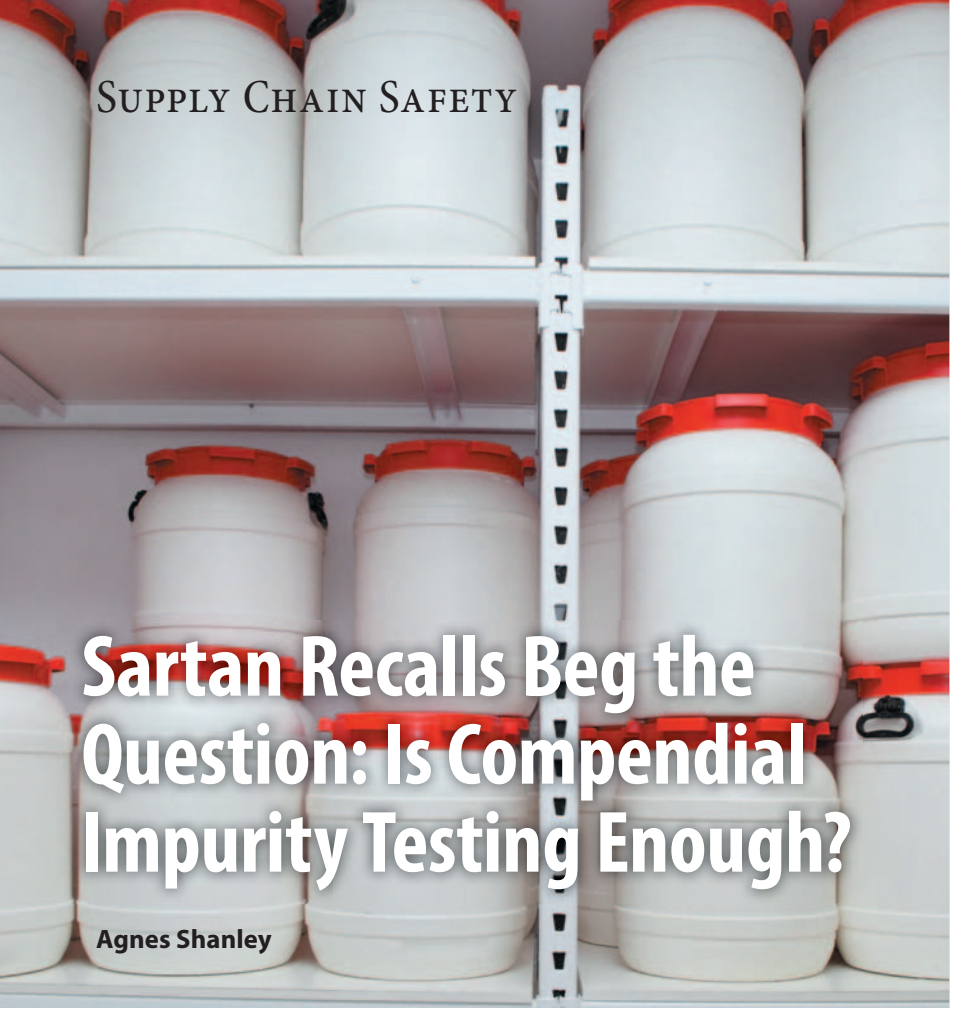
In this industry, the biggest danger to the products are the employees who make them. At Samsung BioLogics, we have skilled, knowledgeable labor on the production floor, and on the drug product team, the most of the senior employees have been with the company for seven years. That means they were making decisions when the clean rooms were designed, when the quality equipment was selected, and when the equipment and processes were validated. The same people who wrote and executed the validations are now transferring my clients' new products into the facility and running the production lines.

Pharmaceutical Technology: With so many specialized drug products companies, why should clients choose Samsung BioLogics as their manufacturing partner?

King: Many of our clients choose Samsung BioLogics because we can manufacture both drug substance and drug products at one site, which results in time and cost savings. When clients first tour the drug product operation, they see we have a state-of-the art facility. This may seem like something that should be common in the industry, but with advancements in technology and more stringent regulatory demands, the age of a facility can hinder the ability to meet or exceed a client's needs. When a new drug product client comes to Samsung BioLogics, they are partnered with a person from our project management team and a person from our manufacturing science and technology team. Regular meetings are established, timelines are monitored, and resource requirements are closely followed. But what really makes us different is the focus on trust and communication that we maintain from kick-off through commercialization. Samsung BioLogics management and employees know that client satisfaction is critical.

Pharmaceutical Technology: Where do you see Samsung BioLogics' drug product business in five years?

King: Samsung's drug product operation will experience growth and expansion. Our Drug Product operation facility in both plants 1 and 2 were designed with extra space, able to accommodate three or four production lines. Within five years, Samsung BioLogics drug product operation will continue to improve its quality management system. Changes will include limiting the human risks to product, and increasing real-time electronic and process controls through regulatory requirements of data integrity. Samsung BioLogics drug product operations will be a leading global CDMO service provider.



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

Agnes Shanley

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

It is not unusual to hear of 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 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 the APIs used to manufacture generic sartans, the angiotensin inhibitor blockers [ARBs]) prescribed to some patients to treat high blood pressure.

By August 27, 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, but compendial testing requirements may not be enough to clue manufacturers into the need to monitor and test for trace levels of genotoxic contaminants. As offshoring and outsourcing trends continue, the recall suggests that developing solutions will be crucial.

"In the end, we can only find what we are looking for."
—Anders Fuglsang, Fuglsang Pharma

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. "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.

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

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FDA and the General European Official Medicines Control Laboratories Network (GEON) published methods for testing 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 September 28 (10), when EMA also revoked its right to sell the product in Europe (11).

In an FDA 483 published on September 21, 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 an outside lab to conduct a small-scale research project 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 outside 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.

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.

"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, Qualandre

"So we arrive at the million-dollar question: Are regulatory agencies and pharmacopeias 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 con-

tamination, performed by independent experts outside of regulatory agencies or pharmacopeias. 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 pharmacopeias and regulators, to finished drug manufacturers, API manufacturers, and national testing labs. "At this point," he says, "that may be wishful thinking."

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 (September 18, 2018).
2. FDA, "Valsartan Products Under Recall," *fda.gov*, August 28, 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," *qz.com*, July 18, 2018, 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, September 21, 2018.
8. FDA, "FDA Announces Preliminary GC/MS Headspace Method for Determining NDMA in valsartan" Press Release, August 14, 2018.
9. EDQM, "OMCLs Release Three Methods for Determination of NDMA in Sartans," Press Release, September 21, 2018.
10. FDA Press Release, "FDA Places Zhejiang-Huahai on Import Alert," *fda.gov*, September 28, 2018, www.fda.gov/Drugs/DrugSafety/ucm613916.htm
11. EMA, Press Release, "EU Inspection Finds Zhejiang Huahai Site Non-Compliant," *ema.europa.eu*, September 28, 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/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM621162.pdf **PT**

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

Christopher Burgess

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

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.

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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).

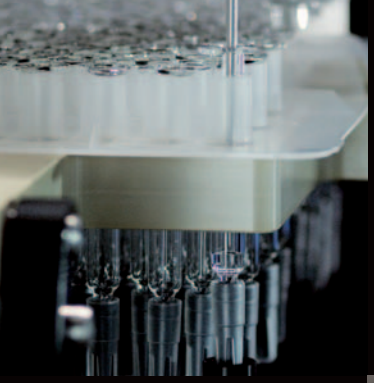
The task is to bring these two parameters into a state of statistical control. This would entail ensuring that the mean and the standard deviations were not varying significantly. This ideal situation is illustrated in **Figure 1B**. This process would then be said to be under statistical control (i.e., 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.

If a process contains special cause variation, it is unstable from a statistical point of view.

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.



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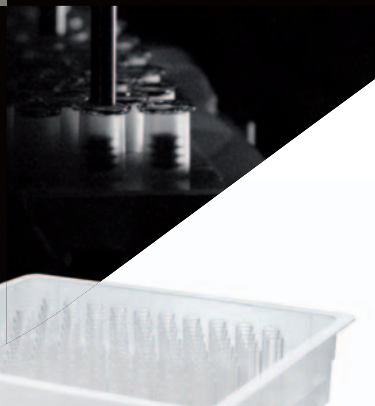

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Figure 1: Process stability and capability (4).

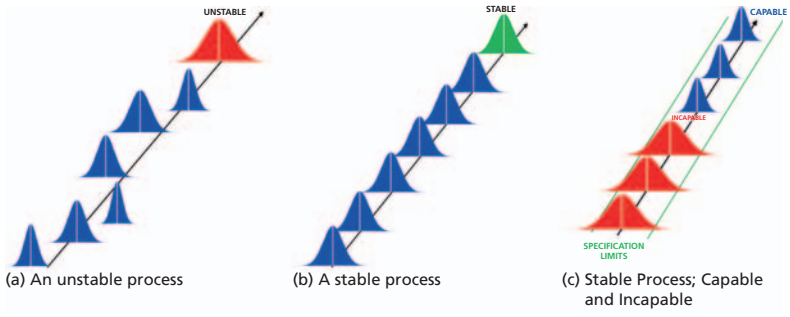
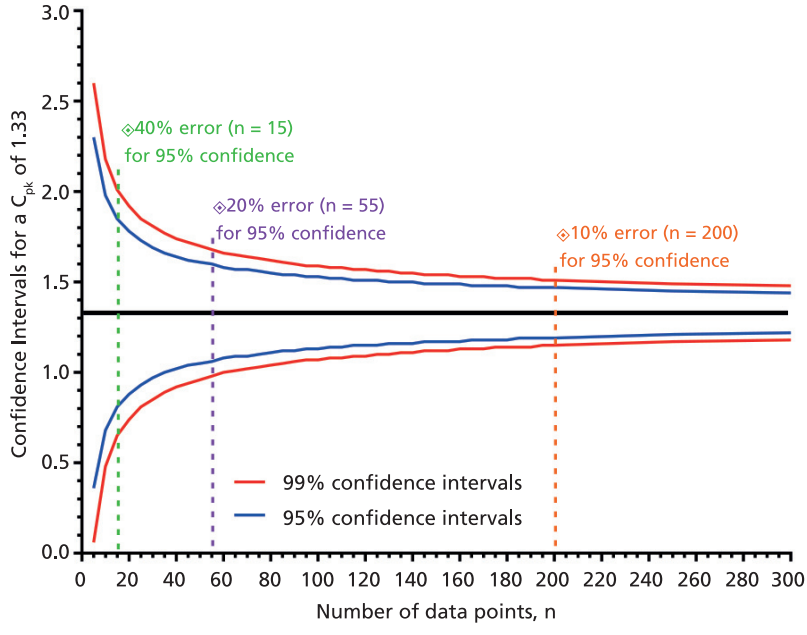


Figure 2: Confidence intervals as a function of sample size for C_{pk} of 1.33.



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 centered, while C_{pk} measures the actual capability in a process, which is off-center or biased. If a process is centered, then $C_p = C_{pk}$.

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

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.

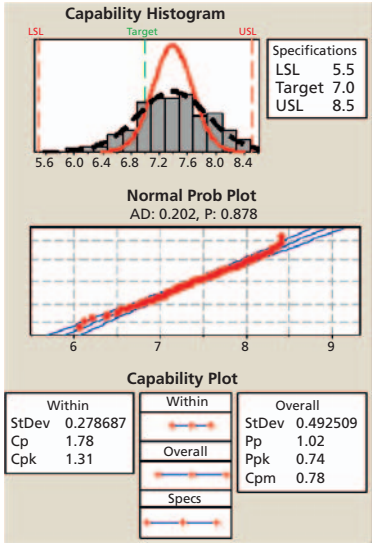
S_w is the within batch standard deviation (called the within sub-group standard deviation in ISO) not the overall process standard deviation. It is usually estimated from a Shewhart mean and range control chart using the formula:

$$S_w \approx \frac{\bar{R}}{d_2}$$ 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

[Eq. 1.6]

FIGURES ARE COURTESY OF THE AUTHOR.

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



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:

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

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). **PT**

Outsourcing Development: Small-Scale to Commercial

Susan Haigney

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

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, Sr. 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, pediatric 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 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

PharmTech: 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 tableting 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 tableting turret dwell time/speed. These modifications may be helpful in delaying the sticking behavior.

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

PharmTech: 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 CQAs 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

PharmTech: 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 validation 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

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

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.

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. **PT**

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A Q&A

Leading the Way in Biologic Drug Formulations through Innovation in Protein Stabilization

Peter Ferguson
Global Marketing Manager
Roquette

A new excipient can help tackle the challenge of an unstable protein.

Molecular inclusion complexes using cyclodextrins have become a standard formulation strategy to improve the solubility or stability of active ingredients. Roquette has pioneered the development of betacyclodextrin technology, developing a full range of KLEPTOSE® betacyclodextrins. Peter Ferguson, global marketing manager at Roquette, recently spoke with *Pharmaceutical Technology* about why the new multi-compendia excipient was developed for small-molecule formulations and the promise KLEPTOSE shows as a multifunctional excipient suitable for biopharmaceutical applications.

Pharmaceutical Technology: What major challenges do you see facing biologic drug formulators?

Ferguson: The number-one concern for any formulator in the biologic space is finding the correct formulation, including the optimal excipients that provide maximum stability for the therapeutic protein. The challenge does not stop when such an excipient has been found. The challenge is then to find a supplier that can consistently produce the material under the highest level of quality standards.

Pharmaceutical Technology: How has Roquette reacted to this challenge?

Ferguson: Roquette has responded to the challenges facing the biopharmaceutical industry by investing heavily within the space to support our partners in bringing life-saving medicines to market. This can be seen most recently via our newest innovation, KLEPTOSE BioPharma, a hydroxypropyl modified betacyclodextrin. Roquette pioneered the use of this excipient in the small-molecule field. We leveraged our technology and experience in small-molecule excipients to bring this new tool to biologic formulae. Scientists working in the field of biologic formulation development are limited by the excipients that are commercially available, as well as by conformance to the biopharmaceutical industry's needs. Roquette has expanded its toolkit with the launch of KLEPTOSE BioPharma.

Pharmaceutical Technology: Can you explain what KLEPTOSE BioPharma does in a biologics formulation?

Ferguson: KLEPTOSE BioPharma is an excipient that provides anti-aggregation

stability within the biologic formulation through a novel mechanism of action. KLEPTOSE BioPharma is a truly innovative application for cyclodextrin technology. Excipients provide their protein stabilization through different mechanisms of action. KLEPTOSE stabilizes proteins through a mechanism known as complexation. This is a new method of stabilization for biologics through the use of a technology that is frequently used within small-molecule therapies. Cyclodextrins are also believed to act as surfactant-like molecules, preventing interface-induced protein aggregation.

Pharmaceutical Technology: How is KLEPTOSE BioPharma different from other excipients on the market?

Ferguson: Other excipients do not stabilize proteins in the same way as KLEPTOSE BioPharma. The precise mechanism of action is not currently known within academia, however, our team in Singapore is working to answer that question. What KLEPTOSE BioPharma provides is a totally new tool in the arsenal of the formulator for tackling the problem of protein stabilization. We believe that this excipient could open up new dosage forms that were not available before as well as provide a new level of stabilization.

Pharmaceutical Technology: What are other benefits of using KLEPTOSE BioPharma as an excipient?

Ferguson: Modified cyclodextrins, such as KLEPTOSE, are not truly one discrete molecule, but instead they are a collection of thousands. As with all modified cyclodextrins, the substitution pattern, and the presence of various isoforms, plays a crucial role in the robustness of the stabilization provided. At Roquette, manufacturing protocols are well-established and proprietary manufacturing techniques give us the ability to produce an extremely well-defined product with incredibly low batch-to-batch variability.

"This year has been the year of biopharma for Roquette. Not only did we launch our new excipient, KLEPTOSE BioPharma, but we will have also officially opened the doors to our new Singapore innovation center."

Pharmaceutical Technology: What investments has Roquette made in innovation and technical services to support biopharmaceutical industry customers?

Ferguson: This year has been the year of biopharma for Roquette. Not only did we launch our new excipient, KLEPTOSE BioPharma, but we will have also officially opened the doors to our new Singapore innovation center. This facility is fully equipped with the latest technology in formulation science and upstream process simulation. Through this new facility, Roquette will be developing an ever-growing portfolio of products as well as offering technical services to our customers.

Pharmaceutical Technology: What does the future hold for biopharmaceutical excipient technology?

Ferguson: At Roquette, we believe we have only just scratched the surface in terms of the potential applications for KLEPTOSE. From serving as cryoprotectants in cell therapies to a new way to stabilizing small-molecule components in antibody drug conjugates, the future for KLEPTOSE is very promising. KLEPTOSE is a truly exciting molecule, however, our ambitions in excipient technology and innovation do not stop there. Through Roquette's wealth of knowledge and experience in carbohydrate chemistry and technology, we are working on a truly compelling portfolio of innovations that we intend to bring to market over the coming years. Our ambition is to be a true partner for manufacturers of biologic drugs. We aim to bring new solutions, in addition to those that we currently offer, for protein stabilization and upstream cell culture applications to help our customers bring biologics to life and make new life-saving therapies a reality.

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Facing Inactive Ingredient Database Challenges?

Navigating the Complexity for Successful Regulatory Filings

LIVE WEBCAST

Tuesday, October 2, 2018 at 11am EDT | 10am CDT | 4pm BST | 5pm CEST

Register for free at http://www.pharmtech.com/pt_p/IID

Can't make the live webcast? *Register now and view it on-demand after the air date.*

The Inactive Ingredient Database (IID) provides information on inactive ingredients present in FDA-approved drug products and is used by industry as an aid in developing drug products.

How can sponsors gain a better understanding of the FDA requirements and avoid lengthy review cycles, unnecessary requests for additional safety studies/information, and Refuse-to-Receive (RTR) letters from the agency?

In this webcast, leading global regulatory experts Dave Schoneker from Colorcon and Priscilla Zawislak from Dow Dupont come together under the Controlled Release Alliance to share their insight and describe how to use the IID to make good formulation decisions, overcome regulatory hurdles, and get to market faster.

KEY LEARNING OBJECTIVES

- Understand the current status of the IID and the FDA requirements
- Unlock the IID challenges that may impact your filing and make better formulation decisions
- Learn how to access and utilize tools in support of your bridging justification for a smooth submission process

WHO SHOULD ATTEND

- Pharmaceutical formulation and product development scientists, regulatory managers, and project managers

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

PRESENTERS

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Sterility Testing

Best Practices and Use of Isolator Technology

LIVE WEBCAST: Tuesday, October 23, 2018 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

Register for this free webcast at www.pharmtech.com/pt_p/isolator

EVENT OVERVIEW:

Sterility testing is a regulatory requirement for all preparations that according to the USP, EP, and JP Pharmacopeias are required to be sterile. Sterility testing is considered a referee test and is not intended as a sole product release test. False negative and false positive results can occur if the proper process controls are not followed.

Many challenges are associated with achieving a suitable test environment to carry out sterility testing under the most ideal aseptic conditions; critical best practices should be followed to demonstrate an accurate, meaningful sterility test result.

Key Learning Objectives

During this webcast, experts will discuss strategies and best practices for maximizing the conditions of the sterility test environment as well as reducing the risk of inaccurate results for sterility testing through the use of isolators and vaporized hydrogen peroxide (VHP).

Topics will include:

- Regulatory guidance and recommendations
- Lab design and system overview
- VHP decontamination cycles/load design and qualification
- Package integrity verification for VHP
- System monitoring and controls
- Training
- Method suitability
- Sterility test methods and techniques
- Pros and cons of isolator vs. cleanroom
- Sterility test positive rate

Who Should Attend

- Bio/Pharmaceutical scientists and managers who are responsible for sterility testing, manufacturing, or regulatory submissions for sterile products

Presenters

Suzanne Williams
Manager, Bio/Pharmaceutical Microbiology
Eurofins Lancaster Laboratories, Inc.

Marcy Hibshman
Group Leader III, Principal Microbiologist, Bio/Pharmaceutical Microbiology
Eurofins Lancaster Laboratories, Inc.

Moderator

Agnes Shanley
Senior Editor
Pharmaceutical Technology

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

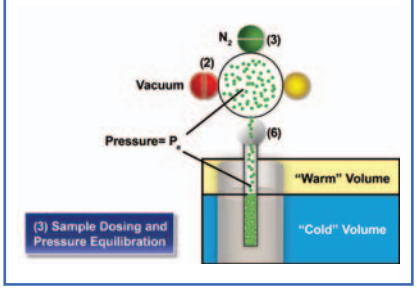
MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

IMPROVING FREEZE DRYING — *contin. from page 45*

This approach offers reassurance that data are obtained under precisely the conditions of interest with respect to stability and reconstitution behavior 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.

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



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 behavior that is inaccessible via surface area and particle sizing techniques that require sampling.

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 **PT**

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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 behaviors (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 programs or systems. Behaviors 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 behaviors, 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, June 27, 2018. **PT**

Your opinion matters.

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

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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 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 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 behavior driven by performance indicators, objectives, and senior management behavior 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 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

Contin. on page 81


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