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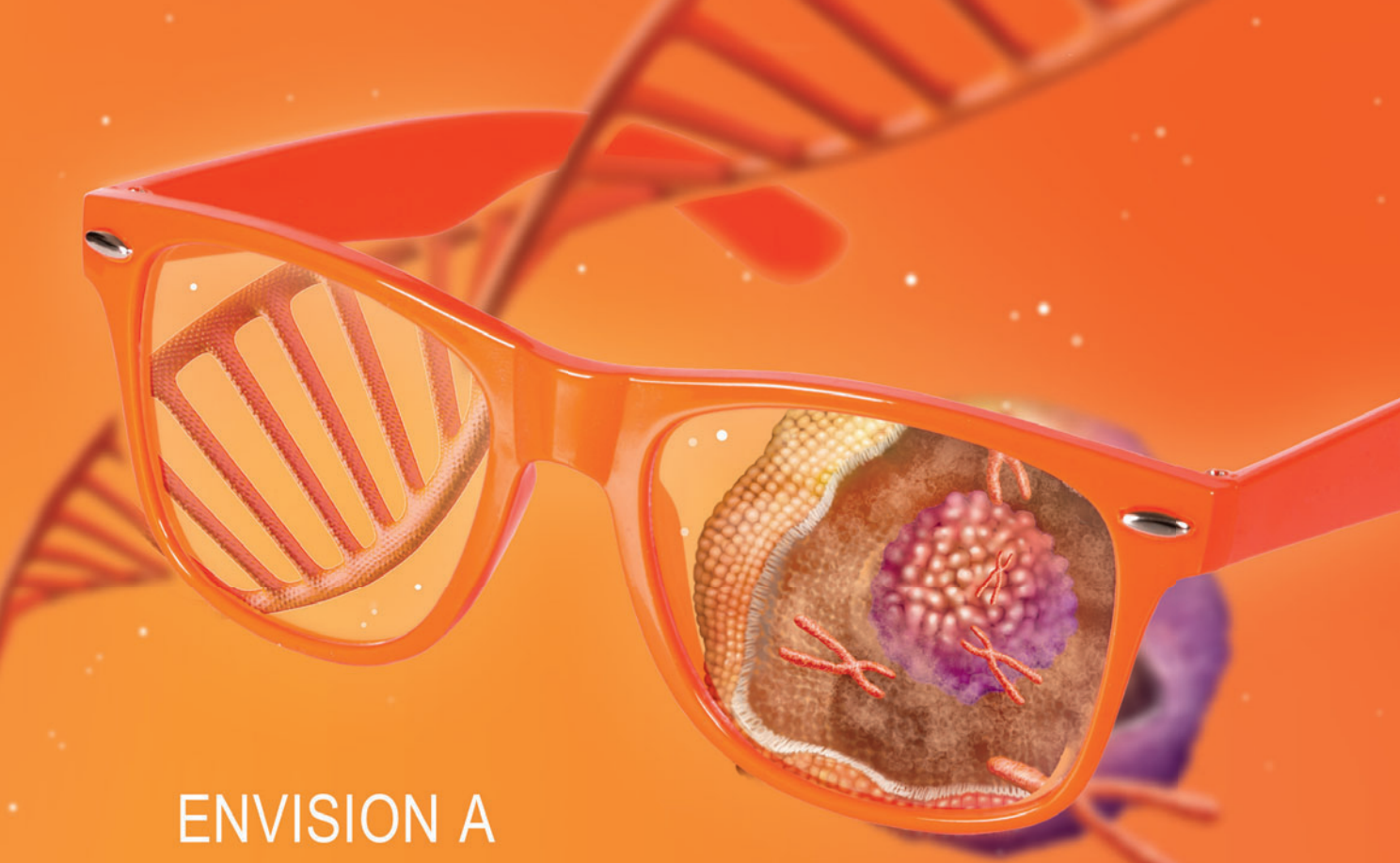

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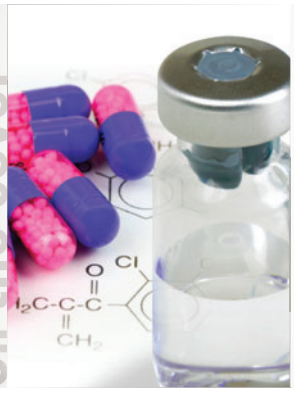

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ASK THE EXPERT

Focusing on whether the product meets its defined quality attributes should help one make reasonable, documentable, and defendable risk-based decisions, according to Susan Schniepp, distinguished fellow at Regulatory Compliance Associates.

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Pharma's Role in Puerto Rico's Future

Rita Peters

Reeling from financial and tropical storms, Puerto Rico needs stable industry for recovery.

Pharmaceutical manufacturing has long played a major role in the economy of Puerto Rico, representing 72.4% of its total exports in 2016, according to the US Bureau of Labor Statistics (1). In 2016, Puerto Rico-based facilities exported $14.5 billion in drug products, 25.5% of the US total and more than the amount of product exported by any US state.

The US territory, which has struggled for years under a heavy debt burden, took another blow on Sept. 20, 2017 when Hurricane Maria knocked out all electrical power and nearly all phone service for the 3.4 million residents. One week after the storm, the power grid, communications, and transportation systems were in ruins. Food, water, medicines, and other living essentials were in short supply. While government agencies and relief organizations initiated humanitarian efforts, pharma companies with facilities on the island assessed the damage to their facilities and contributed to relief efforts (2).

Immediate assessment

AbbVie and Amgen reported minimal damage to facilities, which were running on generators, and were working to restore normal operations. Eli Lilly and Company reported its two manufacturing sites in Puerto Rico had minimal damage, and that operations would not be hindered and there was no supply risk to patients.

AstraZeneca reported via an emailed statement that it was receiving updates regarding the status of its plant in Canovanas and its employees, but believed that the facility fared well. Bristol-Myers Squibb said the company was evaluating the situation around its pharmaceutical operations, executing contingency plans to mitigate product supply risk, and working to bring operations back online.

As of Sept. 27, 2017, FDA identified more than 40 high-priority drugs where short-term disruptions could lead to shortages. The agency is working with at least five companies impacted by the hurricane to prevent critical shortages of medical products in Puerto Rico and across the United States, including coordinating transport of critical drugs from Puerto Rico.

Long-term impacts

Previously, tax laws that enabled US drug manufacturers to send profits from the island's manufacturing facilities to parent companies on the mainland without having to pay federal taxes encouraged companies to establish operations in Puerto Rico. Those incentives expired about 10 years ago, leading to the shutdown of some facilities. Some worry that other facilities damaged by the storm may not reopen (3), hindering the island's physical and financial recovery.

FDA Commissioner Scott Gottlieb expressed similar concerns—in addition to worries about drug shortages—in a Sept. 25, 2017 statement (4). "The island is home to a substantial base of manufacturing for critical medical products that supply the entire world. This industrial base is an important source of jobs and economic vitality for the island. It is a key to Puerto Rico's economic recovery. The manufacturing facilities are also a pivotal source of critical medical products for the entire United States. Helping to bring these resources back in operation is an important goal of ours and of Puerto Rico's," the statement read.

Puerto Rico faces a long, difficult path to recovery. Will Pharma be part of the healing process?

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

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Analytical Data System Update

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A peak integration algorithm in the software can quantify overlapping peaks more accurately, the company reports. The intelligent peak deconvolution analysis (i-PDeA II), which uses analyte UV spectral information obtained by the PDA detector, has been improved and can be used to show data traces for single components more accurately than with the conventional peak purity method, enabling accurate quantitative values, even for co-eluting peaks.

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FDA User Fees Promote Manufacturing Readiness

Jill Wechsler

Industry and FDA face new fee structures and new challenges in implementing fee initiatives.

The US Senate approved legislation in early August 2017 reauthorizing critical five-year user fee programs that fund FDA oversight of medical products, just in time to avoid major agency disruptions (1). The vote was delayed by contentious debate on Capitol Hill over revising the Affordable Care Act. But once the wrangling over Obamacare fizzled out, the Senate quickly enacted the FDA Reauthorization Act (FDARA). It mirrored the bill approved by the House in early July and was signed by President Trump on August 18.

By enacting new fee programs for drugs, biologics, generic drugs, medical devices, and biosimilars before they expired on Sept. 30, 2017, Congress avoided massive FDA layoffs. Equally important for agency staffers charged with implementing new fee policies, this user fee bill is relatively "clean," benefitting from enactment of the extensive 21st Century Cures Act last December, which tackled many of the more controversial proposals for accelerating and streamlining the development, testing, and review of medical products.

Key provisions added to FDARA seek to spur development of pediatric cancer therapies and innovative medical devices and to deter import of illegal or counterfeit medicines. The bill reauthorizes the orphan drug grants program, while limiting orphan drug exclusivity awards to products that demonstrate a clear superiority over existing therapies, and it requires sponsors to conduct studies on new tropical disease treatments to qualify for priority review vouchers. Several provisions aim to speed up field inspections of manufacturing facilities and to assess whether delays in resolving deficiencies found in preapproval inspections block new product approvals. The legislation seeks expedited review of responses to inspection observations for priority applications and for those related to drug shortages.

The increase in funding will help improve FDA's electronic submission process.

Efforts to lower prescription drug prices ended up with largely symbolic language backing patient access to therapies, plus provisions for speeding the development and marketing of generic drugs to enhance market competition. FDARA establishes a priority review track for competitive generic therapies and an accelerated development initiative for high-demand products; brand manufacturers have to update information on products withdrawn from the market to help clarify which drugs have limited competition.

New fees and disclosures

This latest version of the Prescription Drug User Fee Act (PDUFA VI) aims to make revenues more predictable for FDA by relying more on a new product fee paid by manufacturers that is based on number of approved products. At the same time, PDUFA reduces application fees and discontinues levies for manufacturing establishments and supplements (2).

The overall increase in funding will help improve FDA's electronic submission process and IT initiatives and expand programs for hiring and retaining review staff. Because PDUFA already has reduced review times for new drug applications (NDAs) by achieving more first-cycle approvals, the new PDUFA agreement focuses more on managing the mushrooming demand for development-phase meetings, boosting resources for the breakthrough drug program, advancing the review process for rare disease treatments, and bolstering support for combination products. There's continued emphasis on advancing model-informed drug development, biomarker qualification, the use of real-world evidence, and incorporating the "patient's voice" into regulatory decision-making.

Manufacturers of drugs, biologics, and generic drugs face added pressure to ensure that all facilities involved in product development and future production are fully identified in applica-

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tions. Omitting this information in a submission can delay needed facility inspections, says FDA. Under PDUFA, applications that lack full facility information face a three-month approval delay for an NDA or efficacy supplement and two months extra for approving a manufacturing supplement. FDA states that it aims to complete all inspections of clinical and manufacturing sites within six months of accepting a priority application and within 10 months for standard submissions, leaving two months at the end of the review process to address deficiencies found during site visits.

Manufacturers face added pressure to ensure that all facilities involved in product development and future production are fully identified in applications.

FDA's biosimilar user fee program (BSUFA II) is revised to collect $45 million in revenues through program and application fees to support product development and review (3). BSUFA also wants manufacturers to identify all planned production facilities in applications and supplements to avoid inspection delays that could add two months to a review timetable. FDA specifies that mid-cycle and late-cycle meetings will discuss chemistry, manufacturing, and controls (CMC) issues, and that it aims to complete all facility inspections within 10 months of application receipt.

The BSUFA program will advance through publication of guidance on key regulatory issues, including statistical methods for demonstrating similarity and a final policy for developing interchangeable biosimilars. FDA published draft guidance on CMC postapproval changes for biological products in August 2017 (4), and a similar document for biosimilars is scheduled for early 2019, along with final advisories on biosimilar naming, labeling, and clinical pharmacology data development.

The revised Generic Drug User Fee Amendments (GDUFA II) also increases fees overall, to reflect a greater volume of abbreviated new drug applications (ANDAs) submitted to FDA than originally anticipated. More revenues will come from a new program fee based on approved products and facilities, with large generic-drug makers (more than 20 approved products) paying the full $1.5-million fee in 2018, medium companies (5–19 products) paying about half, and firms with less than five approved generics paying one-tenth the amount, or $160,000 in 2018 (5). Fees for filing an ANDA rise from approximately $70,000 in 2017 to $172,000 in 2018; facility fees for finished drugs and active ingredients remain fairly even, with the exception of a sizeable reduction for contract manufacturing organizations (CMOs). In announcing the 2018 fees (6), FDA notes that it will assess facility fees based on information submitted in applications, rather than relying on company self-identification.

Moving on

A number of key issues failed to make it into FDARA, largely to avoid legislative delay, but they may linger, as Congress is under pressure to deal with the federal budget and tax reform proposals by year-end. One topic that could surface is a proposal for establishing user fees to support expedited review and approval of over-the-counter (OTC) drugs (7). FDA and manufacturers have negotiated an agreement for accelerating development of OTC monographs, but too late to include it in FDARA. Congress recently held hearings on the program, and it could be included in other health policy legislation this year.

Another high-profile topic is the right-to-try (RTT) legislation approved by the Senate, which promotes access to certain experimental therapies that have completed Phase I testing for individuals with terminal illnesses and no other treatment options (8). Under the Senate bill, patients would not have to apply for FDA approval to access these drugs, and it limits liability of pharma companies, prescribers, and dispensers for problems arising from early use of such products. This aims to encourage manufacturers to provide a test therapy when requested, but still does not require sponsors to agree to such action. House RTT advocates have proposed their own reform bill, and it may take some time to reach agreement on a measure that satisfies all parties.

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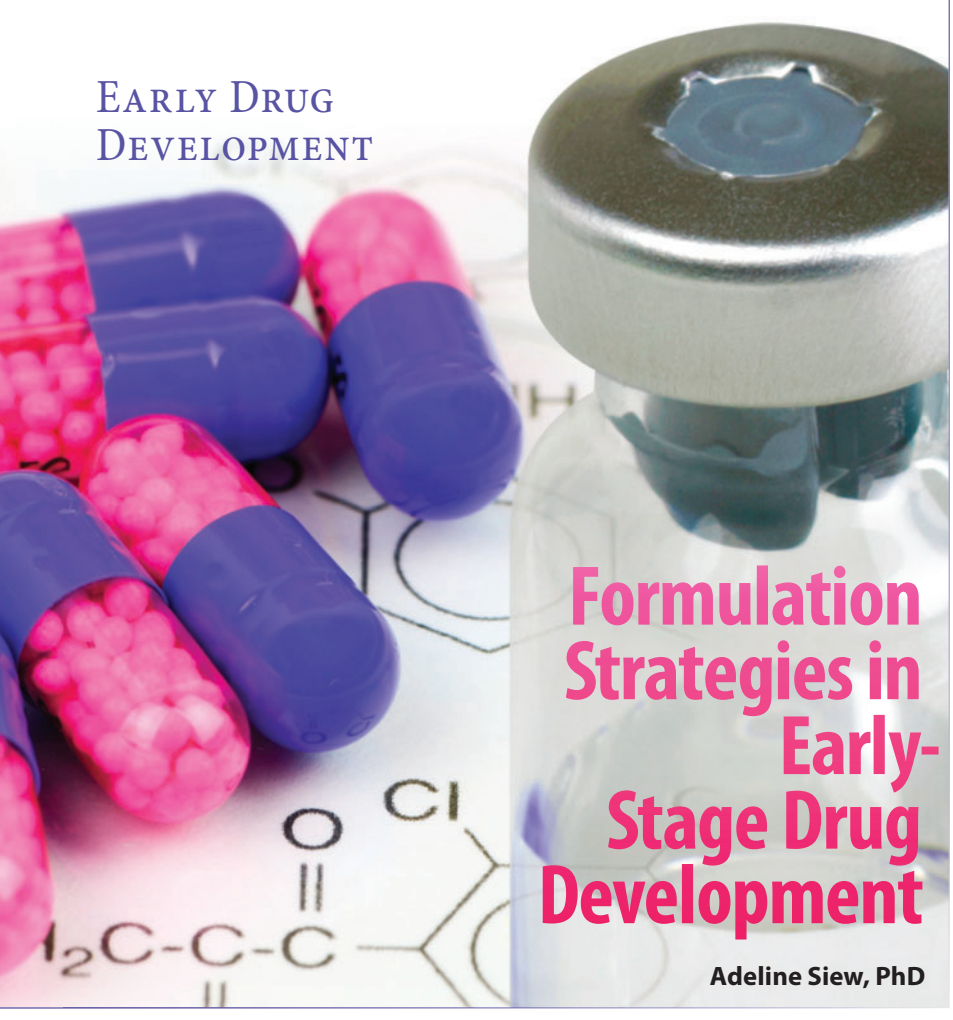

Formulation Strategies in Early-Stage Drug Development

Adeline Siew, PhD

Applying the right formulation strategies early in the drug development process can help avoid costly late-stage failures.

Improving R&D productivity continues to be a key challenge for the pharmaceutical industry. There is increasing pressure to speed up drug development and make it more cost-effective. Companies want to ensure that their most promising drug candidates eventually hit the market. But while speed to market is a crucial element, applying a structured approach starting at an early stage can help de-risk the drug development process and avoid costly late-stage failures.

Priorities during early stage

Efficacy and safety. During the early stages of a drug development program, time is of the essence, notes Torkel Gren, general manager at Recipharm Pharmaceutical Development. Establishing proof of efficacy and safety is the top priority, and formulation development is often left to later stages. Gren finds it strange that such an important activity as formulation development is often overlooked and started too late. "But I see it all the time," he says. "Of course, there is no point starting formulation development before we have selected the drug candidate. The API has to be manufactured in sufficient quantities before formulation development can begin. However, to a certain extent, you can start formulation development with small quantities of non-GMP material. This approach is, no doubt, risky because solid-state properties of different batches can vary considerably at this stage. Nevertheless, especially with simpler formulations, useful information can often be collected from work with early batches."

The rate of attrition is high during clinical trials with only 10% of new drug candidates making it to market, according to Rob Harris, chief technical officer at Juniper Pharma Services. "Therefore, there is a natural reluctance within the industry to invest in the development of a robust dosage form until there is some confidence in the safety and efficacy of the drug."

Pharmacokinetics. Anil Kane, executive director and global head of Technical and Scientific Affairs at Patheon, observes that once a molecule has been selected as a potential candidate, all efforts tend to focus on proving that the drug substance gets absorbed in an animal species before a first-in-human Phase I study. "Typically, a formulation is prepared by simply suspending the drug in a hydroxypropyl methylcellulose suspension, with or without a surfactant, which is then dosed to an animal so that an absorption profile can be established," he says. "In a similar manner, the first dose format prepared for a quick Phase I study is usually a neat API in a capsule."

Kane cautions that while these methodologies or procedures are simple and fast, hence, allowing pharmacokinetic assessments and safety studies to be performed, the results obtained are not always promising. "In many instances, it's found that the drug was not properly suspended, due to hydrophobicity and poor wettability. In Phase I clinical programs, the results can show that the API was not absorbed sufficiently to obtain the desired plasma levels and there was not enough exposure," he says. Gaining speed by deferring formulation development to a later stage has, in many instances, not met the goals of early development, Kane observes.

Aaron Goodwin, principal investigator, Internal Research and Development, Capsugel, now a Lonza company, shares a similar view. He agrees that preclinical formulation development is generally focused on achieving a desired pharmacokinetic response in a translatable animal model while minimizing formulation development

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time and cost. Goodwin, nonetheless, points out that this can be challenging for molecules with poor bioavailability or a narrow therapeutic window given that *in vitro–in vivo* relationships are often not straightforward and, therefore, require additional time and cost to establish. "It's tough to justify the additional cost and timing given the low probability of success for a preclinical API especially for a new mechanism of action," he says. "However, if not addressed adequately, the drug product can be at risk of reformulation or even fail to demonstrate clinical efficacy in late stage when the stakes are much higher."

Giving an example, Goodwin explains that adequate exposure at an initial dose may be achievable in preclinical studies with a crystalline or perhaps a micronized suspension; and progressing a simple, conventional formulation may be the quickest way to the clinic. "But if the compound properties suggest that oral absorption may be solubility limited at high doses, and this is supported by preclinical *in-vivo* data, advancing a simple, conventional formulation may risk not reaching a maximally effective exposure," he says. "Advancing an amorphous form might take a bit longer to get to the clinic, but even if not optimized, it would likely circumvent this risk as well as reduce exposure variability."

Kane emphasizes that formulation development, based on a systematic drug substance characterization and material properties, is required to avoid such failures or loss of time, investment, and opportunity in early development.

Formulation challenges

Solubility. One of the main challenges in developing formulations for new drugs is the poor solubility of many of the compounds emerging from drug discovery, notes Harris. He estimates that 80% of new drug candidates are classified as poorly soluble, and points out that oral bioavailability will be compromised if the drug is not completely dissolved in the gastrointestinal tract.

Karl Werner, senior director, Finished Product Development, Midas Pharma, concurs that the number of Biopharmaceutics Classification System class II and IV compounds has increased tremendously. "There are challenges when trying to formulate these drugs into an oral dosage form," he says. "Poor solubility or bioavailability will result in incomplete or variable absorption, higher impact of pH and food on drug absorption, and poorly controlled pharmacokinetics." In such cases, it is extremely important to develop a formulation that maximizes the chance of good exposure even if doing so requires additional time and cost, Gren stresses. But he also points out that in some situations, it is worth asking if formulation development is really the right solution to a solubility/bioavailability problem or if modifying the molecule may be a better way to develop a successful drug product.

For weakly acidic or basic drugs, salt formation is often the preferred method for improving solubility because it is simple and effective. Other methods that have been widely used to address solubility issues in early development include particle size reduction by micronization or nanomilling to increase the dissolution rate, the use of surfactants or cosolvents, and complexation with cyclodextrins. But with the solubility of new molecules becoming more demanding, Harris notes that the application of more advanced solubilization technologies, such as lipid-based and self-emulsifying drug-delivery systems and amorphous solid dispersions, in early development is becoming more prominent.

Polymorphism and stability. "Formulation strategies in early-stage drug development entirely depend on the complexity of the molecule and its critical nature and behavior," says Kane, noting that some molecules may exhibit polymorphism, for example. "It is, therefore, important to understand the different polymorphic forms, their stability and properties, and potential to convert from one form to another," he explains. "The formulation strategy would then be based on preventing the conversion of the selected polymorph and ensuring its stability throughout the clinical stability or shelf life of the product."

Dose range. Uncertainty over the dose range to be administered is another complication during early development, according to Harris. "A formulation strategy suitable for a 5–50 mg dose range is unlikely to be appropriate for a 100–1000 mg dose range and vice versa," he says. "However, there are modeling software tools, such as GastroPlus, which can be used to predict an appropriate human dose based on physicochemical and animal pharmacokinetic data for the drug substance."

Limited amount of API. "Early-stage drug development is a balance between minimizing time to clinic and developing a progressable formulation that meets pharmacokinetic targets while at the same time has minimal pharmacokinetic variability," says Goodwin. "This can be remarkably difficult when there is limited API for development." In such cases, he recommends using API-sparing *in-vitro* tests to assess what types of formulations are likely to achieve clinical pharmacokinetics targets.

"Only minimal amounts of API are necessary to measure the neutral crystalline solubility as a function of pH, micelle partition coefficient, and amorphous solubility along with precipitation propensity. These values, along with estimates of permeability, can be input into simple models such as a maximum absorbable dose and dose number and dissolution rate models to get a basic understanding of absorption potential," Goodwin explains. According to him, these basic models lack a high degree of accuracy, but they are useful for identifying the limiting factor for absorption and providing an initial estimate of an absorption dose response. "Ultimately, these estimates can be used to determine if a drug-delivery technology is needed to achieve the target pharmacokinetic profile," Goodwin says. "And if an

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STARTING EARLY IS KEY TO DE-RISKING DRUG DEVELOPMENT

The pharmaceutical industry is under tremendous pressure to make drug development faster and cheaper. "There is a need for better treatments that show real-world efficacy, but the price has to be acceptable to payers and at the same time offer good returns to the developing company," says Will Downie, Catalent's senior vice-president of Global Sales & Marketing. "However, R&D budgets are tight and failures are costly." He further points out that the majority of molecules in the pipeline are increasingly complex, thus presenting development challenges.

"There are a number of pitfalls in drug development that can stall, stop, or require you to rework your program," observes Julien Meissonnier, vice-president of Science & Technology at Catalent. "More than 40% of new chemical entities in late-stage discovery are insoluble in water (1). Only one in 10 new molecules in active clinical development are readily bioavailable (2). The rate of attrition is high, with many drugs failing between first toxicity study and Phase I, and the likelihood of approval for Phase I candidates is 9.6% (3)," he says, highlighting the need for early formulation and dose form design. Downie explains that applying the right formulation strategy using structured and rigorous science can help avoid costly failures and re-starts, but it's important to start from an early stage. The key, according to Meissonnier, is to select an appropriate formulation technology and dose form based on the needs of the molecule in development.

Stephen Tindal, director of Science & Technology & Technical Support for Catalent's OptiForm Solution Suite, US, notes that the transition from high throughput screening (HTS) to traditional formulation development requires a significant amount of expertise. "Early on, it is useful to be able to screen thousands of samples at very small scale, to narrow down the sample set to the best few. Whether that can be done effectively will of course depend on the API sample set in question, on the validity/variability of the analytical method, and the screening criteria that are applied, and the ability to manage the amount of data generated," he says. "Done well, HTS can deliver a small set of 'most viable' samples for further evaluation using laboratory techniques at a higher scale, with better validity and less variability. Optimistically, it may even be possible to develop software that performs in-silico predictions to reduce the laboratory work further."

Tindal observes that the screening criteria can vary from company to company. "At Catalent, during a first meeting with a customer, we see very few molecules for which sufficient data has been collected to make an informed decision on which formulation development technology to use," he says. "Most companies pursue simpler formulation options, which are often appropriate only for drugs with good solubility. This is inconsistent given what we know about the prevalence of poorly soluble molecules in development pipelines." According to Tindal, Catalent's OptiForm Solution Suite platform helps address this issue. "We evaluate the API's challenges and consider the technologies that are needed for improving the API profile. We consider salt form, conventional technologies (e.g., powder in capsule), and enabling technologies such as amorphous dispersion, lipid-based formulation, and micronization in parallel, depending on solubility and other data. This saves time and money, and gives a higher chance of success for the estimated 90% of drugs in development where solubility is a problem," he says.

In July 2017, Catalent announced the expansion of its OptiForm Solution Suite platform to include support at an earlier stage of drug development. The expanded service includes in silico and formulation screening tools to select the most viable candidate; molecule characterization to identify development challenges, parallel screening to determine the feasibility of multiple bioavailability-enhancing technologies; formulation development for good laboratory practice (GLP) toxicity studies; and a dosage form strategy and cGMP materials for Phase I studies (4).

"To optimize early-stage development of oral doses, it is necessary to select the best few viable candidate API forms that have been identified during early R&D," explains Ronak Savla, scientific affairs manager at Catalent. "A comparison of the APIs' properties needs to be undertaken, and those with poor chemistry eliminated, before looking to achieve a reasonable level of oral bioavailability in animals to study drug metabolism and pharmacokinetic (DMPK) properties," he says. "Where a drug is poorly soluble, there are opportunities to enhance its solubility. It is also necessary to characterize available polymorphic forms to select the most stable form. At this stage, doses are formulated as liquids rather than finished dose units."

Savla observes that early API characterization and solid-state optimization is typically undertaken by an API supplier and/or preformulation services supplier, and then transitioned to a contract development and manufacturing organization for formulation development activities. "But animal dosing of poorly soluble APIs poses unique challenges requiring a fast, flexible, and cost-effective service, so it's our belief that companies with broad capabilities are better placed to do this work," he says.

Reliance on formulation to solve suboptimal pharmacokinetics of Development Classification System (DCS) Class IIb lead compounds—where the main challenge is the solubility of molecules—has been shown to increase timelines by approximately two years (5). "Instead of pursuing a powder-in-capsule formulation for Phase I, screening for other potential options that maximize a molecule's bioavailability and solubility profile should be investigated if delays in later development are to be avoided," Tindal explains.

Catalent's OptiForm Solution Suite platform was used to assist in the formulation of a drug candidate developed by a London-based pharmaceutical company, Trio Medicines. "The compound, TML-001, had undergone initial clinical trials that indicated poor bioavailability," Tindal says. "An acetylated prodrug was developed, and screening showed that it falls into the Biopharmaceutics Classification System (BCS) class IIa category, where the molecule's dissolution rate was more of a problem than its solubility. Further tests suggested issues with permeability."

Catalent presented Trio with four alternative candidate formulations: a micronized form, a lipid-based formulation, and two amorphous dispersions created by hot-melt extrusion. "The most promising was the micronized API, which was simple to manufacture and showed good chemical and physical stability," says Tindal. "The amorphous dispersions were ranked as the riskiest because they showed greater degradation, possibly as a result of thermal action during processing. In addition to being relatively difficult to process, a crossover study in healthy humans showed that the solid dispersions offered no improvement over the original formulation, and were, therefore, dismissed. In contrast, the other formulations demonstrated enhanced performance, marking a good starting point for further trials, which could be further adjusted to offer improvements to bioavailability later in development."

"Catalent's OptiForm Solution Suite has been designed to help drug developers start early and start smart. It provides a fast and efficient path from candidate selection to Phase I by selecting the right candidate, presented in the right API form, delivered in the right formulation and right dosage form," Meissonnier sums up.

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enabling technology is required, the information can indicate whether simple particle size reduction would work; or if the compound is ionizable, whether a high-solubility polymorph or salt form is likely to be adequate; or whether an amorphous form or lipid solution is necessary. This type of methodology decreases development time and API use by reducing the number of prototype formulations and *in-vivo* studies to nominate a proof-of-concept formulation for first-in-human studies."

Understanding the drug molecule

Before selecting a formulation strategy, one needs to have a thorough knowledge of the physicochemical properties and biological attributes of the drug substance, in particular its solubility and intestinal permeability characteristics, Harris explains. Knowing what dose to administer is also important, he adds, because this information allows the formulator to select the most appropriate formulation strategy for the compound.

Kane agrees that a systematic understanding of the molecule, its properties and challenges, and a sound, phase-appropriate formulation development strategy that addresses those challenges is key to success in early development. "For example, solid dispersions or lipid-based formulations can be used to address poor bioavailability challenges," he says. "For molecules that are unstable, there are various ways of stabilizing the molecule through a detailed understanding of its forced degradation profile, ensuring early- and late-stage drug product stability."

Drug structure and physiochemical properties can also be used to assess formulation risks, according to Goodwin. "Melting point and glass transition temperature are examples of two physiochemical properties that are very informative for advanced drug-delivery technologies and easily measured with small amounts of API," he says. "For example, an API with a low glass transition temperature would suggest that it may be difficult to achieve a stable amorphous form with high API loading in the drug product. A high melting point would suggest that it will likely be challenging to have a practical solubility in a lipid vehicle unless the dose is quite low. Although these are just a few examples, these physiochemical properties provide the basis for a preclinical risk assessment when evaluating enabling technologies for *in-vivo* performance, drug product stability, and manufacturability."

Applying a structured approach starting at an early stage can help de-risk the drug development process and avoid costly late-stage failures.

Manufacturability

Another objective of early-stage development is to ensure the formulation and process developed in Phase I can be transitioned into a scalable, manufacturable process in late-stage development, Kane points out. "The objective of late-stage development is to scale up the early-stage clinical formulation and process to a larger-scale product that can be commercialized, while ensuring and establishing its shelf life to be commercially viable. Keeping an eye on and envisioning a larger-scale process early on will help address challenges early in development. Designing robust processes with a thorough understanding of critical processing parameters that impact drug quality and defining the control strategies at a reasonable scale will ensure a robust manufacturing platform in late-stage development," he says.

Werner stresses that the risk of failure of a molecule is not only related to its pharmacological and pharmacokinetic properties or its toxicity, but also to its manufacturability. With reference to Midas Pharma's systematic screening process for "difficult to formulate" drugs, he recommends including such technical considerations at an early development stage. He cites a project where solubility enhancement was achieved for a molecule, but pilot bioequivalence testing failed because it was found that higher scale production significantly changed the physicochemical behavior of the formulation. "This resulted in a substantial increase in development costs and an extended timeline, which likely could have been avoided by an earlier testing of the robustness of the formulation in terms of its scalability," he says.

Keeping in mind the required commercial viability streamlines the development of new drug products and significantly decreases the risk of failure at later stages, according to Werner. In another example involving a highly potent and poorly soluble compound, he explains how applying the right methodology can help avoid scale-up issues. "The bioavailability of the compound had to be improved and at the same time, become less variable with regard to food effects," he says. "Several technologies were applied, including size-reduction (nanozation), spray-drying, and hot-melt extrusion. The nanoparticles agglomerated, and the first animal trial displayed highly variable adsorption rates. Application of amorphous suspensions, either prepared by solvent-based method (spray drying) or temperature-based method (hot-melt extrusion), showed more promising results. However, manufacturing trials revealed that the yield of the spray-drying process was substantially lower and the use of an uncommon organic solvent was required, which negatively affected the intended commercial viability. Hot-melt extrusion, on the other hand, not only enabled the desired positive effects on bioavailabil-

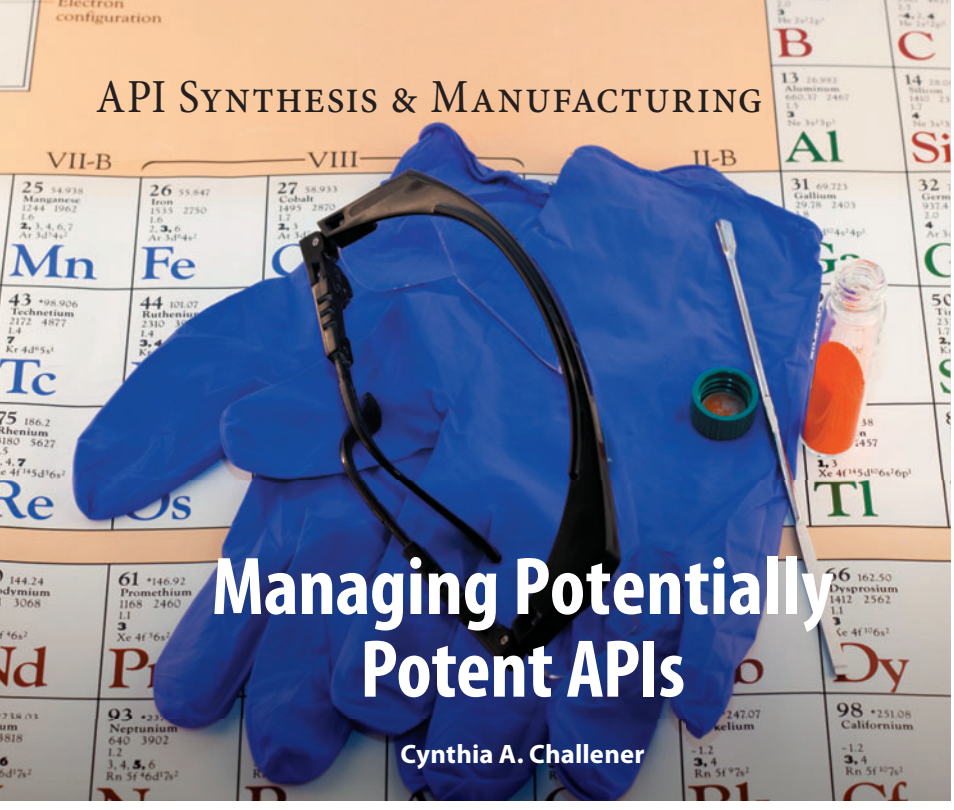
ity and variability, but also helped to avoid the dust formation typical for a spray-drying process (dust formation is undesirable for highly potent drugs)." Hot-melt extrusion proved to be superior in this case.

The right approach

Early-stage formulation strategies should not only focus on developing a dosage form that can be manufactured using simple and cost-effective processes but also one that offers a high probability of clinical success. "A sound formulation strategy is one that is 'phase-appropriate' and not over-engineered to a large commercial-scale in early development," says Kane. "When developing a new drug, the chemistry, manufacturing, and control (CMC) strategy should involve a systematic drug substance characterization upfront to understand the molecule, its material properties, physical and chemical stability issues, and addressing these early in a phase-appropriate formulation development strategy." Kane explains that this approach ensures a significant advantage by not needing to go back and address one or more challenges as they appear in the development process.

According to Goodwin, efficient drug product development can be accomplished using a risk-based approach to formulation design based on fundamental- and mechanistic-based models. The identification of high-risk areas provides a basis for initial formulation selection and optimization. Harris also stresses that risk mitigation is crucial throughout the whole drug development process. "For early stages, it is vitally important to understand as much as possible about the attributes and behavior of the drug substance. This allows for selection of a formulation strategy that gives the compound the best chance of success in clinical trials," Harris says.

One future prospect that is already showing potential in dramatically reducing the amount of API and time necessary for drug product development is machine learning, Goodwin observes. "If trained on a wide diversity of data, these types of algorithms have the potential to predict drug-delivery technologies and processes that have the highest probability of successfully delivering an API—all based on a few simple API-sparing *in-vitro* measurements and calculated properties of the molecule," he says. "In the past decade, this approach has gained a lot of recognition for predicting absorption, distribution, metabolism, elimination, toxicity attributes such as permeability, transporter and metabolism substrates, and estimates for clearance and volume of distribution." Goodwin believes this methodology has huge potential in advancing drug development because of the high degree of prediction accuracy. **PT**



Managing Potentially Potent APIs

Cynthia A. Challener

CDMOs have established strategies for handling new chemical entities with unknown biological activity.

The global market for highly potent APIs (HPAPIs) is growing at a healthy rate. According to market research firm Markets and Markets, demand for HPAPIs will expand at a compound annual growth rate of 8.5% from $16.02 billion in 2016 to $24.09 billion in 2021 (1). Rapid growth in the markets for oncology treatments (including generics) and antibody-drug conjugates is driving this expansion.

The manufacture of HPAPIs requires specialized facilities, equipment, and skills to ensure the safety of operators and the environment. As such, the bulk of HPAPIs are produced by contract development and manufacturing organizations (CDMOs) with these specialized capabilities. One of the challenges for CDMOs when accepting new projects, particularly those involving new chemical entities (NCEs), is identifying the level of potency, or biological activity, in order to establish appropriate safety and handling procedures.

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

Two parts to an assessment

There are two parts to an assessment of an NCE with respect to potency or biological activity. The first part, according to Simon Edwards, vice-president of sales and business development at Cambrex, is a risk assessment that produces an exposure "limit" or an exposure "range" (i.e., occupational exposure limit [OEL] or occupational exposure band [OEB], respectively). The limit or range is in units of mass per volume air (micrograms per cubic meter, mg/m^3). The second part of the assessment is risk management, which involves establishing actions or preventive steps to keep exposures below the limit or range determined by the risk assessment. This work is undertaken through a collaborative effort between toxicology, safety, and engineering departments.

Standardized approach, but no standard system

This general approach to risk assessment is reasonably well-standardized, but the way the results are displayed varies greatly because the application of uncertainty factors differs depending on the individual risk assessor. The standard approach, according to Cambrex, is incorporated into the International Council for Harmonization (ICH) guidance on impurity assessment (2), which is used by the American Conference of Governmental Industrial Hygienists (ACGIH) in a manner similar to the way FDA and the European Food Safety Authority (EFSA) conduct food ingredient risk assessments and EPA undertakes environmental risk assessments.

There is no standard system, however, because there are no regulatory compliance requirements for occupational exposure limits. "Having discussed this in depth with expert consultants, we feel that it is very unlikely that there will ever be a collaborative effort to establish a common system unless a regulatory mandate is introduced," says Edwards.

This lack of a standard classification system is not a hindrance for CDMOs, however, according to Ramesh Subramanian, vice-president of strategic marketing with Piramal Pharma Solutions. "The actual nomenclature is not as relevant as the OELs themselves. So despite using various classifications, the industry is able to move forward with minimal issues, as the OELs provide the clarity that is needed to establish containment solutions," he observes.

Experience required

Because there are many possible pharmacophores and toxicity endpoints, Edwards stresses that risk assessment/risk management of NCEs takes a great deal of experience and chemical intuition. "Managing the potential exposure in manufacturing is not prescriptive either, as it is facility- and equipment-specific, and requires experienced engineers and safety people to implement correctly in order to protect employees, the facility, and the surrounding environment," he states.

The key, according to Vivek Sharma, CEO of Piramal Pharma Solutions, is having an established potent compound category policy that defines the level of containment required depending on OELs or other toxicity data (e.g.,

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LD50) and having predefined default criteria for containment in the absence of such data. "Quality CDMOs tend to default to a higher OEL when in doubt to ensure operator and staff safety," he says. "Achieving a strong track record of safe HPAPI manufacturing also requires an understanding of the systems that are required to minimize the risks associated with potent compounds." Sharma notes that proper facility design and engineering, including the heating, ventilation, and air-conditioning (HVAC) system, barrier isolation, and gowning/degowning areas are key considerations. "Appropriate facilities, engineering controls, and safety protocols are, in fact, increasingly imperative as newer HPAPIs under development have ever declining OELs," he comments.

Ensuring the right level of safety

During early development stages, many drug sponsor companies do not have the toxicity data needed to ensure that their compounds are handled safely. The challenge for CDMOs then becomes ensuring that the right level of safety measures is implemented and followed when handling the molecule and the associated chemistry, according to Vince Ammoscato, site head–Riverview at Piramal Pharma Solutions. In the absence of any data, many companies default to a potent designation Category 3 (10µg/m^3 - 1µg/m^3), he adds.

"The responsibility for containment rests with the CDMO since they are responsible for the safety of their employees. Having environmental, health, and safety (EHS) best practices with an excellent chemical hygiene program, which includes a potent compound handling policy that has been vetted through testing of the engineering controls and procedures, is paramount to ensuring NCEs are handled safely regardless of whether the potency levels have been established," Ammoscato asserts.

There is the additional challenge, however, of the tendency by chemists and operators to make "dread"-based decisions on handling and how to respond to incidents, according to Edwards. "This type of response is really not necessary if the appropriate risk assessment is performed," he notes.

Managing NCEs

The most common strategy when a CDMO is presented with a project involving an NCE, according to Edwards, is to initially ask the drug sponsor for available data, as this information should be available because the results—probably *in vitro*—have led them to move forward in the development of a NCE.

The general approach to risk assessment is reasonably well-standardized, but the way the results are displayed varies greatly because the application of uncertainty factors differs depending on the individual risk assessor.

"In instances where the OEL of the molecule is unknown, there is no one common strategy for NCEs, but most CDMOs use some form of standard operation procedure," Edwards says. "For either an NCE or synthetic intermediate, qualitative, or quantitative structure activity- and reactivity assessment-related data coupled with read-across and *in-vitro* data are used at Cambrex. These data are all important and come from many sources. The amount of data available depends on novelty of the pharmacophore," he explains. Cambrex also calculates an OEL even when the sponsor has provided one.

Ramesh from Piramal adds that firms may use substructure- or chemotype-based OEL estimations that include consideration of the therapeutic class for guidance. "One approach involves comparison of the API's properties to those of similar substances with known toxicities and assumption of a similar level of risk," he notes. Some CDMOs have in-house categorization systems for determining the required safety measures.

"Regardless of the method, if there is any uncertainty, it is best to assume a compound is potent, despite the potential higher costs incurred," Ammoscato states. "Frequent communication between the sponsor and the CDMO is then essential to ensure that necessary data can be generated and an appropriate decision on the potency of the compound be reached as early as possible," he adds. The CDMO should also be prepared to respond as needed if additional toxicity data are developed indicating that reclassification is warranted. Furthermore, CDMOs should perform additional risk assessments as an HPAPI project moves through different stages of development and commercialization to ensure the implementation of optimal procedures and practices that both protect operators and the environment but are also practical and cost effective, according to Ammoscato.

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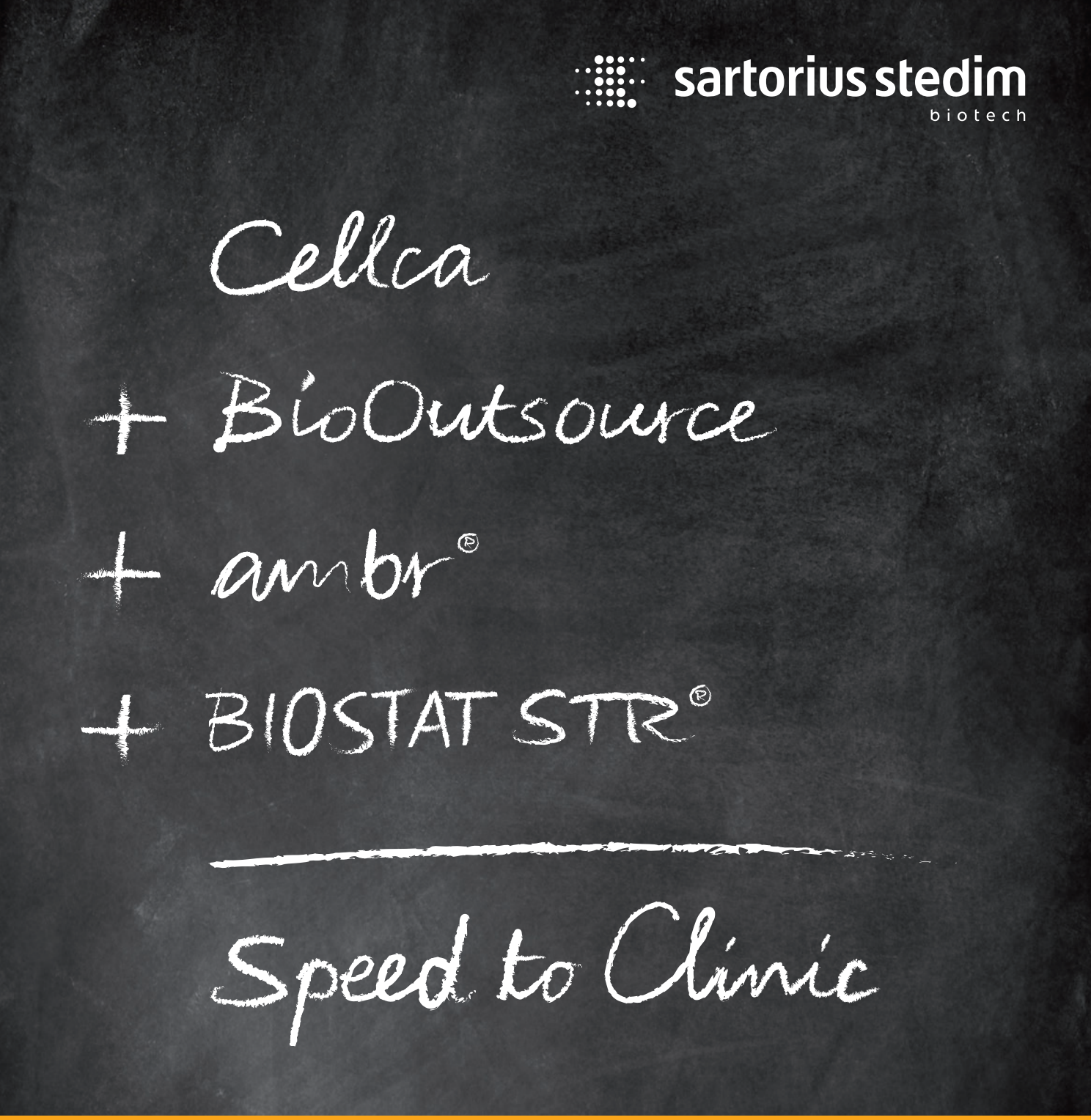

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Kevin J. Wrigley

Choosing between presterilized and bulk sterilized prefilled syringes.

Increased competition among leading brands of injectable drugs, in particular, complex biologics, are driving the need for innovative delivery options and other advantages that can support product differentiation. Such a difference in drug-delivery systems can also act as a valuable lifecycle management strategy, helping bio/pharmaceutical companies succeed in an increasingly competitive environment. While vials remain the established and proven drug-delivery system and continue to dominate the market, prefilled syringes are on the rise. In fact, it is estimated that the market for prefilled syringes will double in size within the next decade (1).

The prefilled syringe market is driven by the rapid growth in innovative and targeted molecular entities such as monoclonal antibodies (mAbs), interferons, peptides, vaccines, and ophthalmics, for which prefilled syringes are a suitable drug-delivery system. Additionally, the rising levels of chronic diseases and cancers have led to a significant increase in the use of injectable drugs. Adding to these key drivers is the substantial growth in biosimilars, which are estimated to reach $55 billion in global sales by 2020, versus $20 billion in 2015 (2).

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Exploring the advantages of prefilled syringes

The global prefilled syringe market is also growing due to the need for a greater degree of safety and ease of administration for patients and healthcare workers. Prefilled syringes are easy to use and only have a few administrative steps, which can improve safety by reducing the potential for contamination, needle stick injuries, and dosing errors. These attributes can also improve patient compliance and dose consistency. The wider adoption of integrated prefilled syringes featuring advanced innovative, single-unit dose delivery systems such as autoinjectors results in less waste of valuable API, lower risk of dosing errors, and lower risk of misuse of leftover product. Prefilled syringes can also attract higher drug reimbursement from payers and increase the value of a product early in its lifecycle by providing a competitive edge. Finally, prefilled syringes can increase the attractiveness of a product to out-licensing partners and improve clinical trial validity and appeal.

Sensitive biologics require the right delivery system

Complex biological-based compounds such as mAbs require special consideration during formulation for a prefilled syringe presentation. For example, compatibility is often a hurdle due to the number of additional components in a prefilled system, such as stoppers or closure systems, and the need to maintain the functionality as well as the shelf life of the product. Tungsten, silicone oil, and adhesives used to secure the needle in the glass barrel can potentially react with sensitive drug products and result in unexpected impurities.

When choosing the right drug-delivery system, specific product characteristics must also be taken into account. These include:

- Is the product liquid or lyophilized?
- What are the therapy requirements?
- Is the therapy self-administered?
- What is the duration of therapy?
- What is the nature of the market (i.e., product lifecycle, cost, competition, etc.)?

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Figure 1: Example of a presterilized syringe filling process.

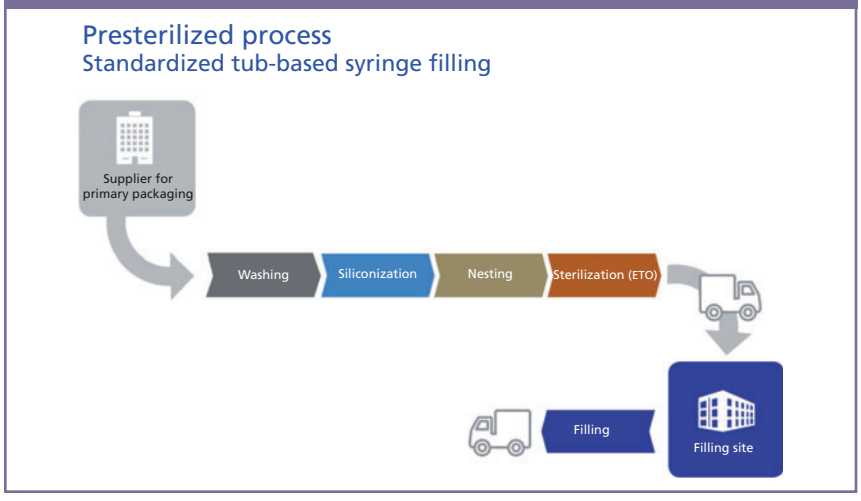
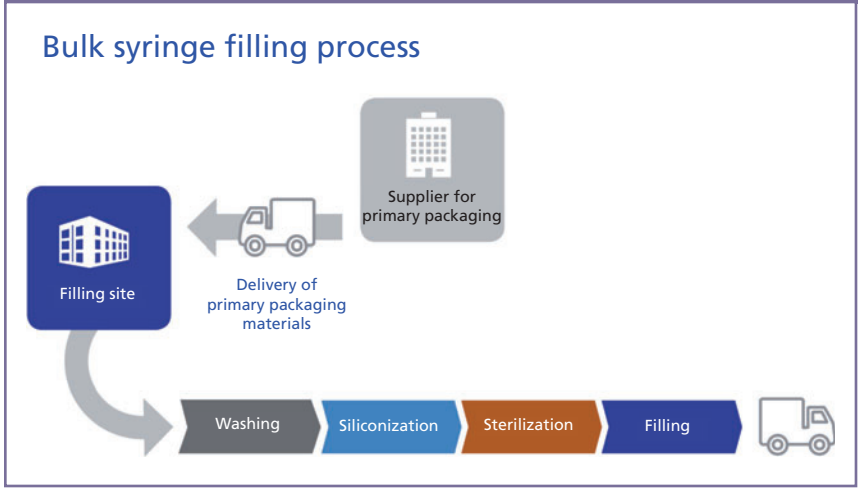


Figure 2: Example of a bulk syringe filling process.



The choice between presterilized or bulk platform

Particularly for sensitive biologics or complex compounds with high product specifications, choosing the right syringe platform technology is of great importance. There are two prefilled syringe platforms available in the market: presterilized and bulk syringes. Knowing which one is the right choice for a compound is usually determined by the specific characteristics of the compound itself.

Presterilized syringes are tub-based, ready-to-use systems and are ideal for a broad range of drug products. The washing, siliconization, nesting, and sterilization take place at the supplier for the primary packaging while filling occurs at the filling site (see **Figure 1**).

When working with sensitive biologics, customization is often desired. Bulk syringes are, therefore, a good option for complex compounds such as mAbs, peptides, interferons, vaccines, or opthalmics. As opposed to presterilized syringes, the pre-treatment steps of washing, siliconization, and sterilization take place at the filling site in a fully integrated, customizable inline-process (see **Figure 2**). This setup results in maximum control of the process and flexible primary packaging material combinations.

The tighter specifications of the bulk process also help reduce particle levels. Silicone levels can be adjusted to meet product requirements and different methods of sterilization can be offered. The flexibility also increases dosing and fill-volume accuracy for small volumes. A full range of readily available bulk syringe formats allow for numerous customizable options.

A case study of dealing with a complex compound

The following case study is an example of how the many challenges of sensitive biologics can be overcome and incorporated into a development program utilizing prefilled syringes.

Recently, a contract development and manufacturing organization (CDMO) was approached to support a bio/pharmaceutical company in developing a specific filling process for a complex mAb compound in a bulk syringe. The main project requirements were:

- Very low filling volume as the product is injected directly into the eye
- High requirements from regulatory authorities to reduce the silicone level to a minimum
- Requirement for a gas-tight system to enable an external sterilization process of the filled syringe.

The compound presented several challenges in achieving these requirements. To reduce the silicone levels of the glass barrels and stoppers, the CDMO employed a static siliconization and customized a bulk, baked-in siliconization process. Static siliconization offers a high amount of precision with the ability to adjust silicone levels. During the siliconization process, there is no contact between the silicone nozzle and the glass barrel, which is an important criteria for some specific indication areas such as ophthalmic medications. Baked-in siliconization is the process of the siliconized syringe undergoing dry heat sterilization. Due to the high temperature, the silicone oil is baked into the syringe, thereby minimizing the risk of loose silicone oil droplets coming into contact with the drug substance. In addition, non-siliconized equipment was used so that the lowest possible amount of silicone oil was used in the process for the siliconization of the packaging materials.

FIGURES ARE COURTESY OF VETTER PHARMA INTERNATIONAL GMBH.

Because the requested product is of high value and concentration, it was necessary to evaluate the liquid pathway to minimize line losses. Thus, ideal positions for the filling components, such as the fill tank or the filter, were defined. To minimize particle levels in the filling process, it was also important to check the support system. Tighter specifications on particle levels for Tyvek bags used for stoppers and other equipment were defined. In addition, abrasion was minimized in the stoppering and static washing processes of the glass barrels.

Achieving outside sterility for use in an operation theatre was overcome through the use of a syringe with a tamper-evident closure system (e.g., V-OVS from Vetter) with reduced gas permeability and higher system tightness, avoiding reaction between the product and the ethylene oxide (ETO) gas during outside sterilization. Finally, the gas-tight rubber components in the closure part made an outer sterilization of the syringe with ETO possible.

During the assembly process, specifications were developed for precise backstop placement with 100% camera control, which avoided incorrect movement of the stopper in the non-sterile area during sterilization. Also, intensive investigation around reproducibility of the stopper position, in-process control (IPC) of filled syringes instead of empty syringes, and 100% camera control at the customer helped to overcome this challenge.

In this particular case, the specific and highly complex compound required a high degree of flexibility and customization, such as a minimum level of silicone in combination with baked-in siliconization. Thus, its requirements were fulfilled by using the bulk process.

Bulk and prefilled syringes offer innovation and value

Prefilled syringes platforms—both presterilized and bulk—offer innovative delivery options and value in sensitive biologics drug development programs. They also have distinct advantages in helping support product differentiation and lifecycle management strategies. The nature of the compound will often drive the choice, but knowing how the two platforms differ will be essential in choosing the right syringe system for the individual drug product.

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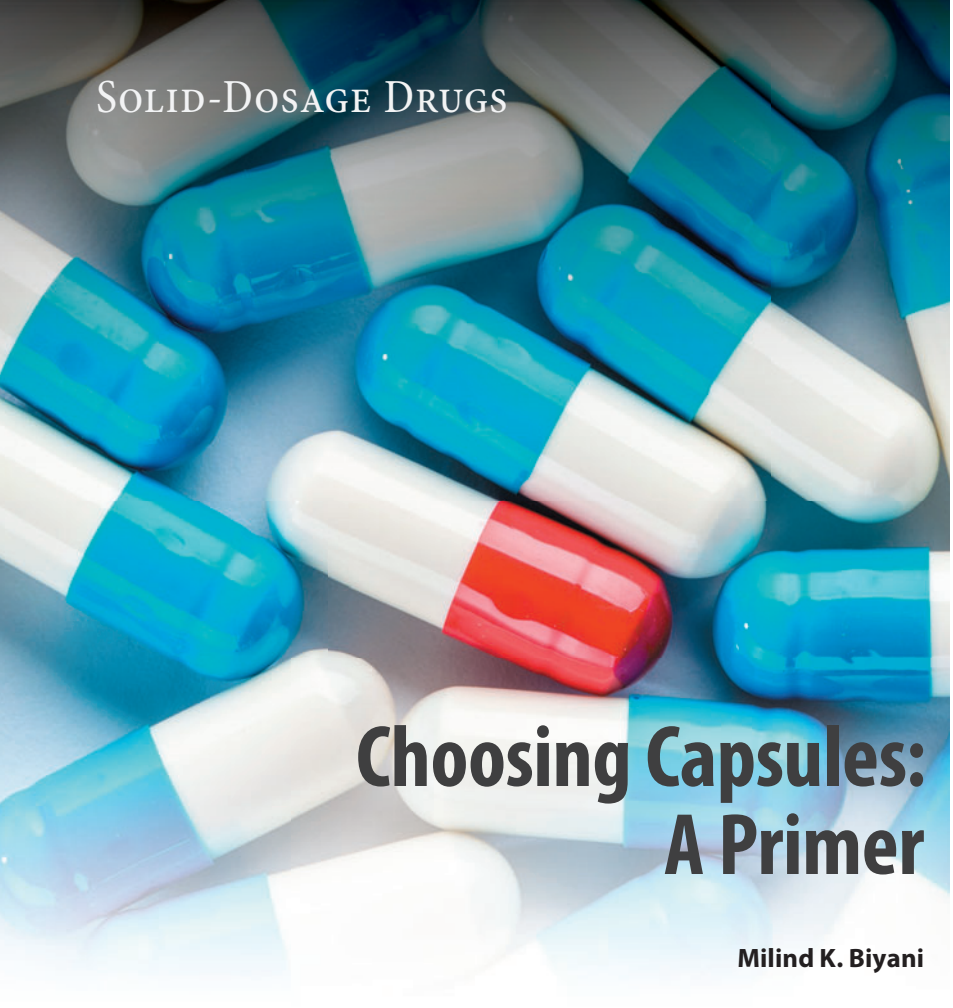

Choosing Capsules: A Primer

Milind K. Biyani

Capsules offer certain benefits over tablets for oral-solid dosage drugs, and several types of capsules are available.

Oral-solid dosage (OSD) drugs can be formulated in tablet or capsule form. Some drugs are available only as capsules or tablets, and some are available as both. Various types of capsules, with shells made of different materials, are available. When choosing a capsule type, formulators should consider factors such as the shell's barrier to water and oxygen, reactivity, and the material it is made of.

Selecting a capsule type

The most widely used capsules can be classified as shown in **Figure 1** and discussed in the following sections. Dry-filled capsules include mainly hard gelatin and hard hydroxypropyl methylcellulose or hypromellose (HPMC) capsules. Liquid-filled capsules include hard capsules (gelatin or HPMC) and softgel gelatin capsules.

Hard gelatin capsules. The gelatin used in the manufacture of most common capsules is obtained from collagenous material by hydrolysis. Gelatin is a natural, safe, non-allergenic, clean, and economical ingredient. The two-piece hard gelatin capsule is available in a range of sizes; from largest to smallest, these sizes are 000, 00el, 00, 0xel, 0el+, 0el, 0, 1el, 1, 2, 3, 4, 5.

The larges size (000) is mainly used in veterinary practice. Fill weights increase with the size of the capsule as well as with the bulk density of the filled material, which can range from 0.3–1.5 g/cc. Fill weights in the smallest capsules might be 39 mg, for example; the largest may weigh 1425 mg.

The shell of hard gelatin capsules contain 13–16% water. Storage of hard-gelatin capsules at very low humidity can cause them to turn brittle. Gelatin capsules do not protect hygroscopic materials from atmospheric water vapor because moisture can diffuse through the gelatin wall. If stored at high humidity, the capsules become flaccid. In such cases, primary packaging material such as aluminum strip packing, moisture barrier blister foil (e.g., Aclar), or bottle packs should be used.

HPMC capsules. HPMC capsules are stable at low humidity levels, have low moisture content (3–8%), and low static charge. These natural capsules are available from size 00 to 4. HPMC capsules are suitable for highly reactive molecules (because they have no cross-linking reactions). Compared to hard gelatin, HPMC is more suitable for moisture-sensitive products, hygroscopic products, and for low relative-humidity applications. HPMC is not of animal origin and does not pose a risk of contamination with organisms that cause bovine spongiform encephalopathy (BSE) or transmissible spongiform encephalopathy (TSE). HPMC capsules are used in a wide range of OSD pharmaceuticals as well as nutraceuticals, dietary supplements, and herbal products, due to the vegetarian nature of HPMC.

Fish gelatin capsules. Marinecaps are made from fish gelatin and do not pose risk of BSE or TSE. They are preferred for filling marine supplements such as EPA [eicosapentaenoic acid]-rich fish oil.

Starch capsules. Starch capsules are made from potato starch. Their dissolution is pH independent, and they are suitable for enteric coating. The moisture content of starch capsules ranges between 12–14% w/w, with more than 30% being tightly bound (1).

Pullulan capsules. These vegetarian capsules are made from tapioca, which is naturally fermented into pullulan. They provide a high barrier to oxygen.

Polyvinl acetate (PVA) capsules. Capsules made from PVA can be used for filling insoluble drugs dissolved in

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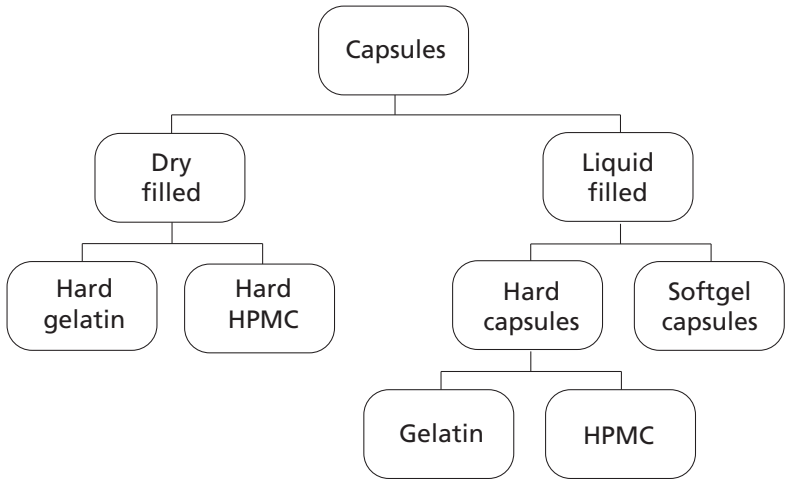
Figure 1: Classification of major capsule types.



polyethylene glycol (PEG) 400. PEG 400 when used as single vehicle is not compatible with other hard capsules. The oxygen permeability of PVA is low, resulting in a high barrier to oxygen.

Liquid-filled hard capsules (LFHC). Two-piece hard capsules made of either gelatin or HPMC can be used for filling and band sealing non-aqueous liquid, paste, suspension, hot melts, and other vehicles that melt up to 70 °C and flow easily. LFHC can also be filled with tablets, pellets, or other capsules as combination fill. LFHC can be used for moisture-sensitive drugs. These can be a cost-effective alternative to some soft gelatin capsule products and can also enhance bioavailability and improve product stability. Liquid encapsulation technology helps overcome many problems associated with the use of softgel capsules including high cost, waste, cross-contamination, migration of the drug into the capsule shell, and issues with low bioavailability. Liquid-filled and semi-solid capsules by their nature are resistant to crushing and powdering and therefore provide a good basis for developing an abuse-resistant formulation. These capsules can also be enteric coated. HPMC hard capsules do not become brittle when they lose water (2).

Soft gelatin capsules (SGC). SGC have soft, globular, gelatin shells somewhat thicker than that of hard gelatin capsules. The gelation is plasticized by the addition of glycerin, sorbitol, or a similar polyol. It may contain preservative to prevent the fungal growth. Large-scale production methods are generally required for the preparation of SGC.

Benefits of capsules as a dosage form

Consumer preference. The growing interest in capsules as a formulation is consumer driven. Consumers prefer capsules because they are tasteless, odorless, and easier to swallow. Capsules are also considered to work faster and better. In a study conducted by Burke Marketing Research, 1000 patients were asked about the form of drug administration they preferred, and more than half (54%) chose capsules (3). Another study, conducted with several hundred patients in two hospitals in Copenhagen and published in 2001, found that 66% preferred capsules (3). This preference has prompted pharmaceutical manufacturers to market products in capsule form even if the product already has been produced in tablet form.

Rapid dissolution. Most filled capsules disintegrate in 5–10 minutes. Some of the immediate release tablets may have much lower disintegration time. Once a capsule disintegrates, however, dissolution may be faster and dissolution levels achieved may be similar to tablets at 15 minutes. HPMC capsule shells can lead to rapid dissolution. However, these differences will not necessarily produce considerable alterations in the pharmacokinetic profiles of the drug product because the f2 value used to determine dissolution differences is often too discriminating, particularly when the dissolution is very fast relative to permeation and/or absorption is very fast relative to disposition (4).

Formulation development. Capsules are easier and faster to develop and manufacture in comparison to other OSD forms because the capsule manufacturing process involves fewer steps and a lower number and quantity of excipients. For example, as per studies conducted by Aspire Advisors, Acetazolamide 250 mg tablet weight is 516 mg but Acetazolamide ER 250 mg capsule fill weight is only 328 mg. Some coarse, free-flowing, Biopharmaceutical Classification System Class I drugs can be filled directly into capsules. Capsules can also be used for poorly compressible drugs.

Capsules provide relatively better stability than other OSD forms. Encapsulation does not create high heat and pressure, thus heat-sensitive drugs can be more readily formulated as capsules. Capsule walls can be made opaque, providing protection for light-sensitive compounds. Sealed hard gelatin caps can be good oxygen barriers. As capsules generally require fewer excipients, drugs that are sensitive to or highly reactive with other chemicals may be more readily formulated as capsules.

Further, due to fewer processing steps, capsules can minimize human exposure to potent drugs. Capsules reduce airborne dust levels, lowering the risk of cross-contamination and offer improved content uniformity particularly at low dosage levels and for potent drugs. Overall, they reduce the capital requirements for dedicated facilities, air-handling, and process equipment.

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Formulation flexibility. Encapsulation technology has made progress in recent years. For example, soft gelatin capsules and LFHC are increasingly being used for filling and/or sealing (band sealing in case of LFHC) of liquid and pastes. Furthermore, a single capsule can now encapsulate not only powders or granules, but also one or more ingredients that are in liquid, pellet, tablet, or another capsule form. Incompatible ingredients can thus be combined into a single capsule, which helps to develop combination products.

Enteric coating of hard capsules or use of enteric hard capsules further expands the scope of capsules usage (5). In addition, capsules can be used for active ingredients that need modified release. Modified-release capsules can now be developed that disperse freely in the gastrointestinal tract, providing more uniform distribution of drug into the bloodstream. These capsules help to maximize absorption and minimize side effects. They also reduce inter- and intra-patient variability. Calcifediol and oxycodone extended release (ER) capsules are two examples of ER capsules approved in 2016 as new drug applications.

Dissolving the active ingredient in a mixture of liquids, semi-solids, or hot-melts can result in better solubility and higher absorption. For example, isotretinoin solubilized in sorbitanmonooleate, soybean oil, and stearoylpolyoxylglycerides filled in hard capsules (marketed as Absorica in the United States) gave higher absorption in fasted state than the original softgel product Roccutane/Accutane (6). Those drugs

Is Your Tablet Hard to Swallow? Guidance Addresses Drug Tablet Design

Patients prefer tablet dosage forms because they look familiar, and tablets are usually coated, making them easy to recognize and simple to take. The disconcerting news, however, is that in a survey of US adults, 4 in 10 reported difficulty in swallowing tablets, negatively affecting patient compliance. Of those 40% with difficulties, 14% delayed taking a dose, 8% skipped a dose, and 4% discontinued the medication altogether (1). Data like these have not escaped the attention of major regulatory agencies, including FDA and the European Medicines Agency (EMA).

Within the past three years, FDA issued two separate guidance documents that encourage drug formulators to design drug products with patient compliance and the reduction of medication errors in mind (2, 3). Commonly referred to in the United States as "safety by design" (SbD), the concepts outlined by FDA reference tablets that should be of an appropriate size, shape, and coating to enhance swallowability and palatability of the drug.

In a guidance document, FDA noted that "coating can potentially affect the ease of swallowing tablets or capsules. The lack of a film coating can decrease or prevent tablet mobility compared with a coated tablet of the same size and shape" (2). Logic dictates that if a dosage has the potential to be a choking hazard, then coating should be considered to aid the patient's ability to swallow and avoid the risk of the patient not taking their medication. This guidance from FDA was applicable to all new drug applications (NDAs) as well as abbreviated new drug applications (ANDA) and over-the-counter monograph drugs.

FDA suggested that generic-drug manufacturers should also ensure that the design of a generic version should not hinder patient compliance. Manufacturers should "consider the size, coating, and palatability of oral products. A drug product can become a choking hazard due to the size of the tablet or capsule. If the tablet or capsule coating is too sticky, it can become lodged in the patient's throat or gastrointestinal tract" (3). The guidance also recommends more attention to dosage shape and size, encouraging manufacturers to reduce cross-sectional areas of larger tablets to improve swallowing. The guidance concludes that "tablet coating, weight, surface area, disintegration time, palatability, and propensity for swelling should also be considered when designing oral products to avoid medication errors related to swallowability and patient compliance" (3).

Patient safety concerns are also being addressed by European regulators. In November 2015, EMA issued a comprehensive guide on minimizing risk for patients, which lists concerns for elderly patients who "may face physical and cognitive impairment, and hence, they may have difficulties in taking their medicines (e.g., swallowing tablets, opening packaging, or reading their user instruction and package leaflet). The pharmaceutical development of medicines for use by older patients should take such aspects into consideration" (4).

Focus on the elderly population continues to be addressed with a reflection paper issued by EMA in 2017 on pharmaceutical development of medicines for use in the older population, especially to address tablet mobility (5). This paper discusses the particular problems that elderly populations face and cites that "elderly patients are more likely to experience conditions which lead to impaired swallowing, such as stroke or Parkinson's disease. This can lead to accidental under dosing, which can be managed appropriately by the development and use of formulations which are easier for such patients to swallow" (5).

Tablets are now being presented as specialized dosage forms: medicines that deliver complex treatments including drug combinations, layered tablets, and modified release forms, for which it is even more important that the patient follows an exact dosing regimen. However, many of these newer dosage forms are presented as larger tablets, which reduces the frequency of dosing but may present issues with swallowing and tablet mobility. The importance of good tablet design to address patient acceptability and compliance is paramount, and addressing this need will help to satisfy regulatory concerns also. The fact that regulators and industry are now actively addressing this topic is good news for patients and caregivers.

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—Rita M. Steffenino, manager, Brand Enhancement and Marketing Programs at Colorcon.

that cannot be solubilized in this manner may be formulated as a self-emulsifying drug delivery system.

Capsules are also useful for clinical trials. Specialized capsules for clinical trials are unique two-piece gelatin capsules that are specially designed to carry out double-blind studies during clinical trials. After closure (locking), the elongated cap closes tightly on the body. Once locked, only the dome of the body is visible, making it almost impossible to open the capsule.

Capsules can be developed faster than tablets for new chemical entities. Because Phase I and II clinical trials are mostly carried out using capsules, additional bioequivalence/bioavailability studies are needed when converting from capsules to tablets. Moving a product to market one year faster can give one year more effective patent life. Similarly, other types of innovations and FDA applications, such as abbreviated new drug applications, can be marketed faster.

Anti-counterfeiting. Capsule manufacturing companies have developed a unique technology that enables capsules to be printed in multiple colors, which creates brand differentiation and serves as an effective anticounterfeit measure. Further, it is now possible to imprint brand logo, brand name, and graphics on the capsule, providing further brand identity (7).

Conclusion

In summary, capsules are an attractive OSD form that enjoys patient preference, improved pharmacokinetic profile, faster development, and formulation flexibility. In addition, capsule formulations offer brand recognition in a crowded pharmaceutical market. Switching to capsules from other OSD forms also gives manufacturers an excellent opportunity to get out of the competitive environment of generics while still enjoying a development process that eliminates most preclinical studies as well as extensive safety and efficacy tests.

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Testing and Simulation Approaches for Single-Use Bioreactor Scale-up

Paul Kubera

Tools aid scale-up and comparison of single-use and stainless-steel bioreactors.

Scale-up (and down) modeling of bioreactors is a valuable tool to support process characterization and improvement in a predictable, timely, and cost-effective manner. The emergence of a variety of geometrically dissimilar single-use bioreactor platforms provides users with both challenges and opportunities as they look to incorporate this technology across the range of scale from bench-top through production. In the ideal case, geometrically-scaled, single-use models of existing production equipment would be available to provide accelerated process development over a range of organisms, media formulations, and operating conditions. More often, one is faced with aligning the performance of what may be different hardware designs at the bench, pilot, and production scales.

A combination of approaches can be used to reduce risk and ensure predictable performance as processes are transferred across hardware platforms and scale. Simple calculations, model experiments, and simulations complement each other to characterize equipment capability and define operating conditions that will deliver desired results independent of platform and scale.

A primary objective for cell culture and bacterial processes is to provide a consistent and uniform environment across scales. Calculation of energy dissipation, shear rate, blend-time, and mass transfer (e.g., of oxygen and carbon dioxide) at small and large scale can be used to assess how critical parameters change with scale (because it is impossible to hold all parameters constant) and how these critical parameters can be managed by changing other design variables (e.g., hardware configuration). Spreadsheet-based analysis readily extends the range of options that can be examined to achieve an optimal solution.

Performance aspects such as oxygen transfer can be highly dependent upon the configuration of what is often a proprietary hardware design. Small-scale model tests can be used to generate baseline data when at-scale performance correlations are not available. These test results can be used to generate hardware-specific correlations and to evaluate the relative performance of different approaches. Different single-use platforms will have different strengths—having relative information available allows one to best match performance to process requirements.

While a mixing-dependent parameter (e.g., oxygen transfer) may be relatively independent of scale, blend-time (i.e., the time to achieve batch uniformity) is sensitive to both hardware selection and scale. Most bioreactor scale-up is based on hardware geometric similarity and equal energy dissipation to drive equal volumetric mass transfer; this approach is straightforward but it guarantees that blend-time will increase as the batch volume increases. For processes where uniformity is a critical parameter, model-scale tests can be used together with computational simulation to quantify and manage blend-time.

Simple small-scale blend-time tests can be conducted using either visual or instrumentation-based techniques to establish performance correlations; multiple hardware configurations can be assessed in a short period of time to evaluate both configuration and operating condition options. Computational fluid dynamics (CFD) can be employed to model the flow pattern and simulate blend-time for preferred configurations. Presuming that there is good agreement between the small-scale CFD simulation and experimental results, simulation can then be used with confidence to model expected performance at full-scale.

Depending upon need, one or more of the above tools can be employed to address scale-up and hardware platform transfer concerns. As an example, in a case where three different single-use platforms, all at

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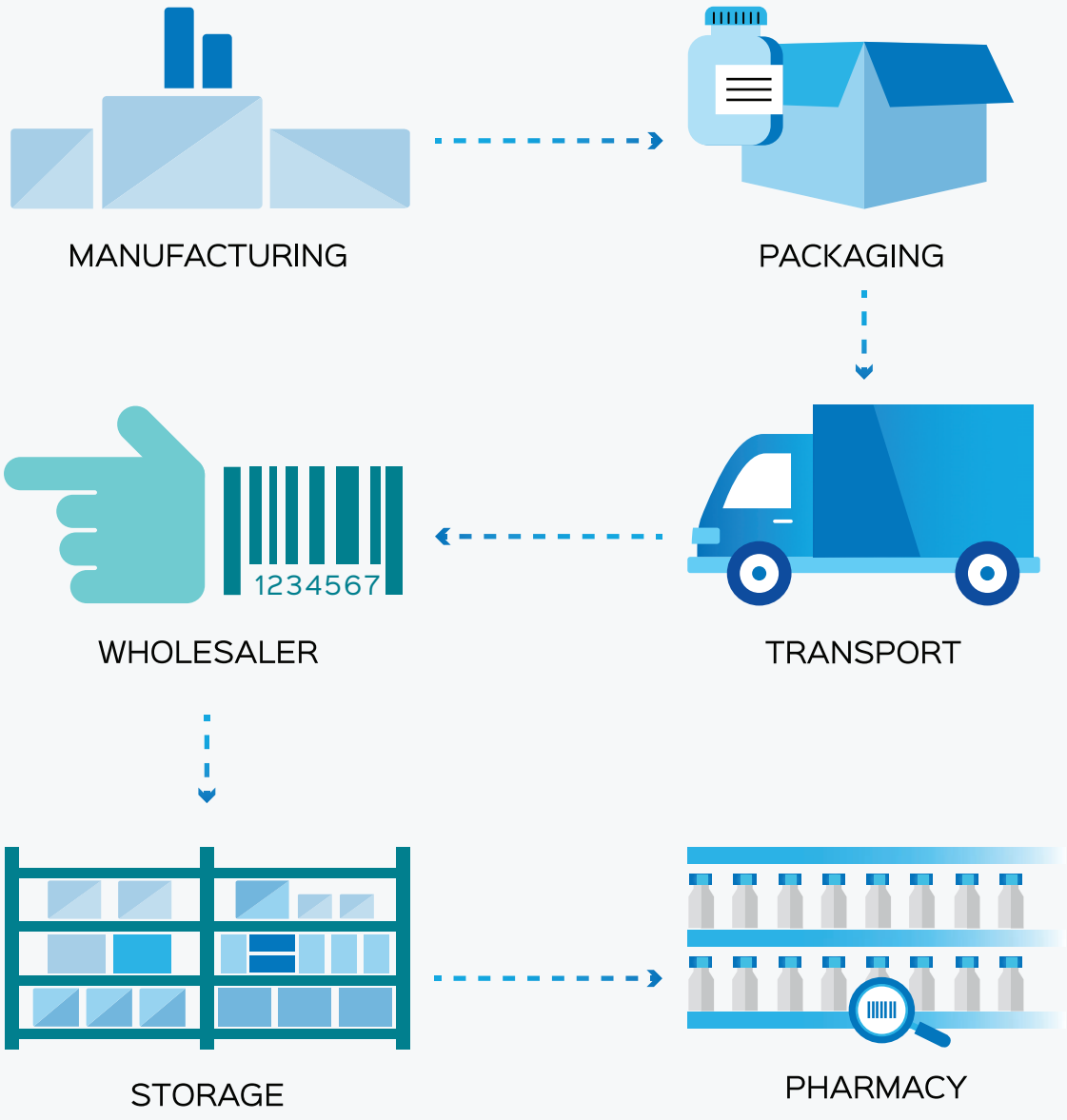

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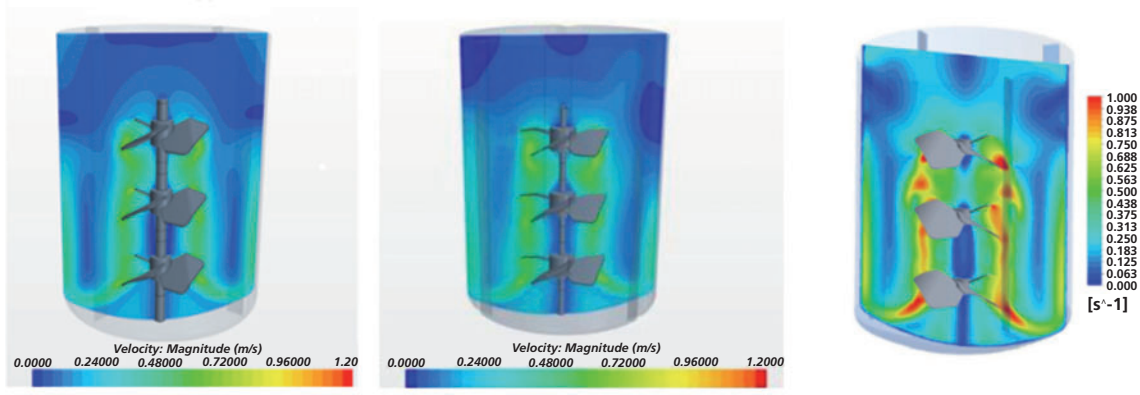
Figure 1: Computational fluid dynamics velocity contours for a laboratory-scale single-use and production-scale single-use and alloy bioreactors compare flow structures; CSR is Custom Single Run (ABEC).



(a) 50%-scale Lab CSR model *(b) Development-scale CSR Bioreactor* *(c) 10x-scale Alloy Bioreactor*

Table I: Parameter comparison: geometrically-scaled bioreactors at equal power per volume (P/V); CSR is Custom Single Run (ABEC) single-use bioreactor.

Parameter	Lab CSR model	Development CSR	Production
Construction	Single-use	Single-use	Alloy
Volume, relative	50%	100%	12.5x
Tank diameter, normalized	0.80	1.00	2.36
Agitator operating speed, rpm	124	109	60
Lower, middle, upper impeller types	HyFoil-4W	HyFoil-4W	A315
Agitator power per volume, W/m^3	62.7	61.9	62.6
Blend time, s	7.8	9.6	15.0
Impeller tip velocity, m/s	1.32	1.45	1.92
Maximum shear rate, s^{-1}	9.9	10.9	14.4
Air sparge, VVM	0.008	0.008	0.008
Gas superficial velocity, mid-depth, m/hr	0.32	0.41	0.81
Oxygen mass transfer coefficient, hr^{-1}	0.76	1.46	2.41 - 1.86
Oxygen transfer rate, mmol O_2/L-hr	0.107	0.223	0.425 - 0.324

different scales, were being evaluated for large-scale production, at-scale characterization experiments were run to establish performance correlations and CFD simulation (validated at small-scale) and desktop calculations were used to project expected performance at large scale.

Case study: comparing a small-scale single-use bioreactor with a large-scale stainless-steel bioreactor

As another example, a multi-pronged approach can also be used to (i) demonstrate equivalent performance between traditional alloy and proposed single-use equipment, (ii) validate CFD simulation, and (iii) extend performance projections to intermediate and full-scale equipment. In this case, a single-use bioreactor with hydrofoil impellers (ABEC Custom Single Run [CSR]) was proposed as a development platform for an existing stainless-steel production bioreactor that was more than 10 times the size of the CSR and was equipped with a proprietary agitator design.

Laboratory tests at 50% of the development-scale were conducted using two different impeller geometries to compare blend-time for the single-use configuration with the stainless-steel alloy configuration. The laboratory data were also used to validate the results of CFD blend-time simulation of the lab-scale CSR single-use geometry (see **Figure 1a**), allowing use of CFD to project performance of the proposed development-scale (**Figure 1b**) and existing full-scale (**Figure 1c**) platforms. The velocity contours in the three plots shown in **Figure 1** illustrate the near identical flow structures across the range of scale for the alloy impeller and its single-use counterpart.

Key bioreactor performance indicators (e.g., blend-time, oxygen mass transfer coefficient, and oxygen mass

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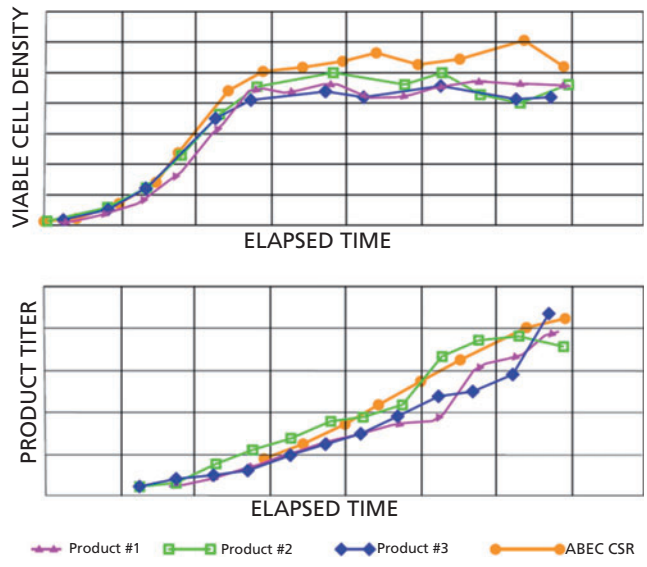
Figure 2: Process performance for development-scale single-use (ABEC CSR) vs. a production-scale alloy bioreactor (products 1, 2, and 3).



transfer rate [OTR]) can be measured in the laboratory and the resulting correlations used to predict performance at development and full-scale. A spreadsheet application (see **Table I**) allows for ease of comparison across scale and platform type for these parameters and others that may impact cell growth and product yield, such as energy dissipation, shear rate, and others.

Equal power per volume (P/V) is a commonly applied approach for bioreactor scale-up because it provides equal volumetric oxygen transfer and thus equivalent cell growth/mass. When equal P/V is used together with geometric similarity, **Table I** illustrates that most other parameters will change; the key is to establish which ones may have a positive or negative impact on product yield and then manage them accordingly. For example, if experience indicates an improved product yield at lower shear rate or shorter blend time, one can change impeller selection and operating speed with scale to achieve the desired result while maintaining P/V and OTR. Because the mass transfer coefficient is a function of both agitator energy input and gas velocity, this side-by-side comparison shows that air sparge rate must be increased as scale decreases to achieve the equal OTR.

Oxygen transfer was identified as the controlling element for the production bioreactor in this example; other parameters (e.g., shear rate, blend-time) were reviewed to ensure that they did not exhibit order-of-magnitude change with scale-up. The volumetric OTR for the alloy production unit was calculated using correlations for similar-style equipment; operating set-points for agitator speed and air sparge rate to achieve the same OTR were proposed for the development-scale single-use bioreactor based on measured performance. Plots of cell density and product titer versus time for a typical single-use development-scale run are presented in **Figure 2**, along with similar information for runs in the production-scale bioreactor.

Cell mass and product titer for the development-scale single-use bioreactor track closely with historic values for the alloy production-scale unit. The ability to effectively characterize and compare the performance of the different platforms and scales before initiating a development or production campaign serves to reduce at-scale experimentation, saving both cost and time. **PT**

How to Monitor HPMC Concentration Through Conductivity Measurement

Anastasiya Zakhvatayeva, Pietro Pirera, Alessandro Resta, Maria Grazia De Angelis, and Carlo De Carolis

Hydroalcoholic solutions of hydroxypropyl methylcellulose (HPMC) can be used in place of gelatin solutions to seal pharmaceutical capsules. The control of HPMC concentration is essential to ensure a complete, uniform, and stable capsule seal. Sealing solution concentration is usually monitored by measuring the solution viscosity through a viscometer. HPMC solutions, however, are pseudoplastic rather than Newtonian fluids, thus their viscosity depends not only on the solution concentration, but also on the shear rate applied during stirring and/or transfer of solution from one container to another. The authors demonstrate that a proper measure of HPMC solution concentration is its electrical conductivity rather than its viscosity. The correlation between concentration and conductivity was tested in the concentration range 12–25% and a mathematical expression was proposed for it. This correlation allows one to control and adjust the solution water/alcohol ratio using a conductivity measurement.

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Capsule sealing is primarily intended to avoid counterfeiting. A sealed capsule can be opened only by breaking it in two parts; therefore, it is impossible to replace its content without compromising the capsule integrity.

Capsule sealing is performed by applying a solution of gelatin or hydroxypropyl methylcellulose (HPMC) (Pharmacoat 603, Shin-Etsu Chemical) on the junction between the capsule body and cap. While sealing with gelatin solution has been used successfully for years, sealing with HPMC is relatively new.

HPMC capsules have the following advantages compared to gelatin capsules:

- Lower and stable amount of moisture
- Higher reproducibility of the manufacturing process
- Better customer acceptability: gelatin is of animal origin while HPMC is obtained from vegetables
- Improved release profile of some APIs.

An important part of capsule sealing is to maintain a constant concentration, and therefore viscosity, of the solution to be applied on the capsules. In the case of gelatin, the concentration is monitored with a viscometer. Evaporation of water from the solution (which is heated to 40 °C) causes a linear increase of the viscosity. When this happens, more water is dropped in the tank with the solution to bring the viscosity back into the target range.

In case of HPMC, the solution is not aqueous but hydroalcoholic. The viscosity of HPMC solution depends not only on its concentration, but also on the mechanical stress to which it is subjected. HPMC solutions are pseudoplastic, meaning that their viscosity decreases with increasing shear rate, as opposed to the Newtonian fluids (e.g., gelatin solutions), which maintain constant viscosity with the shear rate. The HPMC solution behaves differently under different forces (such as stirring or simply transferring it from one container to another).

In a commercial sealing machine, the banding solution is recirculated from the solution vessel to the sealing baths where the capsules are sealed. One problem is that stratification of the solution results in imprecision and irreproducibility of viscosity measurements used for concentration control. Trying to reduce stratification by stirring the product causes vibration that creates error in viscometer measurement.

Because the results obtained with the viscometer were not reproducible, it was decided to control the concentration by measuring the electrical conductivity of the solution, supposing the HPMC is charged; therefore, the higher the concentration, the higher the conductivity.

Method description

This idea was tested by measuring the conductivity of HPMC solution, starting from 25% concentration and by diluting it with solvent until lower concentrations of 12%. This method is off line and time consuming, but it was useful to understand whether there was correlation between conductivity and concentration. In addition to the laboratory tests, the authors evaluated how the conductivity and viscosity varied with concentration using a Hermetica sealing machine in the field.

Conductivity proved to be more related to the concentration than was viscosity, which had much higher range of variation. The conductivity values were between 440 and 520 microSiemens/cm.

The authors defined a linear equation to describe the relation between the concentration and the conductivity: y(concentration%) = mx(conductivity)+q.

Materials

The following materials were used:

- HPMC (Pharmacoat 603, Shin-Etsu Chemical) (see **Figure 1**)
- Ethanol 95%
- Demineralized water.

Instruments and machines

The following instruments and machines were used:

- Capsule banding machine (Hermetica 100, IMA)
- Heated vessel of 30 L to hold the solution
- Conductivity meter (COND 7, XS Instruments)
- Viscometer (Sofast BV, Sofraser)
- Viscometer (MIVI 9600, Sofraser)
- Thermal moisture analyzer (HB43-S, Mettler Toledo).

Laboratory tests

A total of 28 tests (9 laboratory tests and 19 trials on the sealing machine) were made to find a correlation between concentration and electrical conductivity. In the range of interest (12–25% of HPMC), the sealing solution was gradually diluted, so concentration and conductibility values were recorded for every dilution. A refilling solution, 50:50 w/w water and ethanol, was used to contrast solvent evaporation during the sealing process.

For the concentration evaluation in both the laboratory tests and the sealing machine tests, a thermal analyzer was used: 500 mg of the solution were deposited on the weighing plate and heated to 200 °C. The instrument returned the percentage of moisture lost to evaporation, which, subtracted from 100%, gave the percentage content of HPMC (dry residue).

In **Figure 2**, conductivity increases with concentration. Slight deviations from linearity can be attributed to interactions between the polymer chains and the solvent. There are two trend lines because each measurement has been repeated twice to avoid any errors due to the instrumentation (see **Figure 2**).

Figure 1: Hydroxypropyl methylcellulose (HPMC) (Pharmacoat 603, Shin-Etsu Chemical).

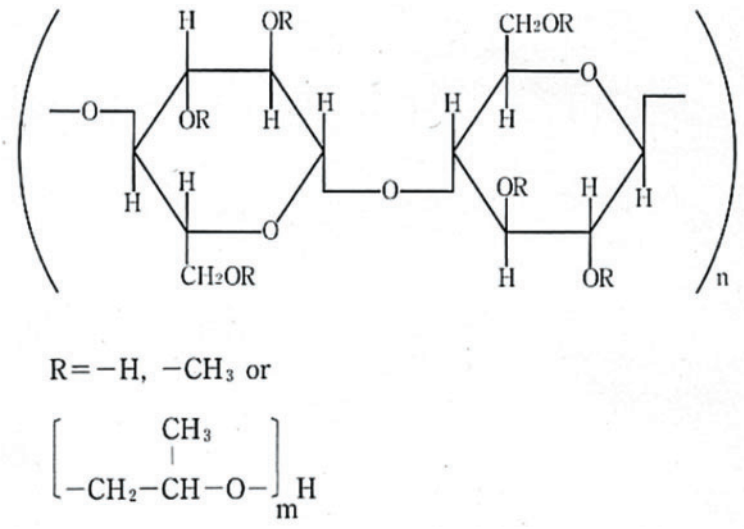
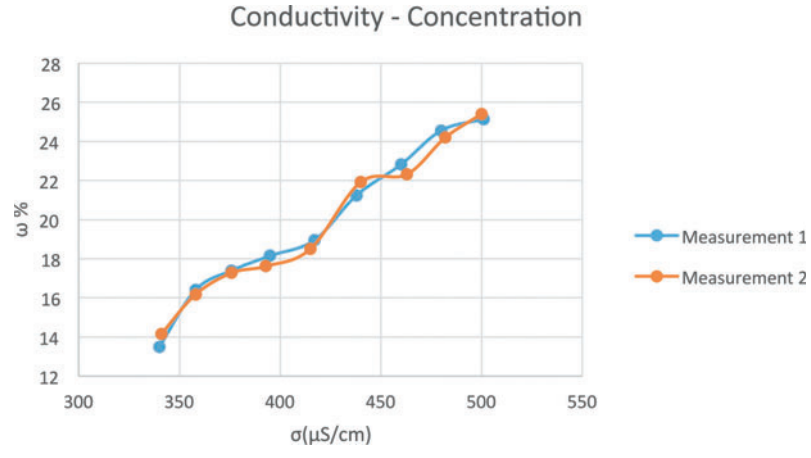


Figure 2: Trend of the concentration as a function of the electrical conductivity of hydroxypropyl methylcellulose (HPMC) solution. (Data obtained from lab test).



FIGURES COURTESY OF THE AUTHORS

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How Polymer Science is Changing the Functional Role of Capsules

New developments in polymer science are broadening the role that capsules play in drug delivery, formulation science and medical research. Today options exist to achieve immediate, delayed, controlled, site-specific or colon-targeted release. Specialized capsules can now play a functional role in improving bioavailability, meet the clinical needs for specific plasma time-course profiles, avoid site-specific degradation in the GI tract, and improve drug efficacy for patients.

DRUG RELEASE WITH HARD CAPSULES

Hydroxypropyl methylcellulose (HPMC) polymer capsules were developed to meet the industry need for a non-animal-derived alternative. HPMC provides greater compatibility with hygroscopic materials and avoids cross-linking that can occur with gelatin under accelerated storage conditions. The ability to withstand temperature excursions without a change in performance and meet religious and dietary requirements make HPMC an important capsule polymer.

Capsugel's introduction of an HPMC capsule manufactured through thermo-gelation provided a means of eliminating gelling agents, a cause of variable *in vitro* dissolution. This gave the new HPMC capsules pH independent disintegration, and was shown in a human biostudy to provide bioequivalence compared to a gelatin capsule.[1]

ACID-RESISTANT CAPSULES

Launched in 2011, DRcaps™ capsules have delayed release properties and are designed for sufficient enteric protection or gastric resistance for nutritional market application. These capsules protect the ingredients from fully releasing in the stomach, and allow complete dissolution in the intestine – a gamma scintigraphy study showed an average of 52 minutes to first opening.[2] DRcaps were also studied using a capsule in capsule concept. Their *in vitro* dissolution and disintegration tests used a double-wall DRcaps capsule which significantly increases the acid resistance (pH1.2) and delays dissolution in the pH6.8 JP2 buffer. In the test, the double DRcaps did not exhibit any significant delay at the pH6.8 JP2 stage. The study showed that DRcaps acid resistance is not affected by the presence of up to 40 percent alcohol (ethanol) in the dissolution media, which may help prevent alcohol dose dumping in delayed-release products. The results also confirmed that these capsules can be considered an option as an extended delayed-release oral dosage form.[3]

Another study – the results of which appeared in medical journals – described how investigators at Massachusetts General Hospital used DRcaps for an unusual treatment of a serious medical problem. They used pre-screened frozen fecal material from healthy donors to treat recurrent diarrhea caused by *Clostridium difficile* (*C. difficile*) infection (CDI), a major cause of morbidity and mortality. The capsules obviated the need for invasive procedures, thereby eliminated procedure-related complications and reduced the cost of treatment. Among the 20 patients treated, 14 had clinical resolution of diarrhea after the first administration and remained symptom free at eight weeks. The six non-responders were re-treated, with five patients having a resolution of diarrhea. The overall rate of clinical resolution of diarrhea was 90 percent.[4]

FULL ENTERIC PROTECTION FOR PHARMACEUTICAL APPLICATIONS

In late 2016, Capsugel introduced a functional capsule that provides a viable alternative for enteric protection and delayed release without adding functional coating. The capsules, Vcaps® Enteric, use a polymer blend of HPMC and Hydroxypropyl methylcellulose acetate succinate (HPMC-AS). While the polymer blend differs from what the enTRinsic capsules use, Vcaps® Enteric offer a similar benefit: simpler enteric delivery implementation from early stage development to commercial manufacturing.

These enteric capsules comply with relevant EP, JP and US Pharmacopeia monographs and have been evaluated *in vitro* across a number of compounds. The results show they protect the stomach from aggressive APIs and delay release to provide maximum absorption. Vcaps® Enteric capsules work with all but the most sensitive APIs.

Capsugel®

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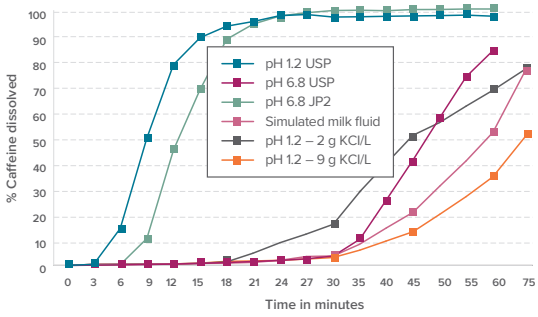
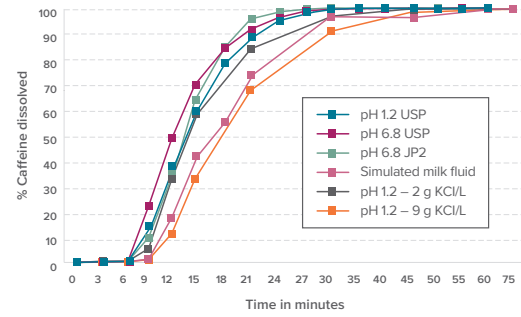
Dissolution variations introduced by gelling systems in HPMC capsules

Influence of gelling systems on HPMC capsules in dissolution testing



In vitro dissolution of caffeine in Vcaps® Plus capsules



ENTERIC PROTECTION FOR HIGHLY SENSITIVE SMALL AND LARGE MOLECULES

The enTRinsic™ drug delivery technology provides full enteric protection and targeted release of acid- and heat-sensitive active ingredients to the upper GI tract without the use of functional coatings. Examples include nucleotides and peptides, vaccines and live bio therapeutic products. The intrinsically enteric capsules, which use approved pharmaceutical polymers, have been shown to rapidly release at pH 5.5, allowing optimal absorption in the upper GI tract. The technology also enables formulators to accelerated product development of acid-labile or gastric-irritating compounds because the capsules eliminate the preparation, application, scale-up and process validation steps associated with functional coatings.

LOOKING FORWARD WITH FUNCTIONAL CAPSULES

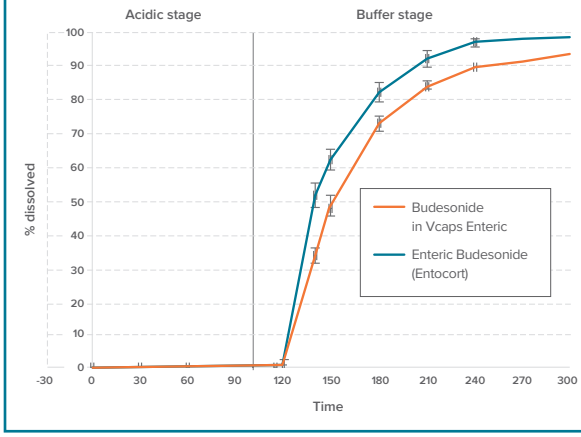
In-vivo tests have shown that soluble compounds are well absorbed from both HPMC-based Vcaps® Plus and gelatin capsules. In most cases, capsules of either material perform similarly, but in some applications they don't.

HPMC capsules, for example, can interact with poorly soluble APIs in a way that leads to a lower crystallization rate in the GI tract. This can be important when there are supersaturated APIs in the intestine, as can occur when dosing either a high-energy salt form or a weakly basic API. In those cases, HPMC-based capsules can help maintain super-saturation by inhibiting crystallization. The degree to which crystallization inhibition affects *in-vivo* performance will depend on a particular application, but HPMC has the potential to play a role as a functional excipient which improves bioavailability.[5] Capsugel's Bend, OR, formulators predict approximately 40 percent of molecules are weakly basic, having a basic pKa between 2 and 7, and almost all these compounds are poorly water soluble. This indicates that there are many compounds that could benefit from HPMC-based capsules.[6]

SUMMARY

Today's HPMC capsules are more than an alternative to gelatin capsules. They offer an array of opportunities to improve drug delivery. From research to human dosing, HPMC capsules provide predictable delivery of simple, immediate-release formulations and address the complex needs of targeted release, moisture protection, and enteric delivery. The variety of HPMC capsules now available, combined with a host of innovative strategies and technologies for drug delivery, offer a means of addressing the challenges of today's APIs and provide a platform to develop patient centric formulations that incorporate the next generation of molecules in development.

Enteric release without the need for coating with Vcaps® Enteric capsules



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contin. from page 47

Figure 3: Trend of the concentration with the conductivity (data obtained from machine tests).

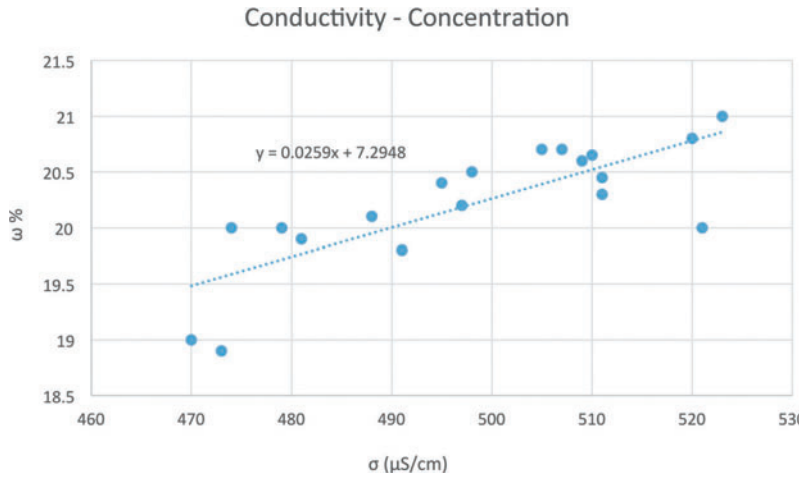
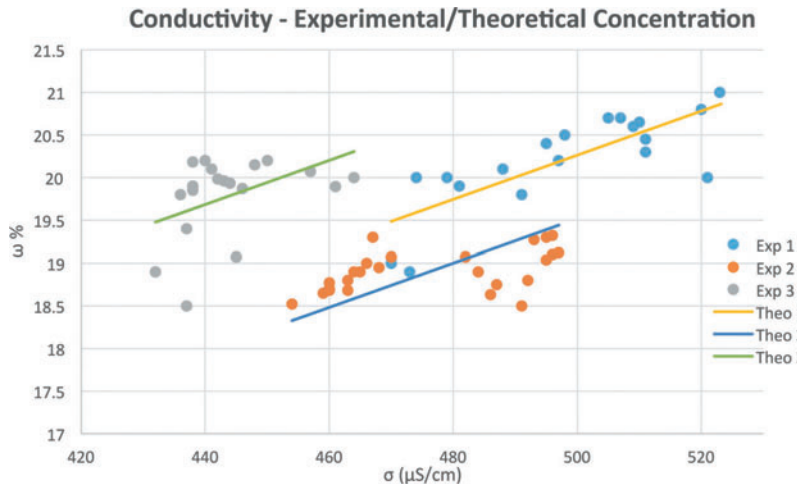


Figure 4: Comparison between experimental and theoretical concentrations.



Experimental description—results

Compared to static tests of the laboratory, the sealing process conducted in the commercial machine is more complex because recirculation of the product causes an increase of the evaporation surface. Furthermore, due to the different evaporation rates and conductivity values (30 µS/cm for water and 3 µS/cm for ethanol) of ethanol and water in the solution, it was observed that, in time, there is a slight increase in conductivity even if the HPMC concentration remains constant, due to the higher conductivity of the water. Thus, in Measurement 1 (shown in **Figure 3**), the trend line obtained has been employed as a line of first attempt.

The line [y = 0.0259x + 7.2948] in **Figure 3** has been used to predict the concentrations of the next tests and, as **Figure 4** shows, the angular coefficient can approximate the experimental data, while the intercept identification is not so immediate. The angular coefficient is the general trend of the concentration with the conductivity, while the intercept depends on all those factors that vary during the sealing: temperature, evaporation rate, mixing rate, and different water-ethanol ratios over time.

To optimize the intercept value for each test (data obtained experimentally are named EXP1-2-3), the standard deviation, Σ (ωsp - ωteo) ^ 2, has been minimized through a generalized reduced gradient method to have the minimum difference between experimental and theoretical concentrations. As shown in **Figure 4**, three lines with the same angular coefficient but different intercept (Theo 1, 2, 3) have been obtained.

Because the concentration remains constant during sealing tests, the conductivity varies in a range between 440 and 520 µS/cm. At 20% of HPMC, the conductibility is on average 480 µS/cm, and the average intercept value obtained is 7.568. Here the equation of the line found:

$$y=0.0259x+7.568$$

The line represents the equation needed to control the average concentration of the polymer during the sealing of capsules based on electrical conductivity measurements.

Additional data

Another set of data was obtained from a sealing trial performed on capsules supplied by a customer. In this case, refilling was performed not in the sealing solution tank but in the sealing baths, which were exposed to the atmosphere, with a consequent increase in the evaporation rate and greater difficulty in maintaining a constant concentration.

Concentration was evaluated as in previous tests (using a thermal analyzer), while conductivity was measured in the sealing baths (see **Table I** and **Figure 5**).

As can be noted from **Figure 5**, the data obtained (blue) were higher than those estimated theoretically from the equation (red). The observed trend is parallel to the theoretical one, except for the outliers (black and orange circle) that were observed immediately after manually diluting the solution. Stirring plays an important role in keeping the solution uniform. If left static, the values can differ due

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Table I: Set of data obtained from a sealing trial with refilling performed in the sealing baths.

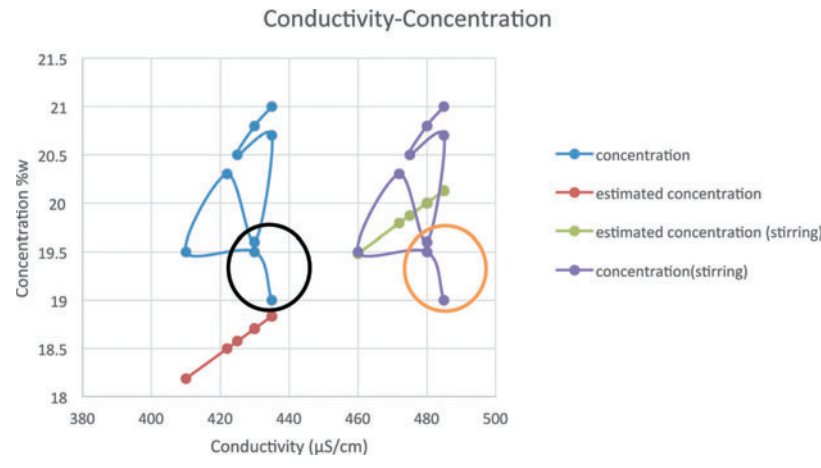
TIME	CONDUCTIVITY	CONCENTRATION	TEMPERATURE	ESTIMATED CONCENTRATION	CONDUCTIVITY (STIRRING)	ESTIMATED CONCENTRATION (STIRRING)
min	µs/cm	%w	°C	%w	µs/cm	%w
10	435	19	21,3	18,8345	485	20,1295
20	430	19,5	21	18,705	480	20
30	410	19,5	18,8	18,187	460	19,482
40	422	20,3	19,2	18,4978	472	19,7928
50	430	19,6	18,6	18,705	480	20
70	435	20,7	19,6	18,8345	485	20,1295
80	425	20,5	19	18,5755	475	19,8705
90	430	20,8	18	18,705	480	20
100	435	21	18,2	18,8345	485	20,1295

to the formation of layers of different concentration.

Therefore, in the sealing baths, where there is no agitation, the values tend to be somewhat lower if compared to the tank where the solution is under constant mild stirring (as in the data from test 1 in **Figure 3** and test 2 in **Figure 4**).

If, to add the agitation contribution, a correction of approximately 50 uS/cm is applied, it can be seen that the two trends in **Figure 5** (theoretically calculated [green] and the experimental data [purple] with the correction) are more similar. The number 50 is due to considerations about previous tests and the current trial; when the solution is added in the sealing baths, it is stirred and an increase of about 50 uS/cm can be noted. This correction doesn't influence the slope but the intercept of the equation, which is the only factor influenced by experimental conditions (temperature and stirring rate).

Figure 5: Comparison between experimental and theoretical concentrations with and without stirring.



The maximum difference observed between the experimental and the corresponding theoretical value (obtained from the equation) is not higher than 0.5% concentration (evaluated with the thermal scale). The error is quite high because of the thermal scale, but for the process purpose the value is quite close to the theoretical one. Consider that this series of data comes from a test that was performed in slightly different conditions (requested by the customer): the refilling was performed manually, and therefore the concentration was not held perfectly constant. Therefore, the theoretical trend is not perfectly identical to the experimental, but the slope value is very similar. The experimental data are shifted (i.e., different value of intercept) because the experimental conditions are different.

Conclusion

The relation between conductivity and HPMC concentration is more accurate than that of viscosity and HPMC concentration; however, further tests are necessary to study better the influence of experimental conditions (stirring rate, temperature, etc.). Therefore, the study is far from being completed. **PT**

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The Real Complexity of Excipient Composition

Brian Carlin, George Collins, Linda A. Herzog, R. Christian Moreton, David Schoneker, Phyllis Walsh, Priscilla Zawislak, and Joseph Zeleznik

This article seeks to promote dialogue among stakeholders to facilitate consensus regarding requirements for excipients.

Since the *United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*) General Notices combined, it could be interpreted that API requirements apply to excipients. In *USP–NF* General Notices, an API equals the labeled entity plus impurities. Applying this logic to excipients, anything NOT the labeled entity would be an "impurity." Most excipients are more complex and less well defined than APIs. The excipient name may not reflect its complete composition. The named entity may be a minor component. The other components may be essential for functionality. This article seeks to promote dialogue among stakeholders to facilitate consensus regarding this topic.

Due to excipient diversity, including highly complex mixtures from animal, botanical, mineral, and/or synthetic sources, differing approaches to characterizing excipient properties may be required. More complex excipients, including excipients produced by biotechnological methods, may require extensive physico-chemical characterization to fully understand their composition.

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Excipients are a diverse group of materials, which are used for a vast range of available drug products. Excipients intended for use by different routes of administration may require different understanding of the composition profile. Excipient manufacturers should seek to establish how their ingredients will be used. However, in commerce, this information is not always available from or shared by the user.

IPEC-Americas and IPEC Europe have published an *Excipient Composition Guide*, which describes the complex nature of excipients (1). There are many excipient types, which have different compositional profiles. These include standard excipients, sometimes referred to as conventional or traditional excipients, mixed excipients, and co-processed excipients.

The excipient composition profile may be defined as a description of the components present in a typical excipient lot produced by a given manufacturing process. The main components of an excipient are those, which in most cases; contribute to the excipient being able to perform its intended function within the drug product(s) in which it is used (also known as "nominal" components). Other necessary components also may be present (i.e., concomitant components, additives, and processing aids). Unreacted starting materials, by-products, degradants, and residual solvents also may be present as a direct result of the excipient's manufacturing process. These components may arise at different stages in excipient processing (**Table I**) and are considered part of the excipient composition profile.

Finally, contaminants may be present (i.e., substances not directly resulting from the excipient manufacturing process [synthesis and/or purification], but as a consequence of extraneous factors such as personnel, equipment, packaging, other products, etc.). Contaminants would not be regarded as part of the composition profile; however, they should be controlled through good manufacturing practices (GMPs).

As excipients are used typically without further purification, excipi-

Table I: Differences in APIs and excipients.

Typical attributes	API (traditional, small molecules)	Excipient
End users	• Pharmaceutical companies • Cosmetic companies	• Industrial • Cosmetic • Food • Pharmaceutical (often only a small proportion of the market)
Manufacturing	• Batch (usually) • Small volume (usually < 1000 kg)	• Batch or continuous • Large volume (up to 100,000 tons per annum)
Synthesis	• Synthesis of specific molecular entity	• Synthesis (including polymerization) of predominant molecular entity • Extraction, processing, and/or purification of naturally-occurring starting materials
Raw materials	• Well-defined chemical intermediates	• Harvested plant matter • Animal products • Minerals (mined) • Fermentation
Composition	• Typical processing reduces or eliminates most impurities. • API = labeled entity + impurities = 100% • Quantitative assay	• Typical API purification techniques (e.g., crystallization, precipitation) are not applicable • Excipient = nominal labeled entity + concomitant components + additives + residual processing aids + impurities = 100% • Variable compositional profile, depending on source/process • Assay may not be available

ent manufacturers should identify and set appropriate limits for components as appropriate. These limits should be based on appropriate safety data, limits described in official compendia, or other requirements and sound GMP considerations. Manufacturing processes should be adequately controlled to ensure that undesirable components do not exceed established limits.

For many excipients, classifying and quantifying all components may not be possible. Composition-related methods and specifications should be justified. There are many traditional, well-established (qualified by use) excipients for which it is neither feasible, nor necessary, for safety purposes to identify all components. Evaluating (re-evaluating) their safety, unless scientific evidence becomes available that suggests otherwise, is generally unnecessary. Where feasible, generating composition profiles should involve each component's identification, classification, and quantification (expressed as a range). If unidentified, an appropriate qualitative description such as a chromatographic peak retention time should be made available. A reasonable reporting threshold is available from the International Council for Harmonization (ICH) Q3A (R2) guideline (2).

In addition to the "nominal" component, excipient components may comprise the following:

- Concomitant components
- Additives
- Processing aids
- Degradants
- Residual solvents
- Additional components may comprise:
  - o Unreacted starting materials such as monomers in polymerization
  - o Residual catalysts or metal reagents
  - o Reaction by-products (e.g., isomers and side reactions)
  - o Raw material components (especially for naturally sourced materials).

Establishing an excipient composition profile

Where possible, excipient manufacturers should establish composition profiles where the main excipient components are identified and their normal concentration variability determined. Acceptable limits, where required, should be based on a risk assessment using sound science. It is typically not necessary to have limits for all components in the composition profile, but the profile should be understood. Limits should only be established when justified by risk assessment to address safety and/or customer-specific concerns.

An excipient composition profile evaluation should be performed by the excipient manufacturer using their manufacturing process knowledge and understanding, which may lead to identifying associated potentially undesirable components. Excipient components (i.e., main/concomitant components, additives, processing aids, and undesirable components) should be identified and quantified using suitable analytical techniques, wherever possible. Appropriate analytical methods may be compendial or suitably qualified manufacturer-specific methods. The materials used for composition profile development should be representative of the excipient, and sampled in a manner consistent with that used for lot release by the quality control unit (i.e., same sampling technique and sampling point(s) in the manufacturing process).

Concerns with current USP policies

The United States Pharmacopeial Convention (USP) merged the General Notices for both the *United States*

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Keys to Successful Implementation of Single-Use Technology

How and why collaboration improves single-use projects.

BY WILLEM KOOLS, PHD, HEAD OF TECHNOLOGY MANAGEMENT, MILLIPORESIGMA

As biopharmaceutical projects occupy an increasingly larger share of the development pipeline, drug makers are striving to implement strategies that bring affordable therapies to market quickly and cost effectively. Over the past several years, the adoption of single-use technology has emerged as one important strategy for improving downstream and upstream processing while avoiding the downsides of traditional stainless-steel bioreactors.

Uptake of single-use technology shows no signs of slowing. A recent market report predicted the single-use market will become a $6-billion industry by 2024, marking a compound aggregate growth rate of 11.1% from 2015 to 2024.[1]

While drug companies are highly motivated to use single-use solutions to speed the development of new molecules, increase production efficiency, and decrease capital expenditures, they still face several complicated challenges such as on-time delivery of materials, regulatory issues, and quality questions.

How are innovators addressing these issues and bringing single-use solutions to the next level?

SINGLE-USE CHALLENGES AND OPPORTUNITIES

While many teams can implement single-use systems to some degree, not everyone has the knowledge and experience to do it well. Some firms believe they are restricted to a one-size-fits-all approach for single-use assemblies. In reality, "single-use" cannot be implemented the same way for every molecule and every project. A knowledgeable third-party expert can efficiently develop single-use assembly elements tailored to a given project while the sponsor company focuses on making its molecule as productive as possible.

At the M Lab™ Collaboration Centers, sponsor companies have access to the Mobius® MyWay portfolio, allowing them the flexibility to choose from three single-use assembly routes. Mobius® Stock solutions can ship within 24 hours for clients with immediate needs. Mobius® Select assemblies give sponsor companies with accelerated timelines the option of using custom assemblies from an optimized component library (six-week lead time). Last, Mobius® Choice offers fully customized solutions for end-users with specialized requirements (standard lead time). This diverse portfolio helps us address the many different needs and challenges that users face.

But with the many choices available to them, how do companies choose the best assembly for their project?

We believe having input from a knowledgeable expert as well as state-of-the-art process development tools are key for designing the best prototypes possible. This pairing—expertise and innovative tools—enables projects to quickly move from the draft stage to one that is fully optimized.

Using our non-GMP facility for this work helps spark creativity and allows end-users to explore the full breadth of options available to them. Clients can troubleshoot unit operations freely with modern tools for both small- and large-scale projects without being bound by regulatory restrictions and standard operating procedures. Experts are committed to helping with demonstrations, evaluations, and education about single-use solutions to quickly optimize and implement applications across various processes.

To support such intricate process development teamwork, we chose to establish our nine innovative M Lab™ Collaboration Centers across the globe which include a host of virtual tools for remote discussions and troubleshooting. Centers are located in North America, Latin America, Europe, and Asia, and we tailor our approaches to the various regional dynamics.

The individualized support and guidance offered at the global M Lab™ Collaboration Centers also helps with any regulatory and validation concerns that arise. For instance, sponsor companies often want to know how to generate the best data for testing processing materials for extractables and leachables. The team at the M Lab™ Collaboration Centers is committed to addressing questions like

this and creating a transparent way to supply data-backed critical information and solid best practices about our technologies in support of process validation and optimized manufacturing protocols. Regardless of where in the world this work takes place, we align our training and educational materials and tailor it to the situation at hand.

This collaborative effort is not only critical for new projects, but also for facilitating the streamlined transfer of projects from a traditional stainless-steel manufacturing process to one designed around single-use technology. Working with a knowledgeable partner helps avoid time and resources lost to errors and retesting.

COLLABORATION IN ACTION

A collaborative approach brings together great people and great minds, overcomes barriers, and accelerates progress. We feel this strategy leads to robust best practices that customers can confidently implement in their manufacturing processes. What follows are four examples that illustrate how partnering in a creative M Lab™ Collaboration Center environment played an important role in the success of customer projects.

CASE STUDY 1: Importance of global network.

A contract manufacturer located outside of the United States did not have a fully automated single-use TFF system to produce clinical material for a US-based client. The manufacturer needed to see what such a system would look like and immediately decide on a strategy to implement. Using a virtual demonstration, we responded very quickly and showcased appropriate systems. We then invited the client to an M Lab™ Collaboration Center in the United States, so they could not only see the most appropriate system, but also discuss the intricacies of the process and how it would translate into recipes they could run. This type of customer engagement would not have been possible without the interconnectivity of our various regional M Lab™ Collaboration Centers.

The contract manufacturer and their client were both very happy with the end result and implemented the system successfully.

CASE STUDY 2: Higher protein concentrations.

The need for higher protein concentrations in bulk drug substances is increasing. One client asked us to collaborate on the use of a 500-L single-use mixer to uniformly mix a viscous drug product without risking protein aggregation. With a joint project team, we designed a set of experiments and showed in an M Lab™ Collaboration Center that our mixers worked well while maintaining drug product quality.

CASE STUDY 3: Virtual solutions.

One client had key team members based in Asia, Europe, and the United States, and wanted employees from all these areas to discuss a specific unit operation. M Lab™ Collaboration Center specialists ran the experiment at our Massachusetts Center with the client's team members in the United States, while other individuals watched the experiment in real time from sites in Europe and Asia using our virtual tools.

CASE STUDY 4: The power of education.

The authorities in Singapore wanted to prepare the local workforce for the influx of new biopharmaceutical R&D and manufacturing projects coming into the country. Because our experts have been deeply entrenched in the industry and regional regulatory issues for years, we were able to train employees of biopharma companies based there and well as regulatory personnel. This collaboration was important to us because we believe an educated workforce is vital to the success of a project—especially in emerging markets where employees may not all have the same degree of regulatory and practical experience in the biopharmaceutical industry. Our involvement in industry consortia like the BioPhorum Operations Group plays a major role in our ability to help clients on this front.

SUMMARY

As companies move away from traditional stainless-steel bioreactors and explore new technologies for accelerating timelines and slashing costs, single-use solutions have come to the forefront as an important option. To fully take advantage of this powerful technique, collaborating with a third-party provider that has an established framework and tools for testing and exploring possible single-use platforms alongside clients is essential for maximizing efficiencies and cost savings.

[1] Single-use Bioprocessing Systems Market: Customizability as per Consumer Requirements Key Feature Driving Adoption, reports TMR," Sept. 27, 2016, http://www.transparencymarketresearch.com/pressrelease/single-use-bio-processing-systems-market.htm

Best Practices for Achieving Virus Safety

The importance of collaboration in achieving virus safety assurance.

BY WILLEM KOOLS, PHD, HEAD OF TECHNOLOGY MANAGEMENT, MILLIPORESIGMA

To avoid production problems and potential supply delays, biopharmaceutical companies must be vigilant in all aspects of virus safety risk management. Regulations indicate that virus control should be employed at every stage of the manufacturing process. While it may feel overwhelming to design and validate layers of virus safety measures, partnering with MilliporeSigma and the large network of technical experts at the M Lab™ Collaboration Centers can make the difference between a proactive approach to virus risk mitigation using methods like Quality by Design (QbD) versus a more costly, time-consuming one that may leave patient safety at risk.

PREVENT. DETECT. REMOVE.

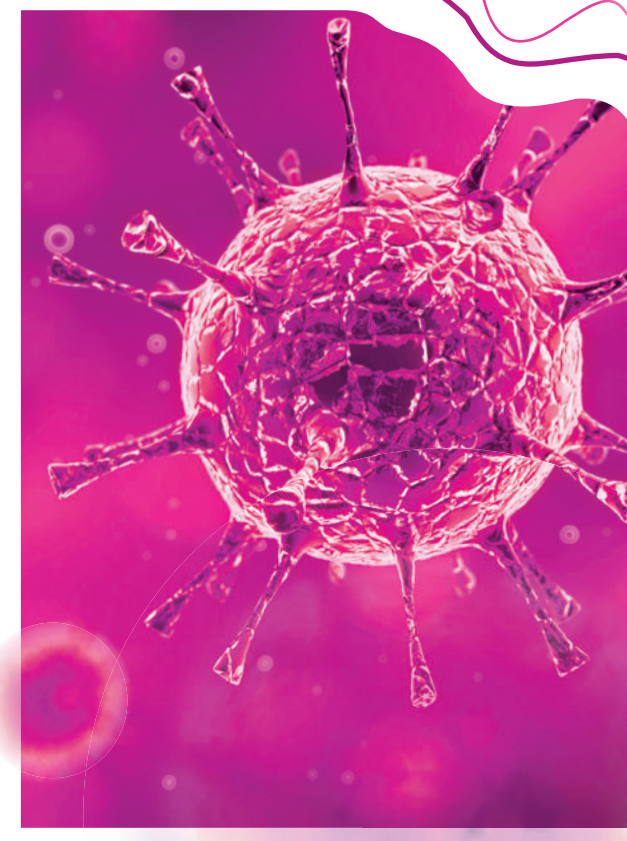
What's the best approach for developing a virus safety process for biologics such as monoclonal antibodies (mAbs) and recombinant proteins?

With its experienced BioReliance® team, MilliporeSigma and the M Lab™ Collaboration Centers rely on a three-pronged approach to virus safety.

- Firms can focus on **preventing** viruses from entering bioreactors by screening and carefully sourcing all raw materials (e.g., cell lines, buffers, and media) for potential contaminants and incorporating technologies to inactivate or remove potential virus contaminants with techniques such as UV-C inactivation and high-temperature short-time (HTST) treatment. Virus filtration of raw materials is another key prevention method.

- Virus **testing** is critical for determining levels of endogenous virus-like particles and for assessing if adventitious virus has contaminated the drug product.

- To eliminate any virus present in the process, manufacturers should employ virus **removal** and/or inactivation operations in downstream purification. This can involve a variety of methods such as chemical inactivation, chromatography, and virus filtration.



> To avoid production problems and potential supply delays, biopharmaceutical companies must be vigilant in all aspects of virus safety risk management.

The MilliporeSigma team has 30 years of experience working with customers on virus filtration in all phases of biopharmaceutical development. As these efforts evolved into comprehensive viral clearance testing and process development services, they saw the need to expand the opportunities for clients to work side by side with the technical experts at the M Lab™ Collaboration Centers. Here, sponsors and the M Lab™ Collaboration Centers team can work on testing new products—both filtration, chromatography and new virus barrier technologies—as well as scale-up processes in

a non-GMP and collaborative environment that inspires creative solutions.

Collaborative testing. The M Lab™ Collaboration Centers' network of scientists and engineers work with clients to identify which product and service solutions or combinations would be best for their processes and help them implement a viral safety strategy with confidence. The open, collaborative atmosphere at M Lab™ Collaboration Centers provides the flexibility to evaluate virus safety applications and processes that might not be possible in the client's facility. In this "sandbox," clients are free to collaborate and learn through hands-on and virtual experimentation. If a customer is facing a specific problem in their process, a suite of innovative digital tools and manufacturing equipment can help determine how to address it under representative process conditions. This scientific "playground" gives customers the freedom to explore without restrictions and sets the stage for a well thought-out and successful virus testing strategy. In addition, virus safety support offered at the M Lab™ Collaboration Centers is complemented by the biosafety testing and viral clearance services offered by MilliporeSigma's BioReliance® team.

> Working with M Lab™ Collaboration Centers not only gives companies access to cutting-edge solutions, but also provides a flexible environment conducive to problem solving and experimentation.

Streamline strategies across production scales. Working with a knowledgeable partner to optimize virus safety solutions for biologics can also help streamline process scale-up as molecules mature. This is vital for keeping costs and timelines on track.

While a molecule is still in development, technical experts in the M Lab™ Collaboration Center can run studies at both small and large scales to ensure the processes meet targets for purification and virus clearance. For instance, a group of technical experts worked with an early evaluator of a new virus barrier filter that wanted to know whether the technology would scale well as their molecule progressed through development and into commercialization. They mimicked the conditions of the customer's plant in the M Lab™ Collaboration Center and conducted a scalability study using the customer's media. Doing that work up front, free from the bounds of SOPs and GMP requirements, was by far the easiest and fastest way for the client to generate reliable scalability data and perform both pilot-scale studies and large-scale operations.

QbD approach for increased efficiency. To bring virus safety to the next level, experts at the M Lab™ Collaboration Center take a QbD approach to virus filtration processes. QbD can help teams understand the process, filter, and feed parameters that affect virus retention in order to develop a robust design space and parameter control strategy for virus filtration, which paves the way for process validation and regulatory approval.

The QbD approach used at MilliporeSigma has numerous real-world benefits. One client, for instance, accelerated their development timelines enabling more-efficient filing of Biologics License Applications as a result of the streamlined process improvements. This is a huge advantage for biopharmaceutical companies that are often under intense time pressures to bring products to market as quickly as possible.

SUMMARY

Creating and implementing a solid virus safety strategy for biologics is essential for all biopharmaceutical companies. Working with M Lab™ Collaboration Centers not only gives companies access to cutting-edge solutions, but also provides a flexible environment conducive to problem solving and experimentation. Clients can try several solutions before committing to them and receive guidance from knowledgeable experts about the best approach for their project. The innovative tools at the M Lab™ Collaboration Centers also help ensure processes scale well while a molecule is still in development, potentially cutting development time and costs. Last, the QbD approach that MilliporeSigma applies to virus safety brings additional efficiencies. All told, extensive collaboration between sponsor and supplier not only simplifies the complicated process of establishing a virus safety strategy, but also adds numerous other cost and time-saving benefits to clients.

Emerging Markets: Strategy for Risk Mitigation

An interview with Willem Kools, PhD, Head of Technology Management, MilliporeSigma

Expansion into emerging markets is a key growth strategy in the life sciences sector, with numerous pharmaceutical companies interested in adding production and/or R&D capabilities there in the coming years. Conducting R&D and manufacturing work in emerging markets is not a straightforward endeavor, however, and numerous challenges must be addressed for projects to run smoothly.

BioPharm International recently spoke with Willem Kools, PhD, head of technology management at MilliporeSigma, about the role of education in breaking down some of those barriers to entry in emerging markets such as Singapore, India, China, Brazil, South Korea, and elsewhere. He explains how experts from the M Lab™ Collaboration Centers are leading the way in making emerging markets a less-risky proposition for biopharmaceutical companies wanting to expand there.

BioPharm International: What challenges stand in the way of a drug company entering an emerging market?

Kools: Seven out of nine M Lab™ Collaboration Centers are located in emerging markets. Given our successful track record working in these areas, we get a lot of questions from clients about how to successfully work and bring technology for biopharmaceutical projects into emerging markets.

The first challenge that comes to mind is access to technical expertise. While some companies have come to emerging markets to develop and manufacture biopharmaceuticals like vaccines, not much more-complex biopharmaceutical work has been conducted in these areas. In many cases, the infrastructure for large-scale biopharmaceutical production is still growing and there is not a large pool of experienced and skilled workers in these areas to draw on.

Thus, it is critical from a risk-mitigation perspective to work with knowledgeable partners who understand how to train local talent with appropriate workforce skills (i.e., technical experience and regulatory understanding) while dealing with the speed-to-market challenges inherent in biopharmaceutical work.

At the M Lab™ Collaboration Centers, we strongly feel that to make a business environment in emerging markets attractive enough for companies to invest, it's critical to take the lead in training and sustaining a qualified, skilled, and knowledgeable workforce. This was the goal of an important collaboration between the M Lab™ Collaboration Centers and the Singapore authorities. Drawing on our years of technical and regulatory expertise, we have trained employees of biopharmaceutical companies and regulatory inspectors based in Singapore for the past eight years. In fact, about 70% of the Singapore pharmaceutical workforce has been trained by our technical experts, with 80% working in manufacturing operations.

For biopharmaceutical R&D and manufacturing efforts to be successful in emerging markets, we cannot be the only ones who know how to work there. In other words, information cannot exist within a silo. M Lab™ Collaboration Centers have seen time and time again that having a strong focus on client collaboration and helping to build a stable and skilled workforce through training programs benefits the entire community and helps avoid road bumps as projects grow.

BioPharm International: How difficult is it for biopharmaceutical companies to navigate an uncertain regulatory environment?

Kools: Our company has a long track record of strong relationships with regulatory bodies in numerous countries, and we support the development and implementation of critical regulations in countries just starting to see increased pharmaceutical development and production. As a trusted partner, we believe it's vital to be on top of the regulations as they stand today as well as to have our finger on the pulse of how they are evolving.

In addition, we want to help local regulators in emerging markets understand the global regulatory dynamic and help them achieve the right level of standards, best practices, and oversight so they can ensure product safety for patients. At the end of the day, that's what we all strive for in this industry.

BioPharm International: How are the M Lab™ Collaboration Centers helping to overcome these regulatory barriers?

Kools: We ensure regulators know all the ins and outs of safe biopharmaceutical manufacturing, what to look for, what not to look for, what is already known, and more. Furthermore, we feel it's important to guide approaches in process characterization and validation toward meeting both local and global standards. Last, a growing focus for us is initiating good discussions about how to evolve regulatory frameworks so that customers in those regions have certainty about the expectations.

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Pharmacopeia (USP) and *National Formulary* (NF) in early 2000. In effect, this means that the same General Notices restrictions apply to both APIs and excipients. It could, therefore, be argued that API requirements also apply to excipients. In the General Notices, an API equals the labeled entity plus impurities. If the same logic is applied to excipients, anything other than the labeled entity could be considered an "impurity."

The current *USP 40–NF 35* "impurity" or "concomitant component" definitions only apply to drug substances and drug products but not excipients. Similarly, ICH addresses impurities in new drug substances and drug products as follows:

- Any component of the new drug substance that is not the chemical entity defined as the new drug substance (2)
- Any component of the new drug product that is not the drug substance or an excipient in the drug product (3)
- Any component present in the intermediate or API that is not the desired entity (4).

These definitions do not specifically apply to excipients and cause confusion when inappropriately applied to them. Excipient-specific definitions are therefore required and should be included in future issues of the *USP–NF*.

The situation regarding excipients is put forth in an excerpt from the International Pharmaceutical Excipients Council (IPEC) Composition Guide:

"For excipients, the situation is more complex as they are frequently multicomponent, and their composition may be less well defined. Their functionality may be dependent on the presence of components other than the labeled entity. The definition of the term 'impurity' as used above for drug product and/or drug substance is thus misleading when applied to excipients. To distinguish these components from true impurities, the appropriate term for describing excipients should be 'minor component' or 'concomitant component' (e.g., the water of crystallization in magnesium stearate required for optimum lubricant effectiveness)" (1).

Advances in analytical technologies can give excipient manufacturers, users, and regulators more quantitative excipient composition detail, but not necessarily increased understanding of excipient functionality. Increased analytical capabilities are to be encouraged, but, taken out of context, can cause confusion and inappropriate or counterproductive actions by users and regulators.

Significant differences between APIs and excipients

FDA defines an "Active Ingredient" (here used interchangeably with the term API) as "any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals" (5). FDA does not have an official definition for "excipient," but rather uses the term "Inactive Ingredient," which they define as "any component of a drug product other than the active ingredient" (6).

The Glossary found in *USP 40–NF 35* General Chapter <1078> Good Manufacturing Practices For Bulk Pharmaceutical Excipients defines an excipient as "Any substance, other than the active pharmaceutical ingredient or drug product, that has been appropriately evaluated for safety and is included in a drug delivery system to aid the processing of the drug delivery system during manufacture; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use" (7).

Some of the general differences between APIs and excipients are summarized (**Table I**). Exceptions exist (e.g., in the case of small-molecule synthetic API-like excipients and naturally derived APIs such as digitalis and fish oil).

In the case of APIs, the labeled entity is generally well-defined and quantified by assay to ensure purity. Other components are considered impurities, that is, the balance of 100% minus the assay. For excipients, the labeled entity can be nominal, and there is not always a specific assay (e.g., microcrystalline cellulose). The labeled entity itself may not even be the predominant component. For example, stearic acid 50 NF can contain as little as 40 wt. % stearic (octadecanoic) acid and as much as 50 wt. % palmitic (hexadecanoic) acid. The latter major component is a concomitant component, not an impurity. There may also be up to 10 wt. % other components. The labeled entity may also be nominal for polymeric excipients, usually reflecting an average molecular weight.

According to General Notices 5.60.10 in *USP 40–NF 35*, "The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all other impurities combined with the monograph-detected impurities may not exceed 2.0% unless otherwise stated in the monograph" (8).

This statement is not appropriate for excipients. If a distinction is not made between concomitant components, additives, residual processing aids, and impurities, there is likely to be confusion regarding excipient applicability of specific impurity identification and quantification requirements typical for APIs. This could encourage attempts to set inappropriate specifications by users and result in excipient shortages, if the specifications are outside the process capability of excipient manufacturers.

The authors propose that the following excipient-specific definitions be adopted by *USP–NF*:

- Concomitant component—A substance found in an excipient that is not the intended chemical entity, may be necessary for assuring the proper performance of the excipient in its intended use, and is not an impurity or a foreign substance. (Formerly referred to as minor component) (9)

- Additives—A substance added to the excipient to improve or maintain a characteristic such as a preservative, flow agent, antimicrobial, etc. (9)
- Processing aids—A material added to a manufacturing step for the purpose of facilitating the completion of that step or subsequent step (9)
- Impurity—An undesirable material found in an excipient as a consequence of the raw materials, excipient manufacturing process, or excipient degradation (9).

Excipient composition example–Polyethylene Glycol 600

Excipients can be complex mixtures of substances, some or all of which may affect functionality. Polyethylene glycol 600 NF (PEG 600), which is a complex mixture of the tridecamer (mol. wt. 590), other oligomers (concomitant components), and impurities, is a good example. It is by no means the only example. Other examples include polymeric excipients, some excipients derived from natural fats and oils, and mineral ores.

Polyethylene glycols are polymers of ethylene oxide and water. In the *NF*, the number after polyethylene glycol or PEG indicates the mean molecular weight of the polymer. PEG 600, which has been safely used as an excipient for many years, is used (among other applications) in hard and soft gelatin capsule formulations to enhance active substance solubility (10).

While the "600" nomenclature indicates mean molecular weight, other higher and lower molecular weight oligomers present impact performance. In addition, the specified impurities ethylene glycol and diethylene glycol must not jointly exceed 0.25 wt. %. A suitable antioxidant (additive) may also be present. The antioxidant would be a stabilizer and thus an additive, not an impurity.

Historically, polyethylene glycol grades were specified by viscosity, but their multicomponent nature is now revealed by modern chromatographic techniques. The Cleaver chromatogram (11) shows multiple oligomers present, most of which are present at levels well in excess of 0.1 wt. %, and the sum of which exceed 2 wt. %. Given the current impurity limits and "definition" put forth in the *USP–NF* General Notices, these oligomers could be construed as "impurities."

However, since finished pharmaceutical formulations using PEG 600 have been based on PEG 600 functionality, which is predicated on the presence of the oligomers shown in the chromatogram, the effect of removing all oligomers except the tridecamer is unknown, even if it were possible to do so. The presence of these oligomers may provide essential contribution to PEG 600 drug delivery properties. In addition, their presence does not pose a health or safety risk.

In the case of ethylene glycol and diethylene glycol, both of which could be present in PEGs, there is a clear need to set limits for the "undesirable substances" (impurities) because they are toxic to humans and animals.

Communication disclosure methods needed for additives and processing aids

IPEC-Americas recognizes the need to provide appropriate details regarding excipient composition. There are excipients in approved medicines, which contain undeclared additives or residual processing aids and yet have a long history of use. Given the large number of excipients involved, and the much greater number of pharmaceutical products potentially affected, there is a need for IPEC-Americas, FDA, and USP to collaborate in developing a path forward and avoiding potential drug product shortages. There has not been a consistent approach to excipient additives and residual processing aids disclosure, even though these ingredients have been used safely for many years. However, it must also be recognized that the presence of certain other components in excipients may present intellectual property issues (trade secrets and know-how). A mechanism is required, and should be developed, for sharing confidential information with FDA and without direct disclosure of the identity and level of additive or residual processing aids to users.

For an excipient having a monograph in the *USP–NF*, there are issues with such additives and residual processing aids. *USP* General Notices 5.20 Added Substances (12) states as follows:

> *"5.20. Added Substances*
>
> *"Added substances are presumed to be unsuitable for inclusion in an official article and therefore prohibited, if: (1) they exceed the minimum quantity required for providing their intended effect; (2) their presence impairs the bioavailability, therapeutic efficacy, or safety of the official article; or (3) they interfere with the assays and tests prescribed for determining compliance with the compendial standards.*
>
> *"The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.*
>
> *"5.20.10. Added Substances in Official Substances*
>
> *"Official substances may contain only the specific added substances that are permitted by the individual monograph. Such added substances shall not exceed the quantity required for providing their intended effect. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s)."*

The presence of undeclared additives and processing aids conflicts with General Notices requirements. A mechanism is needed for confidential disclosure of the presence of additives and residual processing aids without required labeling as specified currently by *USP–NF*.

IPEC-Americas has submitted a background document on this issue to FDA

and has requested a meeting to discuss possible disclosure mechanisms for these ingredients and potential changes needed in the *USP–NF* General Notices.

Conclusion

Many excipients are multi-component with well-established safety profiles. Components other than the labeled entity may also impact excipient performance. For excipients, concomitant components, additives, and residual processing aids should be distinguished from impurities in terms of undesirable substances, which should be absent or controlled for safety reasons.

The current API-specific requirements put forth in the *USP 40–NF 35* General Notices are not appropriate for excipients. It is therefore recommended that USP and FDA take the following actions:

- Revise General Notices 5.60.10 and 5.20.10 to address excipient requirements by incorporating the aforementioned proposed definitions.
- Include excipients in the list of exceptions in the Other Impurities requirements in 5.60.10.
- Provide excipient manufacturers with a means to confidentially communicate additives and residual processing aids presence to regulators without public disclosure.

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Teaming Up for FDA Inspections

Agnes Shanley

Just as FDA strengthens ties between reviewers and plant inspectors, proactive manufacturers are involving different disciplines in preparation for FDA audits.

FDA continues to strengthen its approach to plant inspections (see **Sidebar**), scoping out roles for inspectors and reviewers, and how they should interact (1). Former FDA investigator Christopher Smith, now a consultant with The FDA Group, shared with *Pharmaceutical Technology* best practices and things he wishes more pharmaceutical companies would do to prepare for an FDA inspection.

How FDA changes affect industry

PharmTech: What impact will recent changes at FDA have on inspections?

Smith: All these changes should benefit industry, FDA, and the consumer. Years ago, when I began my career at FDA, inspectors were frustrated by the disconnect between FDA's field organization, the Office of Regulatory Affairs (ORA), and the chemists, microbiologists, clinicians, and others in headquarters who were reviewing new drug applications.

In some cases, we would inspect a company's plant and find cGMP issues, and then issue a 483 to the company. While we worked with the firm on resolving the issues in that 483, we'd sometimes see that the same company had already issued a press release touting approval of its new drug, made at the facility with all the problems. We often wondered why one side of the agency wasn't communicating more closely with the other.

That communication has been steadily improving since FDA started the preapproval inspection program in the 1990s, and funding has been reserved to allow reviewers to accompany inspectors on some inspections, or at least to talk to them and, for example, give them a list of top 10 priorities and what to look for, based on their application under review.

However, these advances have been complicated by the fact that application sponsors today are outsourcing more development, manufacturing, pakaging, and clinical research. Applications have gotten very complex, but any contract partner named in a drug application is subject to inspection and should be ready.

Disconnect between CMC and clinical

PharmTech: Is there still too much emphasis on the clinical side and getting approval, rather than ensuring cGMP compliance?

Smith: There's still a disconnect in industry between the chemistry, manufacturing, and control (CMC) or the cGMP and facilities side of the application process, and the clinical side. If I do an audit of a clinical investigator site or a sponsor facility's clinical program, to help them prepare for an FDA inspection, when I ask questions about the CMC side, representatives from the clinical side are often oblivious to the issues that may have occurred when making or packaging the product.

I see this disconnect not so much at virtual companies but at the larger pharma companies. Typically, there will be a vice-president of clinical research, a number of physicians, pharmacologists, statisticians, and other teammates all focused on clinical studies, patient safety, trial protocols, institutional review board oversight, and data capture, but when you ask about manufacturing, you'll sometimes receive a blank stare, even though GMP issues could affect the results of the clinical study.

PharmTech: What are some ways in which FDA is eliminating the disconnect between its staffers that industry might emulate?

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Smith: One crucial change has been using appropriate expertise to do the audit, and making audits more of a team effort. The agency has realized that, for example, if an aseptic facility must be inspected, it might be best to have someone with a microbiology background handling it. Similarly, an engineer might be selected to look at water systems and piping, as well as specialized equipment with advanced control features.

Preparing for mock audits

PharmTech: Do you take a crossfunctional team with you for mock audits?

Smith: I try to convey the need to do that, but typically companies are concerned about cost and they'll just want one person to do the audit for two days.

PharmTech: How should companies prepare for a mock audit?

Smith: One key suggestion is to be more transparent within their organizations, and with the mock auditors, about what their problems have been. FDA can't look at everything, and an audit is really only a snapshot of what they have seen that day.

For a new drug application (NDA), a company has likely spent years developing this product and has lots of data. FDA then comes in and pulls a batch record or the results of a study and audits it. Their inspectors are trying to find out where the problems are. They have the authority to ask for all deviations and batch failures. People don't want to show their dirty laundry.

You may have good quality systems in place, but FDA inspectors want to know whether your systems can address problems effectively when things go wrong. The only way you can prepare for that is by knowing where all your skeletons are before a mock audit. Look for problems and see whether and how they were addressed, and be able to explain that clearly.

For FDA, the key question is not whether you had the problem but what you did about it. Unfortunately, people usually want to focus on their successes. FDA may want to believe them, but they are, after all, cops on the beat. They won't pull you over to say 'You're a great driver,' but because they want to issue a speeding ticket. Companies need to prepare for that.

PharmTech: How do you typically set up the audits?

Smith: When I perform mock audits with fellow consultants, clients often ask us to pretend to be FDA inspectors. However, very early in the audit, it often becomes clear that their employees aren't addressing things as they should. In such cases, we need to stop, take our FDA hats off, and coach them. In some cases, they may not be explaining the reason for an issue clearly, or may have the wrong person explain it. So the audit becomes a continuous 'hats on, hats off' exercise. In most cases, their employees have never been through an inspection and have no idea what to expect.

PharmTech: Where have you seen the greatest improvement in getting companies to understand FDA's expectations during an audit?

Smith: One of the biggest things I've been able to help companies do is to review how they've managed and documented the handling of problems that have come up in the past. We'll often look at an investigation report, either a lab failure, manufacturing deviation, or a clinical site problem, that happened a while ago.

They'll show what happened and dig out some kind of report, but what becomes very clear is that the decision-making around resolving the problem was poorly documented. Three years ago, everyone understood why the decision was made, but key staffers have left and businesses have changed, so now people are looking for complete documentation and can't find answers. The documentation must be clear and complete during the problem resolution stage, if it is to be clear years later.

contin. on page 88

Teamwork and specialization to govern facility inspections

FDA Communications Manager Jeremy Kahn addressed questions about how FDA is changing its approach to facility inspections with *Pharmaceutical Technology*.

PharmTech: How will FDA change the way it inspects pharma plants?

Kahn: FDA's Program Alignment plan, established in 2013, aims to modernize and strengthen FDA's ability to keep pace with the acceleration of scientific innovation, global expansion of markets, and new programmatic mandates. On May 15, 2017, the agency announced a new organizational model, in which the entire reporting chain for the Office of Regulatory Affairs' (ORA) inspection and compliance staff, from employees on the front lines to the assistant commissioners at headquarters, would specialize in a particular commodity, for example focusing on pharmaceutical quality operations.

This model represents a significant change from ORA's previous geography-based model, where employees, regardless of their area of expertise, may have worked in more than one program area. We anticipate that deepening knowledge by specialty area will strengthen ORA's ability to regulate an increasingly complex and global industry. This approach also ensures that management and compliance can efficiently address issues as they arise.

PharmTech: How will departments within FDA be connecting and communicating with one another?

Kahn: FDA's Center for Drug Evaluation and Research (CDER) and ORA are implementing a new, historic concept of operations agreement to more fully integrate the drug review programs with the facility evaluations and inspections for human drugs. The new operating model will be a key element of meeting the commitments under the Generic Drug User Fee Amendments II to communicate final surveillance inspection classifications to facility owners within 90 days of an inspection. FDA will begin to implement this agreement this fall, applying it to all human drugs, in order to more quickly meet this commitment.

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Automated Visual Particle Inspection

Heino Prinz

This article discusses fully automatic inspection of glass and plastic containers and factors that affect particle detection rate.

The automated visual inspection (AVI) process in glass containers is a well-established process, but not yet perfect when it comes to free-floating or immobile particles. Inspection of plastic containers also has challenges. This article discusses fully automatic inspection of glass and plastic containers and factors that affect particle detection rate.

General approach

AVI as a technical inspection process relies on a contrast difference of a specific particle from its surrounding, under a particular lighting condition, and usually captured by a video camera. Whether it is machine vision or human inspection, if there is no contrast then there is no detection. The smaller a particle, the less contrast it shows, and therefore, the lower the chance of detection. Thus, the first goal in particle inspection is the correct adjustment of light intensity. Light intensity should be high enough to penetrate the container with the liquid, but low enough to provide the best contrast for the smallest particles.

It is necessary to consider the nature of particles and their interaction with light. One may think that a black particle is more detectable than a white one or a transparent one. This assumption is only partly correct and only under ambient lighting conditions. When it comes to machine vision, one is using transmitted light for the inspection scene, and here this impression is wrong. In machine vision, a thin grey metal particle can produce the same contrast as an almost clear plastic particle, and a thin black plastic particle will have a similar contrast to a glass particle of the same size. The differences become larger as the particles become larger, but the limitations of an inspection technique are determined by the boundary samples, which are usually made from the smallest possible detectable size. Considering these limitations, claims of reliable AVI detection of particles with a size of 50, 70, or even up to 100 µm are suspect. Human inspection capabilities have similar limits.

Inspection technique

The inspection technique for AVI is simple and effective. The machines rapidly spin the container to create a vortex and then stop it suddenly, which conserves the liquid's and particles' motion according to their inertia. The rest of the scene must be stock-still, which can be done by cameras moving along with the machine transport or by a moving mirror system. From a series of pictures and their pixelwise subtraction, the moving reflections within the container area—on the picture—will be visible and create a detection signal. Human inspectors perform the same test by shaking, tilting, and flipping the container in their hands and watching for moving contrast.

In addition to packaging in glass vials and prefilled syringes, more injectable products are being packaged in plastic blow-fill-seal (BFS) vials and ampoules. These containers are usually manufactured in large blocks up to 30 or more directly bonded containers. Even when segregated into blocks of four or five containers, the classical method of AVI, which uses high-speed rotation and abrupt stoppage of single containers, is impossible to use. To test blocks of ampoules that cannot

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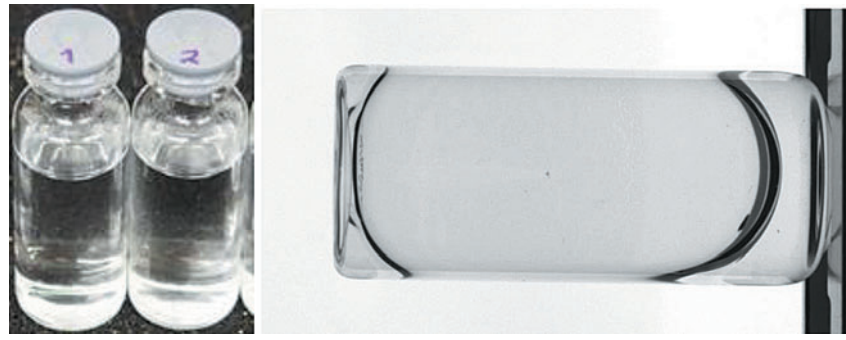
Figure 1: Horizontal orientation improves detection of floating particles by increasing the area of the liquid's surface.



be rotated due to their symmetries, an inspection machine has to copy the human technique by vibration in combination with tilting and swivel motions. Then one observes the scene when the container is still, acquiring the picture series in between the agitations. The rest is identical to the AVI of single round glass vials.

All three scenarios—AVI for singles and blocks and the human inspection technique—have side effects created by moving bubbles, droplets, or light reflections that are mistakenly held for particles, and therefore, false rejects. Apart from reaching the best detection rates, reduction of false rejects is the second major task in setting up an AVI process.

A particle showing sufficient contrast and changing positon within a series of pictures in a perfect liquid is detected as a contamination. But, different particles act differently. Furthermore, clear glass and semitransparent plastic have different transmission and transparency properties. The particle nature, interactions with the liquid, the container material, and the way of agitation must be investigated.

Particle nature as a root cause for non-detection and false rejects

Particles with lower and higher densities compared to the liquid must be treated differently. Material characteristics, such as adhesiveness or particle morphology, in combination with the primary container material, must also be taken into account. Additionally, the container geometry plays an important role in detection probability.

Fibers and flakes, regardless of the material, will or can float on water; therefore, they most likely are found on the surface. The usual camera position detecting these particle types is either tilted downwards from the top or inclined upwards from the side walls. The size of the area of such a surface defines the probability of detection of such particles. In fact, an upright standing container with a diameter of 12 mm is unfavorable for detecting floating particles, whereas a horizontal orientation of such a container magnifies this area to improve the detection rate (see **Figure 1**).

The size of an area where a particle can float is directly related to the detection probability, according to the equation:

$$D_{pr} = D_{phys} * A_{obs} / * A_{tot}$$

Where D_{pr} is detection probability, D_{phys} is probability based on physical factors (size, contrast, visibility), A_{obs} is area obscured or not inspectable (meniscus fringes); and A_{tot} is total inspection area.

The detection probability of floating particles in upright standing containers is limited or will be accompanied by a larger false reject rate than normal due to bubbles and swirls on the liquid surface.

Representatives of this category are fabric fibers, hair, splinters from metal, or chippings from most low density plastic materials.

Heavier and denser particles from metal abrasion, glass breakage, and all high-density materials tend to submerge or hover sometimes. They need to be detected in the body section of a container agitated by vortex or vibration. Vertical or horizontal positions usually provide the same results because these particle types are moving close to the wall and, therefore, showing good contrast. Detection rates up to 100% down to 150 µm and lower are frequently observed.

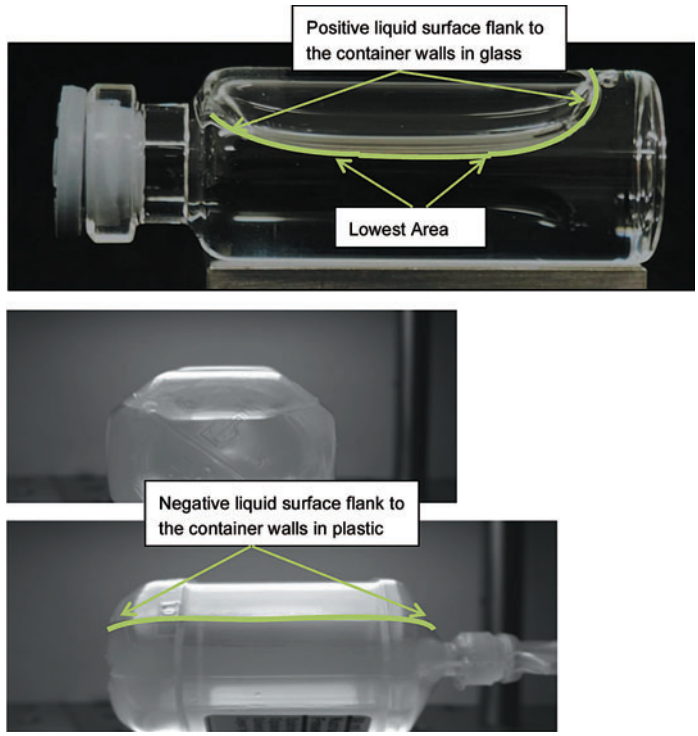
The probability of lifting large and heavy particles into the inspection area by a vortex is directly related to the size or weight, respectively. In the vertical detection position, they require a bottom inspection camera. In the horizontal position, they are detectable as easily as the smaller ones provided the agitation amplitude is large enough.

One disadvantage with bottom inspection of glass vials or plastic containers is the view of the camera into the moving water column above (see **Figure 2**). Refraction of light through the liquid acts like a moving lens systems and creates reflections and moving shadows that can easily lead to false rejects.

In any case, the probability of detection of large glass shards on the bottom of a vial is lower than in the horizontal position, and the false reject rate is far higher than in other inspection positions. In horizontal inspection position and in human in-

FIGURES COURTESY OF THE AUTHOR.

Figure 2: A glass container (top) has a positive liquid surface flank, which improves the probability of detecting floating particles. A plastic container (bottom) has a negative liquid surface flank, which creates a large probability of particles trapped at the side wall that cannot be detected.



spections, quite often a detection rate of 100% is reached.

Particle material can interact with the container material. Plastic particles in BFS processes, for example, are commonly created by the process. Burnt or melted plastic particles may be embedded in the side walls or, if free floating, adhering to the container wall due to Van-der Waals forces. These particles are, thus, quite often immobile and a specific inspection tool is needed. Glass containers have an advantage over plastic containers for AVI; in glass containers, the particles are usually free floating and not showing interaction with the glass walls.

For plastic containers, AVI machines also check for cosmetic defects all over the container surface apart from particle inspection. One can use these specific camera stations for static particle detection. The detection rate directly scales here with the contrast, and therefore with the size.

But there are additional interactions in plastic and in glass. The liquid produces bubbles and droplets when highly agitated, and due to the classification process in AVI, they are mistakenly held for particles when moving within the liquid or when dissolving into the liquid from picture to picture. Some liquids also tend to foam, which is even worse. A major task for every AVI process is to handle bubbles, or remove them or prevent them from being created during the filling and inspection process.

Container geometry can cause difficulties. A black spot on a round vial that is inspected only from two sides (front back side inspection) is missed by one-third of the inspections, which in turn means it requires three cameras to catch it. A block of square-shaped ampoules, which is common in BFS products (not rolling from a table when laid down), requires four cameras to inspect all sides of the wall properly.

Detection rates of static particle defects or cosmetic defects on the outer walls are fairly high and can reach almost 100% even for tiny defects, but they suffer from high false reject rates. These inspection stations require usually a big compromise of inspection sensitivity and false reject rates.

In a probabilistic measurement technique, which AVI represents, detection rates are not only ruled by the probability of grabbing a particle in two different positions in consecutive pictures, it is also a question about how likely a particle is in a position that can be evaluated by the visual inspection tools. Looking at a horizontal glass container, as shown in **Figure 2**, the water surface tension at the walls creates a shallow valley. That means the probability of a particle floating on an unobscured position that can be evaluated with visual inspection techniques is one.

The interaction between water and plastic, in contrast, creates a negative flank on the edges (see **Figure 2**), which means that there is a large probability of finding particles trapped on the side wall in an area that cannot be evaluated. Therefore, the detection probability is lower in plastic compared to glass. Overall detection probability is calculated as follows:

$$D_{pro} = D_{phys} * D_{pos} * D_{pr}$$

Where D_{pro} is overall detection probability, D_{phys} is probability based on physical factors, D_{pos} is position probability, and D_{pr} is detection probability.

In extreme underfilling scenarios of plastic containers, one finds a position probability of zero for any floating particle as shown in **Figure 3**.

Measuring particle size

Although particle size is used as if it were a definite measure, it isn't. A sphere can be said to be 150 µm in diameter, for example, but real particles are not spherical. How then should particle size be classified? Is a 100x300x80-µm particle in the class <100 or 100–200 or 200–300 or even 300–400 µm? Knowing that

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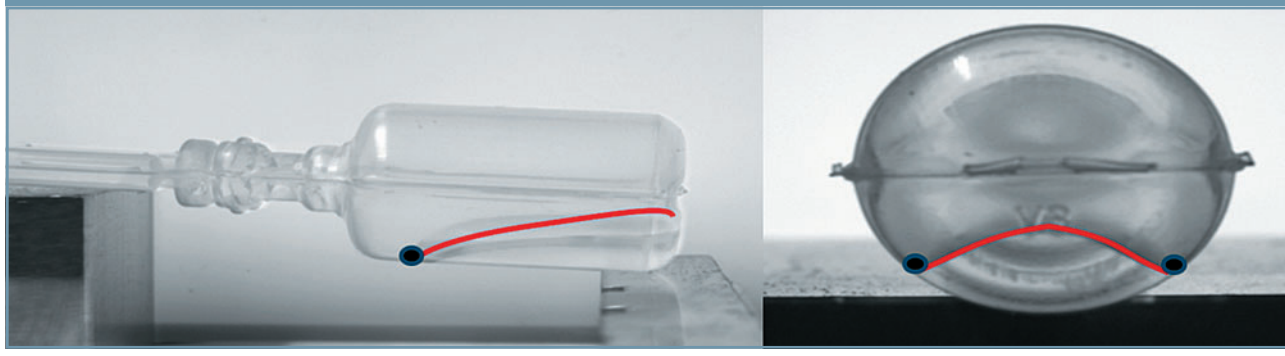
Figure 3: In an underfilled plastic container, the position probability of detecting a floating particle is zero.



the contrast created by this particle is the main measure for detectability, it is fair to correlate this to the virtual area of this particle visible between the light source and the viewer (camera). In this case, one calculates the equivalent circle diameter, which is the closest to what causes the physical effect, as follows:

$$d_e = 1.30\ (a\ b)^{0.625} / (a + b)^{0.25}$$

where d_e is equivalent diameter (mm, inches), a is length of major or minor side (mm, inches), and b is length of minor or major side (mm, inches).

Using a particle with the two larger sides (100 x 300) in this context, results in 180-µm particle size.

Process risk assessment

A risk assessment should be performed on particles created from the process (either extrinsic or intrinsic); particles arising from external process steps, suh as raw materials or pretreatment of containers; and particles arising from human or machine handling. A history of particle and defect findings can become a proper tool when rating the risks associated with particle occurrences.

The overall particle load of a process in conjunction with specific detection rates is often a neglected aspect of risk assessment. The total number of a specific particle in the process is correlated with the detection rate, resulting in the residual risk of delivering contaminated products to the patient. As an example, the process risk of glass breakage in filling of glass vials is rather high due the various handling steps like washing, drying, and sterilization or depyrogenation and the associated possibilities of causing a glass breakage. The particle load in BFS with plastic particles from the process, however, is close to zero with respect to particle findings in the final product. An AVI process may have a detection rate of 90% for glass particles, but the number of contaminated glass vials shipped still is significant. An AVI process may have a detection rate of 65% for plastic particles, but the amount of contaminated plastic containers reaching the patient is still close to zero.

Defect classification

Everyone who inspects product has a certain idea about defects and the related risk. In pharmaceutical products, the finding of a particle causes a higher patient risk than a scratch in a container, and therefore, the rating for particle finding is always critical; the scratch usually gets a minor classification. A vision system can only classify on a logical tool ranking, which could lead to a scenario where the tool used for scratch detection also triggers an alarm when a static particle and no scratch was present. The root cause of the alarm is a particle, but the ranking of the tool is more toward cosmetic defects, and users definitely don't want a particle classification for each minor scratch. Because the probability of scratches is far higher than that of particles, one can argue for leaving the classification as a "minor defect". In implementing an AVI, it is therefore necessary to carefully investigate the possible misclassifications and give a rationale for each class to illustrate the reason for choosing this specific level.

Conclusion

Finally, do not overload an AVI system with requests for finding all the tiniest and minimalistic defects, which compromises the effectiveness of the more important tools. This method always leads to an instable detection process, and believe it or not, the more cameras that are added, the more false rejects occur. Every camera that detects defects always adds false rejects, which reduces the overall throughput.

Although these dependencies and cross correlations seem to add a sort of confusion to the task of defining or building the right AVI system, understanding them is the only way to install the right AVI system for a specific production process. A risk-based approach of investigating the particle behaviors in the specific container designs and materials is suggested to obtain the corresponding detection probabilities and associated false reject rates. With the defect library of a pharmaceutical company, one can conduct a risk analysis to identify the 'real' risks and remove the sole 'potential' risks from the listing. Then one can correlate this with the process risks of certain defects. In the end, the right combination of inspection stations and tools maximizes the detection of higher risk defects and minimizes the false rejects of good product. **PT**

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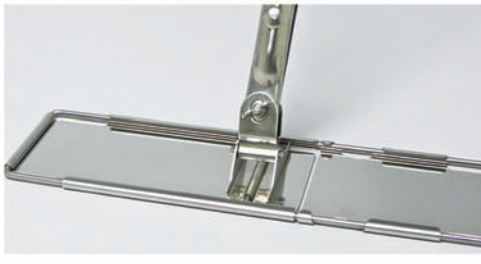

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Reinventing Lean Six Sigma for the Pharmaceutical Industry

Agnes Shanley

Instead of rigidly applying statistical tools, experts suggest that pharma embrace statistical thinking, but focus on reducing variability and adding value for patients.

Six Sigma, both a statistical term and a method developed by Bill Smith, an engineer at Motorola in the 1980s, has allowed companies in a number of industries to improve their business processes, product quality, and overall financial performance. The concept was championed by Jack Welsh when he was CEO of GE, and a number of pharmaceutical companies, including Merck and Johnson & Johnson (J&J) adopted the practice enthusiastically in the past.

The principles of Lean Manufacturing, including its focus on the customer and employees and its emphasis on minimizing waste, enriched Six Sigma's overall framework of "Design, Measure, Analyze, Improve, and Control" (DMAIC). The resulting "Lean Six Sigma" (LSS) programs allowed companies in a number of industries to achieve significant improvements in efficiency and product quality.

However, LSS programs need senior management support if they are to work, says consultant and statistician Ron Snee, coauthor of *Leading Six Sigma – A Step-by-Step Guide Based on Experiences with GE and Other Six Sigma Companies.*

In cases where this has happened, improvements have been dramatic, he says. Snee recalls one company outside of pharma whose Six Sigma programs were driven first by three managers, saving a few million dollars a year, snowballing into $30 million in savings over five years, after the CEO assigned a vice-president-level champion to the project.

A decade ago, LSS programs were trumpeted by many pharma companies. Today, efforts are more subdued, and not only in the pharmaceutical industry. "It has been a challenge in other industries as well, to maintain excitement and initiatives around Lean Six Sigma," says consultant Tara Scherder, a chemical engineer and statistician. Now a partner with Synolostats, Scherder trained employees throughout the enterprise as part of Merck Sigma, Merck's formal enterprise-level Lean Six Sigma program.

Today, LSS programs that once spanned the enterprise live on in a muted fashion, limited mostly to smaller initiatives in manufacturing.

Misunderstandings

Why has LSS failed to become standard practice at more pharmaceutical companies? For one thing, Snee says, people misunderstand the concept. "Some think it's only about quality improvement, while others just see it as training. It's actually about improving the overall performance of an organization." In addition, he notes, some may be fixated on the definition of Six Sigma, in terms of number of defects.

In the process, Snee says, managers may fail to integrate programs and efforts with the bigger picture, and overall management goals. "Programs must be relevant to the needs of the business," notes Scherder. "You must be agile and focus on business context and solutions, not statistical tools," she says, especially because these tools are a relatively small piece of a larger business solution, and they are often not required at all.

Too little problem solving?

That overemphasis on statistics was a weakness in many corporate training programs in the past, says Scherder, at the expense of other beneficial, relevant principles and activities that

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should be part of LSS. For example, she says, it takes time, and mentoring, for individuals to absorb statistical concepts, and to apply them properly to specific business issues, considering the context of the data involved. "Typically, non-trivial statistical concepts (e.g., design of experiments) come fast and furious at the student without time for practice, or adequate interpretation," she says. This can lead to a statistical toolbox mentality, in lieu of statistical thinking. Often, she notes, problems won't even require a statistical solution. "Learning how to assess business and data context and the need and choice of statistical method requires time and contextual practice. This won't be found in JMP or Minitab or any other statistical software out there," she says, noting that the "toolbox mentality" naturally leads to non-value-added analysis instead of the simplest solution.

Pharma bashing

Scherder is also concerned about pharma being compared to other manufacturing industries and criticized for failing to achieve Six Sigma levels. For one thing, notes Snee, Six Sigma has not been achieved for all processes, even within electronics or automotive industries, and it may not always be desirable to achieve it, given business goals. Consider the myriad processes involved in producing a phar-

Six Sigma and the Path to Quality

In June 2017, Lawrence Yu, deputy director of the Office of Pharmaceutical Quality (OPQ), Center for Drug Evaluation and Research (CDER), and his FDA colleague, Michael Kopcha, published a paper on how Six Sigma might help the pharmaceutical industry modernize and improve its quality management systems and overall performance (1).

Yu and Kopcha highlighted the importance of Six Sigma approaches to continuous improvement, as the pharmaceutical industry moves from management- to performance-based regulation, and toward specifications that are based on clinically relevant goals. Yu discussed where he sees Six Sigma going with *Pharmaceutical Technology*.

PharmTech: Why hasn't six sigma become standard operating procedure for most pharma companies today?

Yu: The pharmaceutical industry has traditionally focused more on the discovery and development of new drugs than continual improvement of manufacturing processes. Further, there are relatively few economic incentives for manufacturers to leverage quality. Consumers are not always able to recognize quality, and it's been a relatively recent effort for regulators to place greater emphasis on the measurement of quality. This has created an environment in which there can be a reluctance to adopt Six Sigma and introduce innovations in manufacturing. Still, while Six Sigma is not necessarily standard operating procedure in the industry, there are several examples of pharma companies that have overcome any misunderstandings or problems and embraced it to see clear economic benefits including greatly reduced error rates and cost savings.

PharmTech: What would be needed to make Six Sigma more widely used in pharma?

Yu: The path to get there includes economic drivers, performance-based regulation, quality by design, advanced manufacturing technologies, and continuous improvement and operational excellence. To fully realize the benefits of Six Sigma, there need to be economic factors that recognize and incentivize quality. From the regulatory perspective, shifts from predominantly management-based regulation to performance-based regulation can give industry the flexibility to more readily address and improve quality. Clearly, emerging manufacturing technologies can help with the drive toward Six Sigma, including continuous manufacturing and advanced [process analytical technology (PAT)]. The pharmaceutical sector must embrace quality by design while adopting these new technologies. Finally, continuous improvement and operational excellence must be part of the overall effort to improve the quality of new and legacy drug products.

PharmTech: Are there certain areas where, as articulated for discrete manufacturing, Six Sigma will not yield results for pharma?

Yu: In other industries, product and process understanding is the norm. Optimization is always a critical step in improving quality and reducing cost. In the pharmaceutical industry, 'compliance' with regulatory expectations is often the critical goal. To better serve the patient and move beyond compliance, the industry should emphasize quality, and regulators should create an environment amenable to innovation. One example of such innovation is continuous manufacturing; another is PAT. However, given that Six Sigma is a set of techniques for process improvement, manufacturers can apply it whether their process is discrete or continuous, provided they focus on specifications based on clinical relevance.

PharmTech: What is the most pragmatic way to ease a company into using the approach? What steps are needed?

Yu: Perhaps most importantly, a company needs to commit to quality and recognize that quality-focused efforts can be cost effective. As a step, a company can start to use process capability to measure quality, something the pharmaceutical industry has widely adopted over the past several years. Another powerful step is embracing and committing to a culture of quality and continuous improvement. To foster a company taking this approach, regulators need to create an environment that appropriately balances risks with regulatory expectations (for example, regarding testing and inspections) based on a company's level of process capability and other quality matrices.

PharmTech: What will be needed to move the overall sigma level of the industry?

Yu: The ultimate focus for regulators and industry should always be on benefit to the patient. As improvements in pharmaceutical quality directly benefit patients by helping avoid potential shortages and product recalls, it is in everyone's interest to raise the level of quality above its current state.

A key step is collectively embracing and committing to a culture of quality. In a culture of quality, employees not only follow quality guidelines, but consistently observe quality-focused actions and receive quality-focused communications. This culture requires consistent senior management support and clearly communicated vision, values, and quality goals. For example, performance expectations for individuals throughout a company can clearly link to quality goals and initiatives.

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maceutical tablet, Snee says. Which steps would make sense to bring to Six Sigma levels? "Implementing the six sigma improvement process does not mean that a company has attained, or planned to attain six sigma quality in its processes."

Room for improvement

"Admittedly, the industry has room for improvement in the adoption of LSS principles," says Scherder, "but simple comparisons to other industries are unfair." Consider, for instance, the relative ease of incremental change. The regulatory burden associated with process changes in pharmaceutical manufacturing is extremely high compared to that in other industries, which impedes motivation for continual improvement, she says.

Industry and regulators recognize the benefit associated with reducing this burden over the lifecycle of a product. Signs of progress include the 2016 draft FDA guidance for comparability protocols, and the drafting of a guidance (ICH Q12) for lifecycle management of post approval changes by the International Council for Harmonization (ICH).

Customer-based specifications

In addition, in pharma, manufacturers do not always have customer-based specifications, such as tolerance for a car component, or the dimensions of a semiconductor wafer, says Scherder. Instead, quite often specs are derived from process performance. This is particularly true for some biopharma attributes, where the mechanism of action to the patient cannot be simply described, she says. In these cases, the sigma quality level is essentially bounded to 3, she explains, because the specifications are based on the expected distribution (the mean +/- 3 standard deviations, or similar statistical interval).

Historically, Scherder notes, when variability has improved over time, regulators have required update of the specifications to reflect the tighter performance even though the tighter specifications were not required for patient safety or efficacy. This practice caps the sigma quality level at three or less, she says, because the specifications bracket only the new performance. This type of specification adjustment is not prevalent in other industries.

The use of specification ranges that simply bracket the expected process variability *in lieu* of true customer derived specifications must be considered in any valuation or comparison of pharma industry sigma quality performance. Clinically relevant specifications (customer derived in terms of LSS), are receiving more attention within the industry. The topic is discussed in a paper by Yu and Kopcha (1) (see **Sidebar**), and the International Society of Pharmaceutical Engineers has established a working group to focus on this issue, she says.

Lack of leadership support

Although Merck's CEO, and a few other CEOs in pharma, supported Six Sigma and Lean Sigma,"pharma has not yet had a Jack Welch figure," notes Snee, while companies may abandon an approach that focuses on individual projects.

But problems with some past programs may also be to blame, says Scherder. At some companies, she says, there may have been too much emphasis on training large numbers of Black Belts who went forth with an arsenal of complex statistical tools to solve problems. Over time, at some companies, the title Black Belt may have become synonymous with 'someone who complicates things.' "Today, business priorities have become highly focused," says Scherder. "You have to prove yourself to be relevant and effective in moving product along the lifecycle," she says, or improvement programs will be considered a cost that can be eliminated.

Returning to basics

Scherder sees a need for pharma's LSS programs to focus on the fundamental concept of understanding and controlling variability and driving that throughout the organization. She also sees a need to incorporate the best aspects of Lean thinking in training. "The concentration on many statistical tools taught too quickly comes at the price of holistic problem solving. Instead, we need to develop problem solvers who will drive statistical thinking throughout an organization, to understand variability, reduce waste, and improve processes," she says.

"Everyone needs to have a line of sight from product/process development to commercial supply and back. Application of statistical thinking across an organization would enable the connections needed to optimally develop and continually improve processes," she says. What would happen, she asks, if process and analytical development professionals were made aware of long term variability that could affect process capability and continual improvement?

Finally, she says, resource prioritization should be given to activities that will provide value or protection to the patient."If a process exhibits high process capability, there's no patient benefit to chasing variability that has negligible safety or efficacy implications. In such cases, patient needs are better served by resources spent on new product development, and less capable processes" she notes.

Finally, she says, there needs to be a focus on activities that will add value to the patient. Some companies have developed LSS approaches incorporating the best elements of both DMAIC and Lean. Amgen, for example, took an approach that focused on process monitoring, incorporating elements of Lean, and setting targets for process capability to improve individual process performance and reduce cycle time as well as overall waste (2).

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Singlet Determination Revisited

Christopher Burgess

Is there a difference between a specification and a standard?

In February 2005, Lynn Torbeck wrote "In Defence of USP Singlet Testing," in which he discussed the US Pharmacopeial Convention's (USP) philosophy of singlet testing and the clear differentiation between standards and specifications (1). Later that year, Tim Schofield, David Leblond, and Stan Altan offered comments and an alternative viewpoint (2). Much has changed over the past 12 years, although many people in industry still regard the USP standard as a specification for the release of product to the market. This article reviews these changes based on the latest USP General Notices (3) and provides a view on the meaning of 'singlet testing'.

Standard or specification

Torbeck emphasized the important philosophical difference between a standard and a specification, and he quoted from the *United States Pharmacopeia* (*USP*) 28 (2005) General Notices (1), "Compendial standards define what is an acceptable article and give test procedures that demonstrates that the article is in compliance. These standards apply at any time in the life of the article from production to consumption."

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Furthermore, these General Notices defined the testing, which constitutes a singlet determination.

USP monographs are standards and not specifications.

"Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested directed in the monograph for that article shall comply…," and "Tests and assays in this Pharmacopeia prescribe operations on a single specimen, that is, the singlet determination which is the minimum sample on which the attributes of a compendial article should be measured."

It is this last sentence that has given rise to much debate and dissention. Schofield *et al.* took this to mean that "Every lot of a pharmaceutical products with possibly millions of dosage units per lot must be made by processes that guaranteed that every dosage unit tested by the filed analytical method at any time before expiry conforms with the stated USP standard" (2).

Clearly, this guarantee is unattainable from both a statistical and practical viewpoint and appears to contradict the uniformity of dosage requirements, which they point out. However, what is clear is that USP monographs are standards and not specifications. The current version of the *USP* General Notices and Requirements doesn't mention the singlet determination and clearly states in 3.10 Applicability of Standards (3): "Standards for an article recognized in the compendia (*USP–NF*) are expressed in the article's monograph, applicable general chapters and General Notices." Hence, there is a strict hierarchy for compliance in the order; monograph, General Chapters and General Notices: "The standards in the relevant monograph, General Chapters and General Notices' apply at all times in the life of the article from production to expiration" (3). This has not changed from 2005.

"It is also noted that the manufacturer's specifications and manufacturing practices (e.g., quality by design, process analytical technology, and real-time release testing initiatives), generally are followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed" (3). This is a significant change from 2005. This quotation addresses the valid concern of Scofield *et al.* in 2005 that a singlet determination may discourage a full scientific understanding of a manufacturing process and interfere with the objective of providing quality product to patient.

USP standards are legal benchmarks of acceptable quality or performance and must be met with some acceptable degree of confidence (probability). In testing of a sample, there is no such thing as an exact value. There is only an estimate of the true value with an associated confidence or tolerance interval.

Specifications, on the other hand, apply to reportable results and are decision limits. They must be met or failure occurs. There is no probability level associated with specifications.

Testing and reportable values

What is not disputed is that all acceptance criteria in any monograph must be met to achieve compliance (3). However, the basis for the acceptance criteria often is disputed. *USP* 4.10.20 in the General Notices says, "The acceptance criteria allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions …" and requires in addition that, "An official product shall be formulated with the intent to provide 100% of the quantity of each ingredient declared on the label" (3).

The purpose of compliance testing is to demonstrate that the sample taken from the lot meets the acceptance criteria for the specific monograph. General Notices 3.10 states, "… in all cases, statements about whether the compendial standard is met apply only to the units tested" (3).

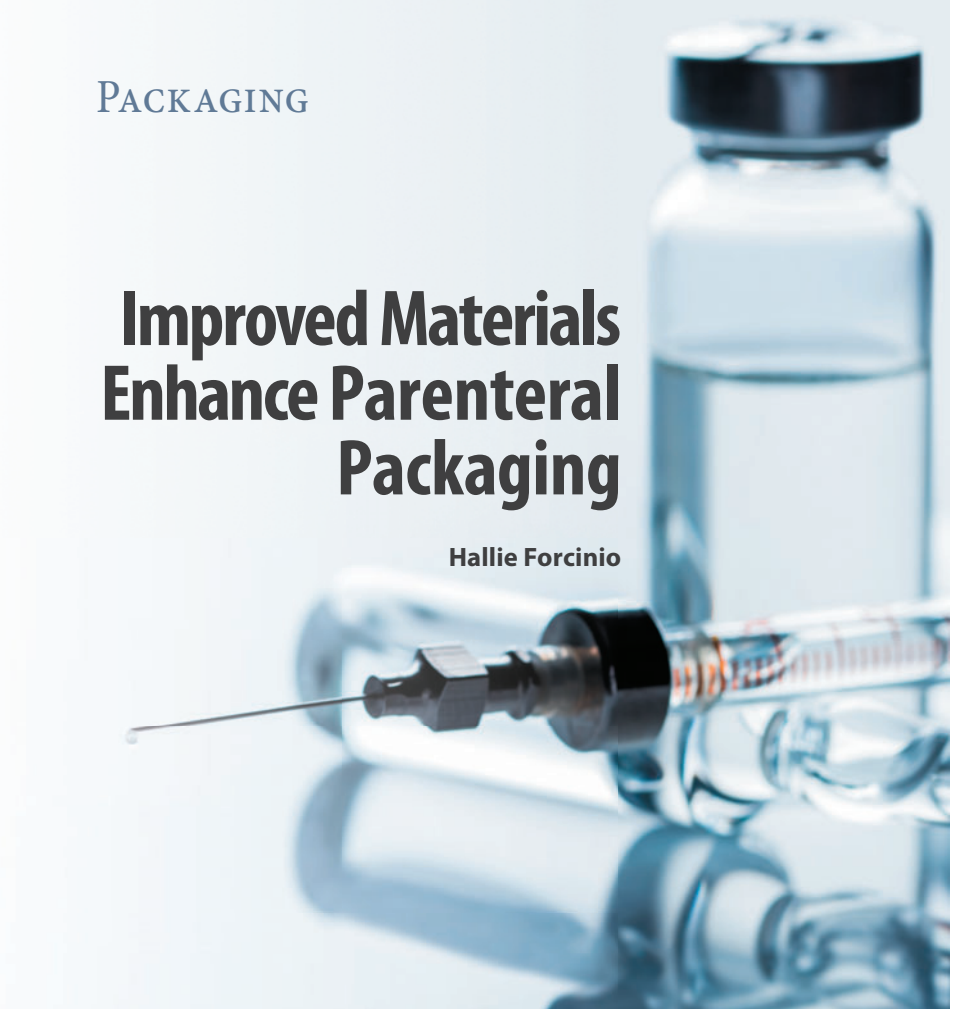
This statement leaves no doubt that compliance with the monograph relates only to the sample tested and not to the batch or lot. Therefore, it is scientifically unsound to use the acceptance criteria of the standard as the release specification for a lot. The General Notices go on to state, "Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor prescribed by the compendia; such decisions are based on the objectives of the testing. Frequency of testing and sampling are left to the preferences or direction of those performing the compliance testing …" (3).

In 7.10, Interpretation of Requirements, the reportable value is defined as: "The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented" (3).

In addition, regarding multiple dosage unit testing, *USP* states, "Some tests, such as those for Dissolution and Uniformity of Dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact one determination" (3).

The statement regarding the singlet determination was removed from the General Notices in *Pharmacopeia* 32 in 2011.

contin. on page 92



Improved Materials Enhance Parenteral Packaging

Hallie Forcinio

Manufacturers introduce innovations in glass and plastic packaging for injectables.

Glass has long served as the traditional primary package for parenteral products. Unfortunately, glass breaks relatively easily and has been known to cause particulate contamination, to delaminate, and to interact with the drug product.

"Current issues with borosilicate glass containers such as breakage, cracks, and particles can lead to patient harm due to contamination, decreased drug efficacy, and drug shortages, as a result of recalls and manufacturing inefficiencies," says John Tobin, vice-president of Commercial Operations at Corning.

He notes, "Current glass packaging has not innovated at the same or even a comparable pace to the scientific breakthroughs in biologic medicines and vaccines throughout the industry. Corning first became aware of glass quality issues with current pharmaceutical packaging for injectable drugs when a major pharmaceutical company and long-time customer asked us to develop a substantially more robust glass solution that also eliminates delamination and reduces particles. At the time, FDA had recently issued an advisory regarding the formation of glass lamellae in certain injectable drug containers. It became very clear to Corning that the industry needed a 21st-century glass package that provides the enhanced quality required to protect 21st-century drugs and, more importantly, provide more reliable access to vital medicines for patients around the world."

To target the problems encountered with Type I borosilicate glass, Corning's glass experts worked in collaboration with Merck and Pfizer to develop Valor Glass, an aluminosilicate glass, which is now commercially available. As a drop-in replacement for borosilicate glass, the new glass type is compatible with existing stoppers, caps, labels, and fill/finish lines.

Corning used glass chemistry and an ion-exchange process, and lowered the coefficient of friction of the surface to produce a glass that is inherently strong and damage resistant. Traditional borosilicate Type I glass contains a significant amount of boron. However, Tobin says, "When introduced to heat, such as during the converting process, the boron in the glass network becomes volatile and evaporates out of the glass, creating surface heterogeneities (regions of non-uniform glass composition) on the interior drug-contacting surface of the package. Corning intentionally removed boron from the Valor Glass composition because of its volatility, which can cause delamination. The other glass components are the same but the ratios are slightly altered to enable a high degree of chemical durability. As a result, Valor Glass has a pristine, chemically durable drug-contacting surface both before and after the converting process, effectively eliminating the root cause of delamination."

An ion-exchange process also minimizes issues such as breakage, cracks, and particulate contamination. Despite the difference in chemistry, Valor Glass meets the current *United States Pharmacopeia (USP)* Type I hydrolytic criteria and has low extractable concentrations. Work is underway at *USP* to broaden the definition for Type I glass to include Valor Glass.

A protective coating on Valor Glass lowers its coefficient of friction and eliminates cosmetic flaws. Eliminating high-friction vial-to-vial contact protects the surface of the containers, re-

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Figure 1: Glass-to-glass contact damages traditional Type I borosilicate glass vials, but has little effect on Valor Glass vials.

sults in a more uniform container flow, and enhances machinability. As a result, vials and cartridges run smoothly on fill/finish machines. Incidents with downed vials, jams, and broken containers are virtually eliminated, and throughput increases. For drug manufacturers, fewer line interventions mean less downtime and a decreased risk of contamination and quality defects. Trials on commercial filling lines have confirmed performance and shown a 96% reduction in peak particle counts, according to Corning.

Valor Glass has drawn the attention of more than 40 pharmaceutical companies. Tobin reports, "We initially thought interest would be for pipeline products, but it's being looked at for marketed drugs as well. Corning has filed a drug master file for Valor Glass with FDA and will continue to work closely with pharmaceutical manufacturers to provide supporting information to facilitate adoption."

Merck has announced plans to convert several products to Valor Glass pending regulatory approvals. At a press conference on July 20, 2017, Kenneth C. Frazier, Merck's chairman and CEO, said, "Biologics today are on the leading edge of scientific innovation, and Valor Glass represents a similar advancement in materials science: glass that is purpose-built for medicines and vaccines." At the same press conference, Valor Glass was described as a potential game changer. "Our initial trial results with Valor Glass show promise, and we are working with Corning to assess the full potential of this glass solution on products at several of our manufacturing sites," said Ian C. Read, chairman and CEO at Pfizer (1).

As the designer of the composition, technology, and manufacturing platform, Corning manufactures and sells Valor Glass and oversees all purchases of it. In addition, established partners, such as Gerresheimer and Stevanato Group, are providing converting and related expertise to speed delivery to the industry and patients.

Syringe capacity grows

With usage of prefilled syringes continuing to rise, Schott has doubled polymer syringe production at its syringe competence center in St. Gallen, Switzerland. The new capacity started up in June 2017 and builds on a previous expansion. Additional capacity is being installed and will be operational in 2018 (2).

"Schott has optimized singular process steps based on our existing quality and production experience," says Tom van Ginnecken, global product manager, Polymer Syringes at Schott. He notes, "Typical improvements involve the state-of-the-art technologies for transportation and handling to further reduce the risk of cosmetic defects. In addition, Schott is getting prepared for future pharma requirements in automation and data exchange."

He explains, "We see a growing trend toward customized delivery systems. The first reason for this trend is the focus of pharmaceutical companies on orphan diseases. With a highly individualized injection solution, the pharmaceutical companies try to increase patient comfort and increase drug adherence by offering a tailor-made solution that is compliant with the patient group's impairments and abilities. Another driver for more customized delivery systems is the need for product differentiation. More pharmaceutical companies use the injection device as a way to differentiate their drug in the market. In a fiercely fought market space with a lot of competition, such as generic drugs; this method of differentiation could mean the success or the failure of a drug. Also, the injection molding process of a polymer syringe inherently offers a broad range of customization possibilities."

Polymer syringes offer advantages beyond customization and differentiation. The material maintains glass-like transparency, resists breakage, and offers excellent barrier properties to keep the medication stable throughout its shelf life. Schott polymer syringes are available in 1–50-mL sizes and delivered ready-to-fill in a nest-and-tub configuration. For more sensitive applications, Schott TopPac SD syringes feature a reduced extractable and leachable profile that ensures high drug stability (2).

Glass ampoules

Glass ampoules remain widely used to package injectable drugs, and demand is actually growing in emerging markets. Although typically used for high-volume, mainly small-molecule drugs, ampoules "could be interesting for biopharma products as well," notes Neus Ferré, global product manager, Ampoules at Schott.

Schott's glass ampoules combine dimensional stability with 100% inspection to suit either end of the spectrum: long runs at high speeds or flexible fill/finish systems for small batches. "At Schott, we are following a zero defect philosophy, resulting in ampoules of high and stable dimensional quality,"

FIGURE IS COURTESY OF CORNING.

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reports Ferré. She explains, "On the one hand, this is achieved by an excellent raw material—Fiolax Type I borosilicate glass—combined with a precise manufacturing process. On the other hand, we have invested in intelligent camera inspection systems that help to improve both cosmetic and dimensional quality even further."

Primarily plastic vials

The DualFusion vial from Wheaton, now DWK Life Sciences, combines the best properties of both plastic and glass into one container. Using plasma-enhanced chemical vapour deposition, an organosilicate protective layer is fused with a silicon dioxide barrier layer that is fused to a cyclic olefin polymer (COP) shell to form a robust, covalently bonded material. The outer COP shell provides mechanical strength, protects against breakage, and can withstand temperatures from -196 °C to 121 °C without cracking. The inner barrier layer prevents permeation of oxygen, water vapour, and other gases, protects against delamination, and eliminates concerns over leaching of metal ions, which can compromise the integrity of vial contents (3).

Each ready-to-use, ready-to-sterilize DualFusion vial has a unique barcode for traceability and authentication. Applications include highly toxic drugs and biologics (4). More recently, there's been interest for freeze-drying applications. The vial has a completely flat bottom that allows efficient temperature transfer from the lyophilizer to the drug product, and the vial's barrier layer allows extended storage time, says Jeffrey Reid, strategic markets manager, DWK Life Sciences.

Serving small batches

The increase in personalized medicine is driving growth in small batch fills. "Therefore," says Reid, "pharmaceutical companies require smaller pack-outs of ready-to-use (RTU) packaging components." To address this need, DWK Life Sciences will begin supplying RTU packaging components such as vials, rubber stoppers, and seals grouped together in one box with an average packout of 200 pieces per component. "This will allow our customers to shift to smaller fill runs and not have to worry about a large scrap rate of packaging components," concludes Reid.

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FDA Audits—*contin. from page 66*

PharmTech: How can managers be sure they're answering the right questions?

Smith: As product development progresses, it is crucial to stay on top of things. You don't want to discover problems after you've filed the NDA. You need to have difficult conversations with staff and contract partners before filing, and relevant documentation must be in order.

PharmTech: Are companies taking a team approach, internally, to audits?

Smith: We are starting to see more firms doing internal audits with teams, where, for example, the quality assurance department does a mock audit of a key operation, but brings in a manufacturing operations expert, an engineer from metrology, and an IT staffer to help. After all, quality assurance staffers can't be experts in everything.

PharmTech: How often should mock audits be done?

Smith: It depends on the complexity of the product and the size of the operation. For instance, an oral solid-dosage form manufacturer who has filed many NDAs will have fewer challenges when filing an NDA for a traditional process than a manufacturer who is using a new process and new equipment. The new process will likely require more frequent audits. Working with vendors

PharmTech: What should companies do when they are working with vendors overseas that may be used to less stringent regulatory oversight?

Smith: The most important thing to clarify with FDA is how you handle vendor selection, auditing, and monitoring. It's amazing how often sponsors don't check on day-to-day performance of some of their contract partners. Recently, I just worked with a mid-sized company that had filed an NDA, and half way through clinical studies they found that the offshore contract research organization (CRO) they were working with was doing a poor job. They could have caught problems earlier if they had been paying attention. Strong selection and oversight are crucial.

And this goes for subsidiary contractors too. One company had hired a contractor to handle its water treatment issues. When I asked about this contractor, the plant manager handed me four lab notebooks. There were no signatures or any other signs that anyone from his company's quality department had been observing and signing off on this contractor's performance. These are the kinds of things that prevent you from being in control, and they're red flags for FDA inspectors.

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Up and Away, M&A

Jim Miller

Mergers and acquisitions are positive for the CDMO industry, but there is a downside.

Mergers and acquisitions (M&A) are a central feature of the contract development and manufacturing (CDMO) industry today. Several new deals are being announced every month, some of them quite substantial, and these deals are reshaping the industry.

CDMOs are in great demand by both strategic buyers (i.e., companies in the CDMO business or a related business) and financial buyers (i.e., private equity firms). Valuations of companies acquired in M&A deals are reaching high levels as buyers compete to win the prize. While private equity investors typically use a "rule of thumb" to value businesses at 10 times earnings before interest, taxes, depreciation, and amortization (EBITDA), some deals have gone as high as 20x EBITDA. One small CDMO that recently went through a process reported that they had received nearly 10 offers from potential investors.

The interest in CDMOs as acquisition targets is driven in large part by the demand for contract development and manufacturing services from emerging bio/pharmaceutical companies. Those companies generally lack internal development capabilities and are highly dependent on CDMOs and contract research organizations (CROs). Emerging bio/pharma companies themselves have attracted large amounts of investor capital as they have become a major source of new product candidates for global bio/pharma companies. Thanks to growing demand from emerging bio/pharma companies, CDMOs have enjoyed high double-digit growth rates in recent years, and investors in CDMOs are betting that those rates of growth will continue into the next five years at least.

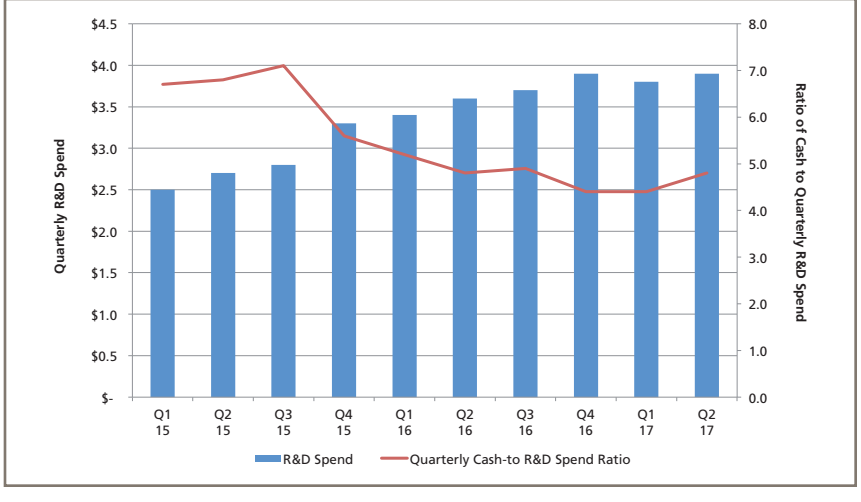
Therein lies the rub: today's high valuations are based on current market conditions, but history tells us that extrapolating today's market well into the future is dangerous. External financing for emerging bio/pharma companies is notoriously cyclical: a boom in the late 1990s collapsed along with the bursting of the dotcom bubble in 2000. After several poor years, the market rekindled again in 2004 but collapsed with the global financial crisis in 2008. Public financial markets did not really open again for emerging bio/pharma companies until 2012–2013, and the industry is now four years into the current financing rebound. While an imminent collapse in bio/pharma funding is not predicted, history suggests that caution is warranted.

The challenge for the industry is illustrated in **Figure 1.** R&D spending by publicly-traded emerging bio/pharma companies has risen rapidly since the beginning of 2015, although it has been flat in the first few quarters (blue columns). However, most of those companies have cash on hand equivalent to just over four quarters' of R&D spending (red line). If external financing becomes more difficult to raise, as it did in 2016, companies will slow their rate of spending in order to conserve their cash until they can raise more. With just four quarters' of cash on hand, spending could slow quickly if conditions worsen.

Downside risks

The implications of making acquisitions in an overheated market will differ depending on the motivations of the buyer, and the way the buyer finances the deal. Strategic buyers have a long-term perspective, and measure success in terms of market share, revenue growth, and enterprise value. The motivations of fi-

Figure 1: R&D spending and cash on hand for emerging bio/pharma companies.



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nancial buyers, however, are often more complicated. They typically make acquisitions with defined investment horizons of about five years, and their focus is on how to optimize their cash return on investment over that period. While concerned with enterprise value at the end of the holding period, private equity investors may also seek a faster return by using the company's cash flow and debt capacity to finance dividends. Their take on what makes an acquisition attractive is often different from that of the strategic buyer.

The conflict between near-term cash returns and long-term investments can be particularly severe in the case of pharmaceutical manufacturing and development. A substantial capacity investment can take two-to-three years to design, construct, and validate, and ramping up utilization of that capacity increment will take several more years after that. For a financial investor with a five-year horizon, an investment that is cash-negative for most of that period may not be attractive, even if it enhances the long-term value of the business.

Lingering concerns

This is not to suggest that private equity firms are not welcome buyers of CDMOs. Often the businesses private equity buyers invest in are short on the capital, know-how, financial discipline, and executive skills necessary to take their businesses to the next level. The best private equity firms are very good at providing the resources to enable business growth and maturation. In an environment of frothy valuations, however, investors in debt-financed acquisitions may be challenged to feed businesses all the resources they need to grow.

But using a lot of debt to buy a business at the top of a cycle can be dangerous. As revenues flatten out or fall on the downside of the cycle, debt-laden businesses will struggle to make the necessary investments as well as service their debt. A number of CDMOs experienced financial challenges in the wake of the downturn in the late 2000s and were forced to restructure or close down altogether. Bio/pharma companies should do careful financial due diligence when qualifying CDMOs, especially for commercial requirements.

Another concern is the impact that M&A activity has on customer perceptions, especially global bio/pharma companies. On the one hand, M&A creates companies with broader capabilities and scope, which enables bio/pharma companies of all sizes to simplify their supply chains.

However, the M&A activity also creates uncertainty around the supply chain. Given the current rate of activity, there is no assurance that the CDMO a biopharma company contracts with today will be the same company that is fulfilling its order two years from now. The business model, objectives, culture, and operating skills of a new owner may be different from the owner the CDMO originally contracted with.

Global bio/pharma companies may be particularly concerned about changes in ownership. Already reluctant to outsource and keenly attuned to supply chain security issues, too much churn in the supply base can make those companies wary about working with CDMOs.

Overall M&A is a positive for the CDMO industry. The current activity attests to the industry's robustness and long-term prospects, and rewards the entrepreneurs who have built admirable businesses. But buyers and sellers need to be wary of the downsides of the overheated market. **PT**

STATISTICAL SOLUTIONS— *contin. from page 83*

The USP requirements for sampling remains very weak. The only mention is in 6.60 Units necessary to complete a test, "Unless otherwise specified, a sufficient number of units to ensure a suitable analytical result shall be taken" (3).

Key learning points

This review of changes to the meaning of singlet testing raises the following points:

- It is important to understand the difference between a standard and a specification
- A singlet determination did not mean testing must only be on one sample to determine compliance. It was the minimum sample size.
- The degree of testing replication necessary to arrive at a reportable value must be determined and justified by the manufacturer or tester in a documented procedure.
- Monograph acceptance criteria relate to the samples (units) tested for compliance and not the manufactured lot. It is therefore scientifically unsound to use the acceptance criteria of the standard as the release specification for a lot.
- The monograph acceptance criteria assume that the amount of specified material is targeted at 100% of claim.
- Sampling is not addressed well in the General Notices and only General Chapter <1010>, which is non-mandatory, considers it (4).
- The manufacturer needs to have in place risk-based in-house specifications designed to take into account sampling, analytical, and manufacturing variation with the objective of ensuring with a high degree of probability that any sample take from any manufactured lot would meet the acceptance criteria given in the monograph. Such a risk-based approach is available based on the ISO guard band principle (5, 6) and references therein.

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Virgin Atlantic Cargo, Delta Cargo Unveil New Pharma Zone

On Oct. 2, 2017, joint venture partners Virgin Atlantic Cargo and Delta Cargo opened a new Pharma Zone at their joint facility at London Heathrow Airport. The Pharma Zone is a fully-segregated area for handling and storing pharmaceutical shipments within a strictly-regulated temperature environment with active container storage. The area will support the temperature-controlled healthcare and life-science products being carried by both airlines.

The new facility includes two walk-in pods capable of maintaining 2–8 °C container off load (COL) and 15–25 °C controlled room temperature (CRT) ranges for loose pharma shipments. Above the floor of the area is a temperature-controlled storage system for 24 pallets, split into six separate chambers, each of which can be safely maintained within either a 2–8 °C or 15–25 °C temperature range.

Eurofins Opens New UK Analytical Testing Facility

On Sep. 29, 2017, Eurofins Scientific, a life-sciences company specializing in analytical testing, opened a previously announced pharmaceutical chemistry and microbiology facility in Livingston, Scotland, following a £4-million (US$5-million) investment.

The 5800m^2 facility, which will move to Livingston from its current site in Newbridge, Edinburgh, Scotland, will provide greater capacity for the company's biopharmaceutical product testing business. The site will also facilitate new laboratories for the company's water testing business, which provide analysis to assess the safety of water in cooling towers, hot and cold water systems, closed systems, and recreational waters such as swimming pools and spas.

The company's product testing business will look to expand on finished product and raw materials testing. According to the company, employee numbers are anticipated to double to more than 100 in the next few years, with an increased number of technical specialists being added to work on method development and validation.

Fresenius Kabi Breaks Ground on $250-Million Facility Expansion

On Sep. 21, 2017, Fresenius Kabi, a German specialty and generic pharmaceuticals company and a subsidiary of Fresenius SE & Co. KGaA, broke ground on a $250-million expansion of its Melrose Park, IL manufacturing facility. The site, announced in August 2016, will facilitate the aseptic manufacturing of generic injectable medicines. The expansion of the facility will include several new buildings, with completion expected by 2026.

This investment is part of a recent series of business endeavors by the company. In April 2017, the company publicized an agreement to acquire Akorn, a US-based manufacturer and marketer of prescription and over-the-counter pharmaceutical products, for $34 per share, equivalent to $4.3 billion, plus approximately $450 million of net debt. During that time, the company also announced plans to acquire Merck KGaA's biosimilars business, which closed in September 2017, for the purchase price of EUR 656 million (US$769 million).

BASF Plans Amine Facility in Nanjing

BASF will build a new specialty amines plant at its existing wholly owned site in Nanjing Chemical Industry Park in China, the company announced in a Sept. 25, 2017 press release. The new multi-product plant can manufacture 21,000 metric tons per year and further extends BASF's amines portfolio at the specialty amines complex in Nanjing. The plant is scheduled to come on stream in 2019 and will mainly produce 1,2-Propylenediamine (1,2-PDA), n-Octylamine (n-OA), and Polyetheramine (PEA). 1,2-PDA is a building block in the manufacture of pharmaceuticals as well as other chemicals.

"This investment will help us to meet the increasing Asia Pacific demand for specialty amines used as intermediates in a diverse range of industries …," said Narayan Krishnamohan, senior vice-president, Intermediates Asia Pacific, BASF, in the press release. "Through this expansion, we will be able to better serve our customers in Asia Pacific with steady and timely supply of quality products."

BASF also has manufacturing capacities for both 1,2-PDA and n-OA at its Ludwigshafen Verbund site in Germany.

GE Launches New mAb Purification Resin

On Sep. 22, 2017, GE Healthcare announced a new Protein A chromatography resin, MabSelect PrismA, for improving monoclonal antibody (mAb) purification capacity by up to 40%. The resin is alkaline-stable, meaning it can be cleaned with a higher concentration of sodium hydroxide, offering better control over cross-contamination and bioburden risks, according to the company.

Protein purification is an obligatory step in biomanufacturing, with the target protein used to make the final biopharmaceutical product extracted from cell culture. Nearly all mAbs on the market use Protein A resin as the first purification step. Protein A resin offers an efficient, common platform for different mAbs, according to the company.

With the increased efficiency of mAb production over the years, purification processing times have increased, which increasingly consumes chromatography resins. This puts pressure on purification technologies. GE's new resin, which has a high binding capacity, addresses a number of these challenges, including the increased upstream titers. Its binding capacity determines how much resin is needed to purify a certain amount of protein.

The new resin was developed and will be manufactured in GE Healthcare Life Sciences' site in Uppsala, Sweden. GE is annually investing up to $70 million in this production facility to significantly increase its capacity.

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EVENT OVERVIEW

The path through drug development is marked by detours, roadblocks, and very few shortcuts. At times you can feel that you're the only person keeping your molecule on its critical path. Unexpected delays can lead to missed milestones, rework, and delayed timelines—setbacks that no one wants to explain to investors.

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Who Should Attend

- Chief Medical Officer
- Chief Science/Scientific Officer
- Head of R&D
- Head of Chemistry, Manufacturing and Controls (CMC)
- Chief Development Officer

Key Learning Objectives

- Balancing a science-first focus with demanding business goals
- Eliminating road blocks by proactively managing your molecule's critical path
- Supplementing your team with the right science at the right time

Presenters

Aaron Williams, PMP
Program Manager,
Patheon OneSource™ Pharma Services
Patheon, part of Thermo Fisher Scientific

Anil Kane, PhD, MBA
Executive Director,
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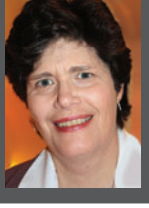

Moderator:
Rita Peters
Editorial Director
Pharmaceutical Technology

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Spectroscopy Advances for Improved Reproducibility and Easier Compliance

ON-DEMAND WEBCAST **Aired September 28, 2017**

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

EVENT OVERVIEW

Handheld Raman and near infrared (NIR) have nearly limitless applications in the pharmaceutical industry, from raw material identification to residual water in lyophilized products and granulation monitoring. Whatever the application, a persistent challenge in successful implementation of spectroscopy is ensuring the analysis method is well defined and executed by different users and sites.

The reliable deployment of NIR measurement methods and analysis models across an enterprise is key to achieving consistent, accurate measurements. Handheld Raman instruments are not immune from method deployment issues as many "black box" instruments hide methods from users and very little customization is possible.

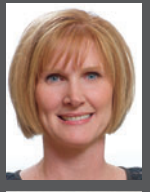
In this webcast, spectroscopy experts will discuss recent advances in handheld Raman and NIR technology that lead to faster, more effective implementation and improved regulatory compliance. New developments in instrument hardware and software will be discussed in the context of the compliant lab and manufacturing environment.

Key Learning Objectives

- The benefits of implementing spectroscopy solutions to improve materials screening and quantitative analysis throughput in all phases of production
- How a client-server approach can speed instrument deployment and simplify compliance
- How method-driven Raman can be implemented in a 21 *Code of Federal Regulations* Part 11 environment

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

Presenters



Denise Root
Field Product Specialist
Metrohm USA

Adam Hopkins, PhD
Spectroscopy Product Manager
Metrohm USA

Moderator:
Rita Peters
Editorial Director
Pharmaceutical Technology

Who Should Attend

- QA/QC, lab managers, analytical chemists, process engineers and production managers from the pharmaceutical, nutraceutical, and food industries
- Those currently inspecting and qualifying raw materials in the laboratory and are looking for a higher throughput solution
- Those who need to improve coordination between production sites

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

Enteric Capsule Technologies to Help Fast-Track Pharmaceutical Drug Development

ON-DEMAND WEBCAST Aired October 5, 2017

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

EVENT OVERVIEW

Simplifying enteric delivery for heat or acid-sensitive and/or gastric-irritating drugs from early-stage development to commercial manufacturing is a longstanding challenge in the pharmaceutical industry. Conventional methods for enteric coating require a complex process development, scale-up, validation, and clinical / bioequivalence testing. In this webcast, Dr. Jule will review considerations for applying enteric coating, and present about a novel solution – developed through a combination of polymer science and capsule engineering – that provides the industry with a viable alternative to achieve enteric protection without functional (enteric) coating. This rapid-advancement tool can speed development for Active Pharmaceutical Ingredients (APIs) requiring full enteric protection and delivery to the small intestine, and provide manufacturing efficiency through reduced process complexity.

Key Learning Objectives

- Review pros/cons of conventional enteric coating processes vs. new innovative polymer science solutions
- Learn how to simplify and accelerate the development of drug products requiring full enteric protection and/or delayed release
- Understand potential applications of a new technology for functionality, product development, branding and intellectual property protection

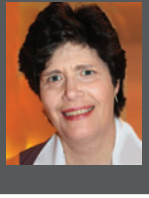
Who Should Attend

- Professionals who work in drug formulation, R&D, or product development
- Anyone working with an API that requires delayed release or enteric properties

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

Presenters

Dr. Eduardo Jule
Director, Pharmaceutical Business Development
Capsugel
—Now a Lonza Company



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MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

Ad Index

Making Decisions Based on Risk

Focusing on whether the product meets its defined quality attributes should help one make reasonable, documentable, and defendable risk-based decisions, according to Susan Schniepp, distinguished fellow at Regulatory Compliance Associates.

Q. I am a quality assurance professional in a manufacturing plant. I still struggle with the concept of risk-based decision making. Can you provide me some advice on how I can make appropriate risk-based decisions?

A. The pharmaceutical industry continues to change rapidly. Over the past 10–15 years, there have been a number of developments that have impacted how companies approach various aspects of their business including the emergence of the generic industry, biosimilars, virtual companies, contract service organizations, compounding pharmacies and 503B outsourcing facilities, mergers and acquisitions, and more sophisticated information technology platforms. The complexity of the industry today makes risk-based decision making seem convoluted at best.

Risk-based decision making is difficult no matter what position or department you are in at a company or how many years you have been in your position. Most employees are comfortable when the answer seems to be yes or no. It is much harder to make a decision when the answer lies somewhere in-between the yes and no. So, how do we go about making an appropriate risk-based decision? There isn't any magical formula or calculation to guide you. To make an appropriate risk-based decision, we need to understand the interrelationship of the product, process, and any associated deviations and investigations that occurred during manufacturing.

Let's take a look at a situation that might help clarify the risk-based decision process. You are the vice-president of quality for a manufacturing organization. One of your products for treatment of cancer is on the drug shortage list because the current API supplier has decided they will no longer provide the API. You were trying to secure a new API manufacturer but could not find one that could reliably provide the API that met the expected quality attributes, so the company has decided to cease providing the drug to the market.

You have the last three available lots of the API and have manufactured the associated final product lots. The product is aseptically filled and then lyophilized. During the inspection of the second product lot, the quality inspectors inform you that they have detected a defect and the lot has failed its second acceptable quality limit (AQL) for the defect. The defect detected is defined as product between the vial and the stopper and it displays as a white dot the size of the head of a pin. The standard operating procedure (SOP) defines this defect as 'cosmetic'. The inspectors also inform you that they expect the product lot will fail the third AQL inspection and that the product will need to be rejected per standard operating procedure requirements. They also inform you that the product has passed all other quality attributes including those determined by chemical analysis and that there were no deviations associated with the manufacturing. You ask your inspectors to halt the inspection for this particular defect while you look into the matter. The question you need to ask is: what further information do I need in order to be sure I make an appropriate decision?

The easy decision is to perform the third AQL inspection, fail the lot if it doesn't pass, and document the reason for the failure. The harder decision is to make a risk-based decision to release the lot. Let's take a look at some additional information available to help you make your decision. The first thing to determine is the medical indication for the product. In this case, the product is a cancer treatment drug. The second piece of information to determine is if the cosmetic defect has any impact on the potency of the product. In this case, through laboratory analysis, it is determined that the potency or stability of the product is not affected by this particular defect. Based on this information, you document a material review of the situation and recommend ceasing inspection of the cosmetic defect and releasing the product.

What information made you comfortable in making this decision? Because this is a life-saving drug that is in short supply, you realize that doctors will potentially need all of this product to be able to safely transition patients to an equivalent treatment because it could take more than one treatment cycle for the doctors to find an appropriate drug substitution. You were also able to determine through chemical analysis the potency was unaffected by the defect and would not pose a threat to patient safety. You will still need to investigate the defect and try and determine its root cause, but based on the data available you should be confident that the product is safe for the patient. If there is any magic formula to risk-based decision making, it is to keep patient safety in mind and focus on whether the product meets its defined quality attributes. If you keep these points in mind you should be able to make reasonable, documentable, and defendable risk-based decisions. **PT**

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