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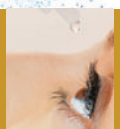

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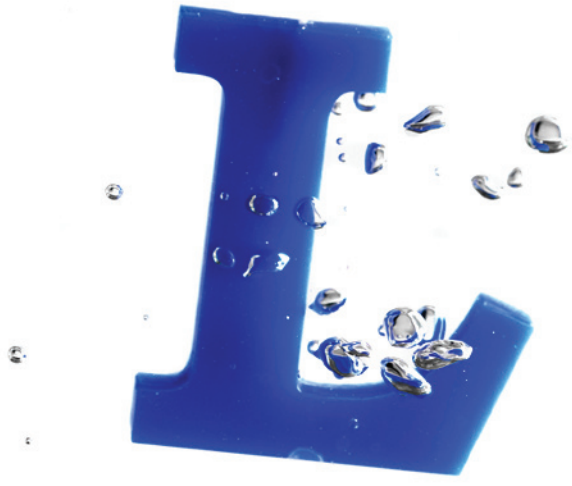

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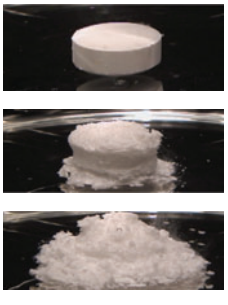

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On the cover

COVER STORY

22 Excipients for Formulation Success

Excipients play a crucial role in the manufacturing of solid-dosage forms and the performance of the finished drug product.

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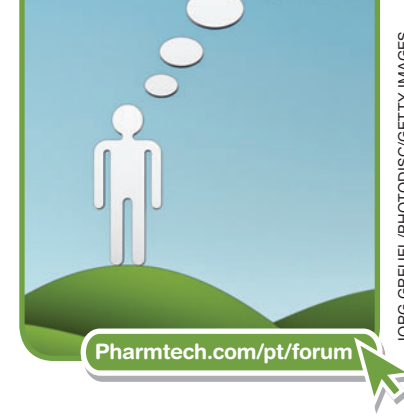

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Calling All Authors

Rita Peters

The editors seek drug development experts to contribute technical articles for 2017.

Although the calendar says October 2016, the editors of *Pharmaceutical Technology* are thinking ahead to 2017. Our publishing schedule requires that we plan in advance, starting with a comprehensive editorial calendar for the coming year, and then looking at specific topics to cover in each month.

As part of this planning process, I invite experts in drug development, formulation, and manufacturing to contribute to the print and online issues of *Pharmaceutical Technology*. The editors welcome manuscripts on subjects pertinent to all aspects of bio/pharmaceutical drug development including API development; excipients; manufacturing advances; formulation; drug delivery; quality and regulations; analytical technologies and methods; packaging, facilities design and expansion; supply chain and logistics; laboratory operations; outsourcing; and serialization/track and trace.

Ways to contribute

Both peer-review and technical article submissions are welcome. All submissions must be original, and cannot have been published previously in any format—including company literature or website postings—or any language. In addition, the articles must be objective and cannot promote a company's products or services. Authors are expected to provide suitable references to published third-party literature to support all statements in submitted articles.

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

The editors call for contributions to *PharmTech* in 2017.

We seek manuscripts that offer technical and scientific discussions of ongoing drug development challenges and solutions, which are sufficiently novel to be of interest to an experienced audience. Topics should be timely and useful and should focus on the development of small- or large molecule therapies.

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Manuscripts submitted for peer review are double-blind reviewed by the publication's editorial advisory board using procedures standard for scholarly and technical journals. Four types of peer-review submissions are considered: standard data-driven, novel research; technical case studies/application notes; topics literature or patent review; and science-based opinion paper. Accepted manuscripts are scheduled for publication in *Pharmaceutical Technology* on a first-accepted basis.

Technical articles

Pharmaceutical Technology accepts technical article contributions from scientific and technical experts from biopharmaceutical companies, academia, industry suppliers, and contract service organizations for publication in monthly issues, supplements, and as online articles.

Articles related to topics listed on the *Pharmaceutical Technology* 2017 editorial calendar are considered. You can access the editorial calendar via the Author's Guidelines link on www.PharmTech.com.

Submission guidelines

The editors have prepared guidelines for submission of peer-review papers, technical articles, and other contributions for publication in *Pharmaceutical Technology* and on www.pharmtech.com. The guidelines explain article rights, originality, and licensing; provide instructions for preparing an article for submission; list acceptable file types for figures, tables, and images; and include a style guide for references.

The *Pharmaceutical Technology* Author's Guidelines webpage explains the submission process, provides links to the editorial guidelines for peer-review and technical paper submissions, and contact information for authors. To access this information, visit www.PharmTech.com and click the Author's Guidelines link on the navigation menu. Of course, you can always reach me directly at rita.peters@ubm.com. **PT**

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Manufacturers Face Major Changes under PDUFA VI

Efforts to accelerate drug development will alter fee structure and require ready production sites.

FDA officials and industry leaders have agreed on a set of recommendations for revising and updating the Prescription Drug User Fee Act (PDUFA) and are looking for broad support from patients and the medical community to spur Congressional approval of PDUFA VI. The legislators need to reauthorize FDA fees for drugs and biologics, along with similar programs for biosimilars, medical devices, and generic drugs, before the fees expire on Sept. 30, 2017. The pressure is on because a change in administration in January 2017 will delay Congressional consideration of new programs and policies for several months.

For PDUFA VI, the agreed-on commitment letter maps out strategies to make the program less burdensome and complex, while also providing more flexibility for expediting the assessment of certain innovative products (1). An emphasis on hearing the patient voice will support development of breakthrough therapies and treatments for rare diseases and encourage innovative clinical trial designs. FDA will hold public workshops and develop a series of guidance documents for collecting patient input on disease burden, treatment impact, and clinical outcomes assessment, with an eye to enhancing reviewer understanding of the benefits of a test therapy to patients, in addition to risks.

Related initiatives are to further incorporate real-world evidence and benefit-risk assessment into drug development so that these approaches can help evaluate efficacy, in addition to tracking safety issues postapproval. FDA also plans to expand the Sentinel System to enhance drug safety monitoring and promises timely, advance communication to manufacturers on emerging safety signals.

More streamlined oversight of combination products is another priority of PDUFA VI, and FDA plans to expand staff and promote more coordination between at the Office of Combination Products and review centers for drugs, biologics, and medical devices. PDUFA will fund an increase in reviewers for these complex products, development of guidance on bridging studies and labeling, goals for timely review of protocols for human factors studies, and an independent evaluation of the combination program.

Revising fees

These and other initiatives will be supported by a significantly revised PDUFA fee structure. A new "program" fee will replace current levies on manufacturing facilities and on products, and will be calculated to yield 80% of the anticipated $1.2 billion collected by PDUFA in 2018. Application fees will add up to only 20% of program cost, thus reducing FDA's reliance on revenues that can vary from year to year.

A related change is to drop user fees altogether for efficacy and manufacturing supplements. FDA has found this aspect of PDUFA difficult to administer, and supplement fees have not been a major source of revenue for the program. The change also aims to encourage manufacturers to update labeling on a more-timely basis and to pursue improvements in production systems to ensure quality operations.

The new program fee will be based on the number of approved drugs and biotech therapies marketed by a firm. This move away from facility fees reflects industry's expanded use of contract manufacturers for drug production, which often makes it difficult to assess the portion of a facility allotted to each pharmaceutical client. FDA and manufacturers have found it hard to administer the billing process for facility fees due to frequent changes in the drugs a contractor produces and the clients involved.

Levying a larger fee for each marketed product, however, could encourage manufacturers to halt production of older drugs that are only marginally profitable. Another risk is that high product fees might discourage development of personalized therapies that may have 5, 10, or more different formulations of the same product. To prevent that outcome, the negotiators agreed to set program fees on a maximum of five versions of the same therapy; additional formulations would not pay another fee. Despite some uncertainty about how fee changes may influence production decisions, manufacturers and FDA are optimistic that the new fee structure will be more predictable for all parties and that the PDUFA program will be more sustainable and manageable.

At the same time, PDUFA VI puts more pressure on manufacturers to fully prepare and identify production sites before submitting a new drug application (NDA), biologics license application (BLA), or supplement so that all relevant facilities can be listed in the filing. The user fee program sets increasingly short timeframes for the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) to take action on applications, especially those for more innovative therapies. FDA may delay product approval if an application lacks certain important data, and now that specifically applies to information on manufacturing facilities.

The aim is to provide FDA with sufficient time to inspect and evaluate all planned production sites. PDUFA VI gives FDA authority to extend an approval goal date by two or three months if a sponsor fails to identify a facility in its initial list, a serious shortcoming according to Kay Holcombe, senior vice-president of the Biotechnology Innovation Organization (BIO).

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She commented at the August 2016 PDUFA public meeting that industry is obligated to submit complete and high-quality applications to FDA, and that failing to mention where the firm plans to make a drug or biologic is "shocking." But evidently, agency staffers have run into enough incomplete facility listings to single this issue out for specific attention.

Streamlining operations

FDA also plans to tap user fees to improve certain internal operations and programs. There will be added resources to make the agency's electronic submissions process faster, more transparent, and more predictable. And PDUFA will support strategies to keep FDA staffers from drowning in meetings. While agency officials encourage sponsors to meet early and often with staff to discuss and gain agreement on product development plans and strategies, this approach has overwhelmed CDER and CBER with some 3000 meeting requests in 2015, which also involve pre-review of thousands of pages of background data. Agency officials seek to improve the process by resolving some issues in writing, instead of in-person meetings, and to provide staff with more time to examine meeting documents.

A main goal for FDA in negotiating PDUFA VI was to gain stakeholder support for a more concerted effort to improve the agency's hiring process. FDA wants to bring more scientists and experts into the agency, but has difficulty competing for talented professionals due to low salaries, strict conflict-of-interest (COI) policies, and a long and convoluted hiring process. While the low-pay and COI issues reflect broader federal employment standards that FDA cannot easily change, this latest PDUFA plan sets clear goals and timeframes for filling vacancies more expeditiously. New procedures would clarify and simplify job announcements and bring in head hunters to identify prime candidates.

A new high-level office will oversee recruitment and retention of qualified scientific and medical personnel, reflecting a commitment by top FDA officials to improving its staffing situation. The current shortfall of 200 employees in CDER's Office of New Drugs is not just an FDA issue, commented Holcombe of BIO, but "a public health problem." Without added expertise, stakeholders believe that FDA cannot meet the many goals and challenges of the PDUFA program.

Reference

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Pharmacovigilance of Biologics Under Scrutiny

Regulators are tightening up on post-marketing monitoring of biological medicines to detect deficiencies caused by manufacturing problems, particularly those stemming from post-authorization changes in the manufacturing process.

The European Union introduced a guideline (1) in August 2016 on the monitoring of the safety of biological medicines on the market amidst industry worries about the ability of regulators to deal with quality deficiencies due to manufacturing variations in biopharmaceuticals. Manufacturing standards can have a bigger impact on the post-marketing safety and efficacy of biological medicines than those of chemically synthesized pharmaceuticals with which different producers can achieve a uniform quality.

"[With biologicals], the manufacturing process—including choice of cell line, raw or starting materials, fermentation and purification process, final formulation—is as much a determinant of the product's quality as the active substance," states the guideline (1). "Minor changes in any manufacturing step can affect the product quality and subsequently its safety and efficacy." As a result, the guideline, published by the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA), constantly highlights the need to find the "root cause" of a suspected adverse drug reaction (ADRs) by tracing the product back not only to its manufacturer but also to its batch and the individual medicines within it.

Lack of traceability

The guideline applies to reference biological medicines, biosimilars, and related biological products such as interferon and faction VIII. Traceability is the vital tool for discovering what could be responsible for the lapse in quality during the manufacturing that has impacted the safety and efficacy of the medicine on the market. It has become even more important in the wake of a rise of approximately 50% in the reporting of suspected ADRs in Europe, a large proportion of them relating to biologicals.

In 2014, biologicals accounted for 42% of 181,000 side-effect reports on centrally approved medicines in the EU or 27% of all suspected adverse reaction reports. Yet, the pharmaceutical industry has been protesting about the weaknesses of the traceability system operated by the European regulatory network, headed by EMA and the regulatory authorities of 28 EU member states represented by the HMA.

Dissatisfaction with the standards of traceability, especially tracking medicines back to the batch and product stages of their manufacture, was evident in the industry's comments during a public consultation on the last draft of the guideline (2) before the issue of its final version. Comments (3) made during the consultation were published with the guideline.

The European Federation of Pharmaceutical Industries and Associations (EFPIA), Europe's main trade association for research-based drug companies, and its sister biotechnology organization, European Biopharmaceutical Enterprises (EBE), welcomed the guideline's emphasis on the importance of batch traceability. "But overall, [it] does not appear to acknowledge the sheer practical challenges of obtaining batch numbers when a suspected ADR is reported for any product and especially biological medicinal products where the reporter may not even be aware of the batch number," the two organizations said (3), referring to medicines such as insulin, which had been on the market for decades, but also more recent products.

The current pharmacovigilance legislation

Marketing authorization holders have had a low response rate to repeated requests to the ADR reporter, usually a healthcare professional, for batch data. This has often been due to hospital supply difficulties resulting in substitution so that the prescribers did not know that the patient had been dispensed a biosimilar rather than the original brand, according to EFPIA and EBE. Because of differences in member state regulations on issues such as substitution and hospital prescribing, EFPIA and EBE doubted whether the EU's present pharmacovigilance legislation on post-marketing surveillance of medicines could provide an adequate traceability system, especially for biologicals.

"Until there is a consistent system in place across the EU that reliably tracks batch numbers of medicines dispensed to patients and follows this throughout the entire treatment pathway, it is unrealistic to expect such information to be collected via current routine pharmacovigilance activities," the two organizations said (3).

The EU's current pharmacovigilance (PV) legislation (4) was approved in 2012 with EMA being made responsible not just for monitoring centrally approved medicines but coordinating the whole PV system in the EU and the three non-EU states of Norway, Iceland, and Liechtenstein. EMA also maintains various central databases storing information on ADRs both in Europe and worldwide.

Member states of the EU have been criticized for delaying the transposing of the PV legislation into their national laws with some holding back the transfer to 2014. In addition, the publication of PV guidelines on a range of aspects of the legislation has been slowed down.

The European Association for Bioindustries (EuropaBio) has, for example, urged that the biologicals guideline should only come into effect with other relevant guidelines whose revision has yet to be finalized, particularly dealing with risk management of known and potential safety issues. In addition to the issue of manufacturing variability and

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traceability, the guideline pinpoints other major challenges with pharmacovigilance of biologicals, such as immunogenicity and stability of the medicines during distribution. Nonetheless, EMA and HMA have made few significant changes in the guidelines following the comments during the public consultation, despite the increased burden on the industry in dealing with the big rise in ADR reports.

In the final version of the guideline, the need for MAHs to give details of numbers/codes of batches and their geographical distribution in safety update reports, particularly after changes to manufacturing processes, has been deleted. But it does refer to batch information as being "required data" when MAHs assess new ADRs needing further investigation. The guideline also mentions the necessity to obtain information on batch numbers when MAHs submit or update risk management plans particularly in cases of batch-specific matters.

The European industry has been calling for more consistency in the application of pharmacovigilance by the EU's member states.

Recording ADRs

The importance of healthcare professionals and patients giving batch and product data when reporting ADRs is stressed even more strongly in the guideline's final version. EMA and HMA are hoping that the increased transparency of the PV system will encourage the two groups to become more active in post-authorization surveillance.

The guideline suggests that information on the manufacturing process for biologicals and its variability should be communicated to not just healthcare professionals but to patients as well. Medicines for Europe, formerly the European Generic and Biosimilar Medicines Association (EGA), said that regulatory authorities should consider as an "essential step" the continuous training of professionals on the new PV rules on recording of ADRs and related product information.

The European industry as a whole has been calling for more consistency in the application of pharmacovigilance by the EU's member states. More uniformity has been particularly important in areas where there seems to be a clash between the PV responsibilities of MAHs to find the "roots causes" of ADRs and the freedom for countries to take their own initiatives in post-marketing surveillance.

"It is important to have a clear separation between activities falling under member state responsibilities and expectations of the marketing authorization holder in terms of traceability," an EFPIA spokesman told *Pharmaceutical Technology*. He points out that the guideline stresses that different products with the same international non-proprietary name (INN) should be "readily distinguished so safety issues can be traced to a product, batch, location, or patient."

Pharmaceutical packaging regulation

Yet member states will be able to exempt hospitals and other healthcare facilities from certain safety features under an EU pharmaceutical packaging regulation (5) due to come into effect in early 2019. The regulation, which is part of the EU's Falsified Medicines Directive (FMD) to combat counterfeiting of pharmaceuticals, stipulates that individual medicines should have a 2D matrix serialization barcode containing a "unique identifier," consisting of a product code, serial and batch numbers, and expiry date. The packaging safety features scheme will be an 'end-to-end' system under which the serialization and other data on each pack can be verified by a pharmacist with a scanner at the dispensing point.

The regulation is seen by both regulators and industry as a possible effective means of tackling traceability problems with biologicals. "[Yet] member states can exempt healthcare institutions—including hospitals and in- and out-patient clinics—from the obligation to verify safety features on the packaging, including the unique identifier," says the EFPIA spokesman. "It needs to be understood that the traceability will depend upon the way each member state implements the (regulation)."

Due to manufacturing variability between a growing number of biosimilars and their reference products and increases in changes of manufacturing processes, an effective PV system covering biologicals throughout their lifecycle will become even more vital. A high level of efficient traceability will be a crucial part of that.

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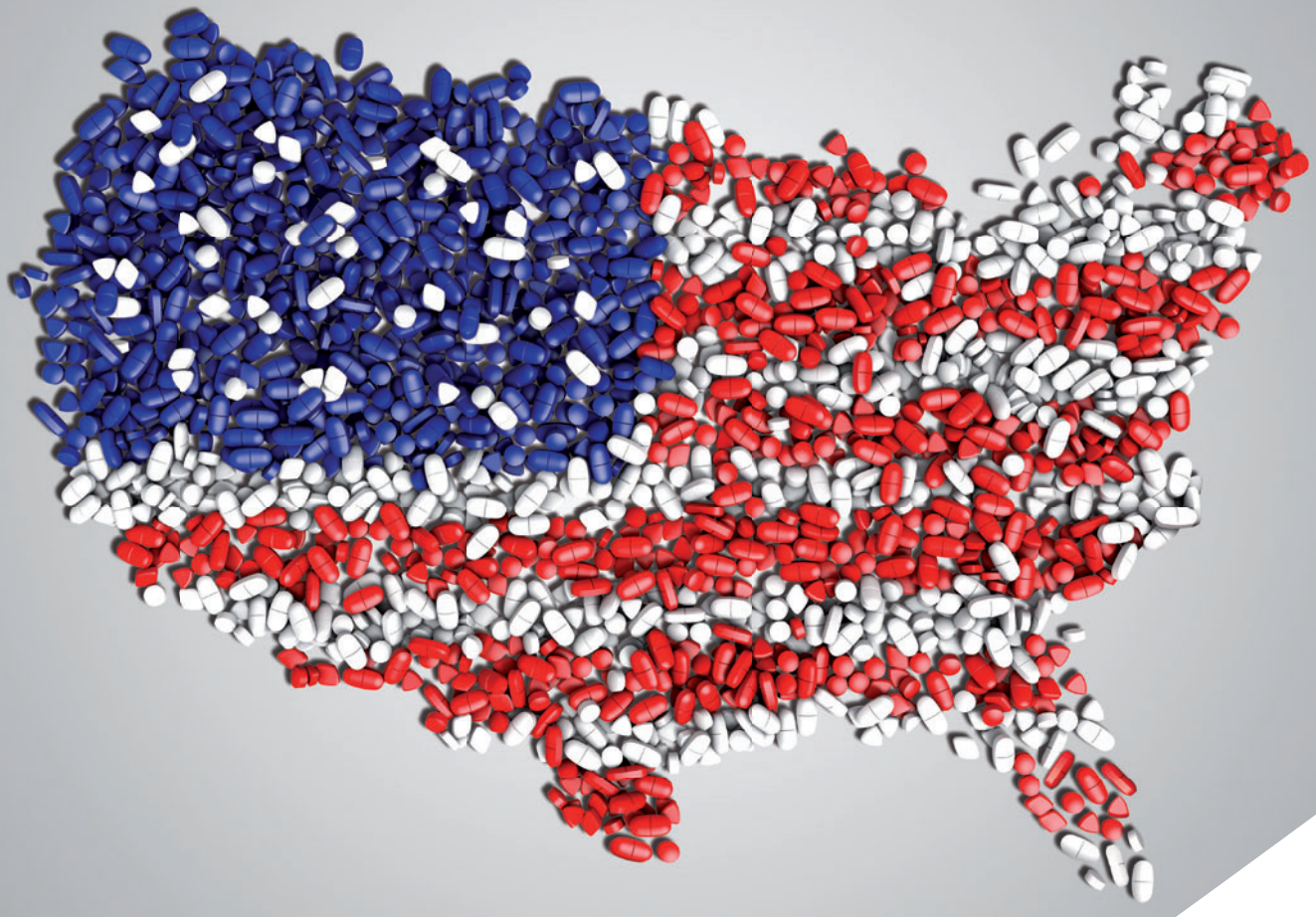

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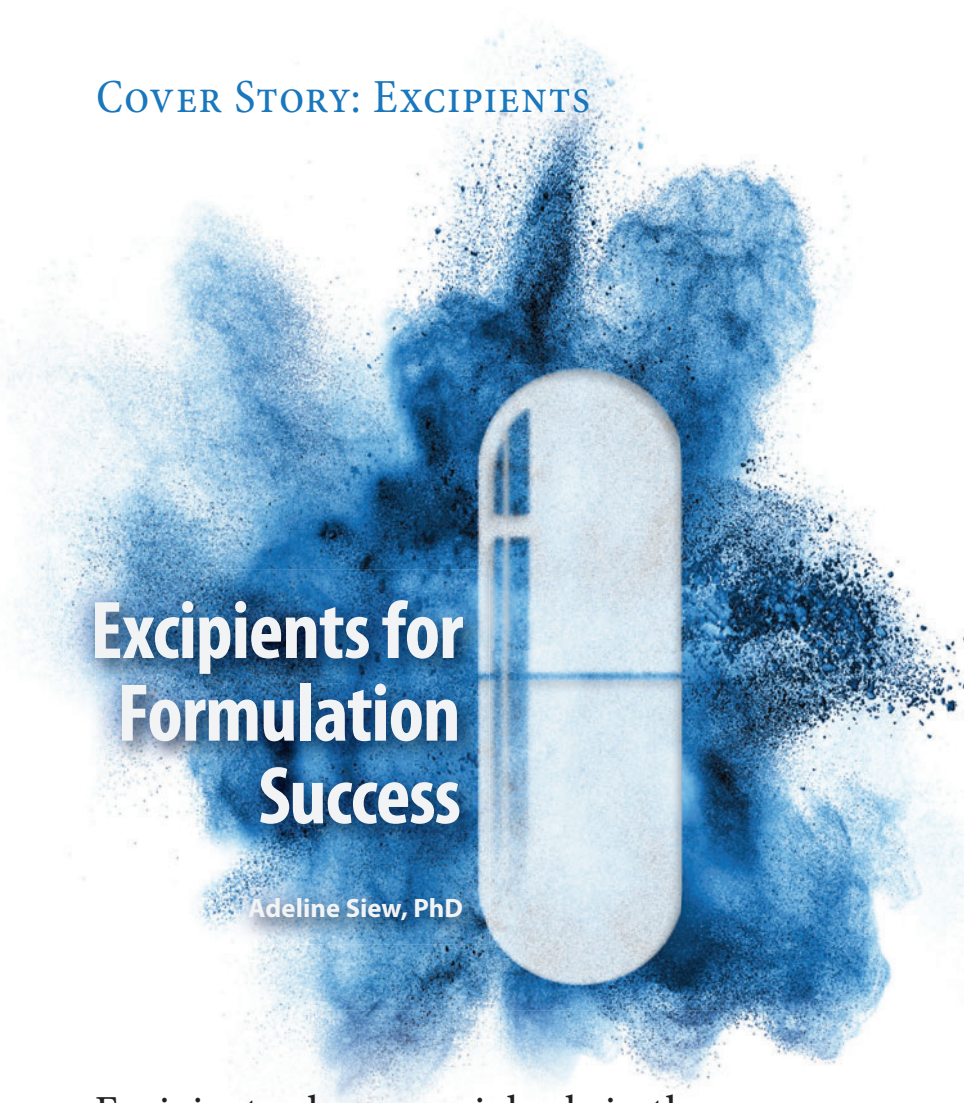

Excipients for Formulation Success

Adeline Siew, PhD

Excipients play a crucial role in the manufacturing of solid-dosage forms and the performance of the finished drug product.

Excipients are typically the major components of a solid dosage form. These non-active substances have well-defined roles in the development of tablets and capsules, and are included for a number of reasons such as to aid the manufacturing process or to add functionality to the formulation.

Excipients for processing

Excipients can be divided into several broad processing categories for functionality, notes Paul Skultety, vice-president, Pharmaceutical Development Services, Xcelience, a division of Capsugel. Bulking agents such as lactose, dibasic calcium phosphate, or microcrystalline cellulose are used to make the dosage form bigger in size, he says, firstly, so that it is easier to manufacture, and secondly, to achieve a practical tablet weight for patients to handle. The minimum tablet weight is typically approximately 50 mg.

Binders such as pregelatinized starch, microcrystalline cellulose, and various polymers are included to facilitate the granulation step. Binders hold the granules together, making the powders easier to compress. Glidants (e.g., colloidal silica) promote powder flow by reducing interparticulate friction and cohesion, enabling the powder to flow better in the hopper and when filling the tablet or capsule dies. Good bulk powder flowability is essential in high-speed processing and reduces problems associated with content uniformity, which can happen if the powders do not flow uniformly, explains Skultety. Lubricants, such as magnesium stearate or stearic acid, are often used in combination with glidants to reduce the tackiness of the powders. Lubricants prevent sticking of the granules or powders to the dies or punches during compression.

Excipients are also included to protect the API. Antioxidants such as ascorbic acid, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) are used with compounds that may be susceptible to oxidation, says Skultety. In cases where it is necessary to control the pH of the local environment, pH modifiers such as citric acid or sodium acetate can be added. These agents can help if solubility or stability is better in a certain pH range, he explains. Wetting agents such as polysorbates or sodium lauryl sulfate can be added to help wet the API and get it into solution faster.

Direct compression

In recent years, the term "functional excipient" has been used more often to describe an excipient that can provide an added function or quality over and above the "conventional" excipients, observes Rob Harris, chief technical officer at Juniper Pharma Services. For instance, powder flow for direct compression formulations may be improved with the inclusion of co-processed silicified microcrystalline cellulose, he says.

According to Andrew Bulpin, head of Process Solutions Strategic Marketing and Innovation at MilliporeSigma, an ongoing trend in the industry is toward direct compression for oral solid-dose forms to reduce process complexity. As a result, there are specific requirements regarding the particle structure of the excipient that excipient manufacturers have to address. JRS Pharma's silicified microcrystalline cellulose (Prosolv SMCC) is a unique combination of microcrystalline cellulose (MCC) and colloidal silicon dioxide (CSD). This functional excipient was developed to address common problems of conventional binders such as low bulk density, poor flow, loss of compatibility, stickiness, and sensitivity to lubricants (1). According to the

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excipients manufacturer, the production process of Prosolv SMCC leads to homogenous and much finer CSD particle size distribution. Surface area is increased as a result, which enables better flowability and compactibility, and subsequently improves the content uniformity and stability of the formulation. It can be used for direct compression, in which it reduces the number of required excipients and use levels (1).

Solubility enhancement

Ensuring sufficient API bioavailability is a prevalent challenge for formulators, Bulpin highlights. While there are various solutions available, one approach is to use functional excipients to improve solubility, which will in turn lead to bioavailability enhancement. Inert drug carriers can be used as a vehicle for poorly soluble APIs, he says, and Parteck SLC, a silica carrier with unique pore structure, is well suited for this application.

Mesoporous silica grades, such as MilliporeSigma's Parteck SLC, are a relatively recent addition to the excipient listing, observes Harris. According to him, they are becoming popular in formulations due to their highly porous structure, which can be used to hold liquids (effectively converting liquids into free-flowing solids) or to hold poorly-soluble drugs in the amorphous form, thus enhancing solubility of the drug. Parteck SLC's mesopores provide a surface area of up to 1000 m^2/g for depositing an API, and the API is kept stable. A user-friendly particle size of 5–25 µm and bulk density of 0.32 g/mL allow easy loading, tableting, or capsule creation (2).

Polymers and copolymers—such as cellulosics (e.g., hydroxypropyl methylcellulose [HPMC], hydroxypropyl methylcellulose acetate succinate [HPMCAS]), polyvinylpyrrolidone (PVP), acrylates and methacrylates, polyethylene glycol (PEG), and polyethylene oxide (PEO)—also play a crucial role as solubilizing excipients, particularly in the formulation of amorphous solid dispersions. These polymers are amphiphilic in nature; the hydrophobic and hydrophilic sites enable them to interact favorably with the lipophilic drug and yet disperse and dissolve in aqueous environments such as the gastrointestinal tract. The specific interactions of the polymer with itself, the API, and the aqueous medium can result in a range of solubilizing structures, including micelles, colloids, and ionic complexes (3). Examples of such solubilizers include Soluplus (BASF), Affinisol (Dow), Eudragit E, and Eudragit L 100-55 (Evonik).

The majority of modified-release technologies are based on the use of polymers to encapsulate the API and control its rate of release.

The cyclodextrins form another class of functional excipients that are widely used for solubility enhancement purposes. Cyclodextrins are cyclic oligosaccharides derived from starch that take the shape of a truncated cone consisting of a lipophilic central cavity and an outer hydrophilic shell. The mechanism of solubilization is based on the ability of the cyclodextrin to form water-soluble inclusion complexes with the poorly soluble drug. Besides enhancing solubility, formulation with cyclodextrins has also been shown to improve the physical and chemical stability of some APIs (4). A number of cyclodextrin-based products are already on the market, for example, Takeda's cefotiam-hexetil hydrochloride tablet (Pansporin T), Novartis' nimesulide tablets (Nimedex), and Janssen's itraconazole capsules (Sporanox), to name a few (4).

Modified-release applications

To increase patient compliance, it is crucial to tailor an API release profile to maximize API efficacy and at the same time reduce side effects, as well as dose frequency, Bulpin points out. Modified-release, functional film-coating systems can be used to delay or extend the drug release from the dosage form, says Pankaj Rege, general manager, Manufactured Excipients, Colorcon. He adds that besides providing product differentiation and branding, film coating can help improve patient compliance by aiding swallowability and taste-masking unpleasant APIs.

The majority of modified-release technologies are based on the use of polymers to encapsulate the API and control its rate of release. Ethylcellulose polymer has long been used as a coating material for such applications. Colorcon's Surelease and FMC Biopolymer's Aquacoat ECD, for example, are aqueous coating systems in which ethylcellulose works as the rate-controlling polymer for drug release. The principle is based on drug diffusion across a water-insoluble membrane. Ethylcellulose aqueous dispersion provides a stable, reproducible, pH-independent drug-release profile with similar dissolution profiles in both fed and fasted states (5). The drug-release profile can be tailored by adjusting three critical formulation attributes—plasticizer, pore former concentration, and film thickness.

According to Kathrin Nollenberger, director of Formulations and Polymers, Evonik, recent developments focus on further improvements of existing excipients, for example, to simplify the use or increase the efficiency of coating systems by easy-to-use or ready-to-use premixes (e.g., Eudragit E PO ReadyMix). Applying such coating systems reduces the risk for failures, as well as saves production and storage costs, she says.

Another focus is to address new challenges such as alcohol-induced dose dumping (ADD) from modified-

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release formulations, Nollenberger highlights. Dose dumping may occur if the polymer matrix or film coating, which controls drug release, is compromised through dissolution in hydro-alcoholic liquids. Dose dumping is the rapid release of the entire dose or a significant fraction thereof in a short period of time.

One solution to ADD, according to Nollenberger, is to combine the use of existing excipients to novel formulation systems. "An example for such an enabling formulation system is Evonik's technology platform Eudratec ADD, which offers a portfolio of novel coating formulations for extended- and delayed-release formulations using combinations of existing functional polymers for ensuring alcohol-resistant coatings for monolithic and multiparticulate dosage forms," she says. "Reaching this target without any chemical modification of approved and monographed polymers allows an easy and direct application without additional regulatory hurdles."

Moisture protection

An immediate-release dosage form of a moisture-sensitive API will require measures to protect the drug from humidity, both from the excipients and during processing, Harris highlights. Excipients chosen would either be anhydrous or have low water activity, he says, adding that a "dry" process for manufacture would be required, either by powder blending/direct compression or dry granulation by roller compaction.

According to Rege, formulation development of a moisture-sensitive API requires selecting excipients that mitigate moisture migration as well as applying a moisture-barrier film coating. The low water activity of Starch 1500, a partially pregelatinized maize starch from Colorcon, makes it a good choice as a filler and disintegrant for moisture-sensitive formulations, he notes. Starch 1500 acts as a moisture scavenger, and when used in combination with microcrystalline cellulose, it produces a great mix of good tablet hardness and rapid disintegration, Rege observes. In addition, moisture-barrier film coatings such as Opadry amb II (Colorcon) have been reliably used and are proven to improve the stability of the product in-use and in long-term accelerated stability studies, he says.

Dose dumping may occur if the polymer matrix or film coating, which controls drug release, is compromised through dissolution in hydro-alcoholic liquids.

Excipient selection

"The selection of excipients is crucial to ensure you end up with components that provide a stable drug product with the desired pharmacokinetic properties," says Skultety. "For example, if the dosage form is a gelatin capsule, it may be best to avoid excipients that are very hygroscopic as they will have a tendency to adsorb moisture from the capsule shell, which can make the capsule shell brittle." HPMC capsule shells, which contain much less moisture, can be used as an alternative. According to Skultety, these shells are more flexible and are resistant to crosslinking, which provides a better formulation option for hygroscopic and moisture-sensitive ingredients.

Before starting any design-of-experiments (DOE) work to support the quality-by-design (QbD) approach, Skultety recommends reviewing all the excipients to determine which ones may be critical to the formulation. Upon identification, formulation optimization work and varying the quantities of critical excipients to determine the robustness of the formulation should be performed. "For controlled-release formulations, it is best to do some DOE work around the release-controlling excipients," he says. "DOE will help to define what the critical parameters are and provide a design space in which the formulation can be successfully manufactured." Skultety also stresses that the polymer being used to control the release of the active ingredient needs to be consistent so that the drug release from the dosage form will be consistent from lot to lot of polymer used.

Nollenberger points out that the variation of polymer properties is of particular relevance for polymers taken from natural sources such as cellulose derivatives, starch, or carrageenan. "For these naturally derived polymers, small changes in the raw material source can lead to significant changes in the drug product performance," she explains. "However, for excipients manufactured by fully synthetic processes (such as, the Eudragit polymers), variations of properties are typically much less pronounced, leading to a defined performance and a better control and prediction of their behavior in the formulation."

As a rule of thumb, Nollenberger asserts that the development of an oral-dosage form should always be based on at least three different batches of the determining excipients, as the performance of the drug product is an interplay between API, excipients, and the manufacturing processes applied. DOE studies are crucial to determine the optimum parameters for ensuring a robust process, she says. During development, each excipient should be selected on a sound justification of its function in the formulation. Control measures to ensure the functionality need to be developed and thoroughly assessed. Also, the selected quantities need to be determined and justified by meaningful DOE studies, says Nollenberger.

The impact of excipient variability

Today, the industry has a wide variety of excipients compared to past years, notes Anil Kane, global head of Formulation Sciences at Patheon. The excipients used in solid oral-dosage forms are available from various sources and a variety of grades, he says. Although the selection of excipients

with the proper functionality and their corresponding levels in the drug product formulation are crucial to drug product performance, a deeper understanding of how variability in the excipients can affect drug product performance and the proposed control strategy is also an important component of improved drug product development (6).

According to Kane, a number of drug product recalls identified excipient variability, and therefore, a lack of an adequate control strategy, as a key contributor to why the drug product failed. This problem further underscores the need for improved excipient variability understanding, he asserts. However, evaluating the impact of excipient variability on drug product performance has presented a greater challenge to date than evaluating API and process impacts on drug product performance. This difficulty is partially due to the pharmaceutical manufacturer having more internal capability to manipulate the API and the manufacturing process for experimental study, he explains.

For excipients, the observed lot-to-lot variability for an individual grade is a function of the control strategy put in place by the excipient supplier, Kane notes. Due to the scales of excipient manufacture and the broader industrial application of many of the materials used as pharmaceutical excipients, it can be difficult for pharmaceutical manufacturers to easily obtain an ideal set of samples to adequately investigate the impact of excipient material properties on drug product performance. Furthermore, the number of excipient material properties combined with the number of excipients in a drug product formulation presents a financial and logistical challenge for executing manageable experimental designs, he says. Risk-based approaches to identify the most impactful excipient material properties have been previously examined as a way to streamline experimental evaluation of excipient variability impacts of drug product performance (7). In addition, Kane believes that a data-based analytical method, which uses quantitative physicochemical property data included in vendor certificates of analysis to further evaluate excipient lot-to-lot variability for a larger number of excipient properties reported by the excipient vendor, could be useful (8).

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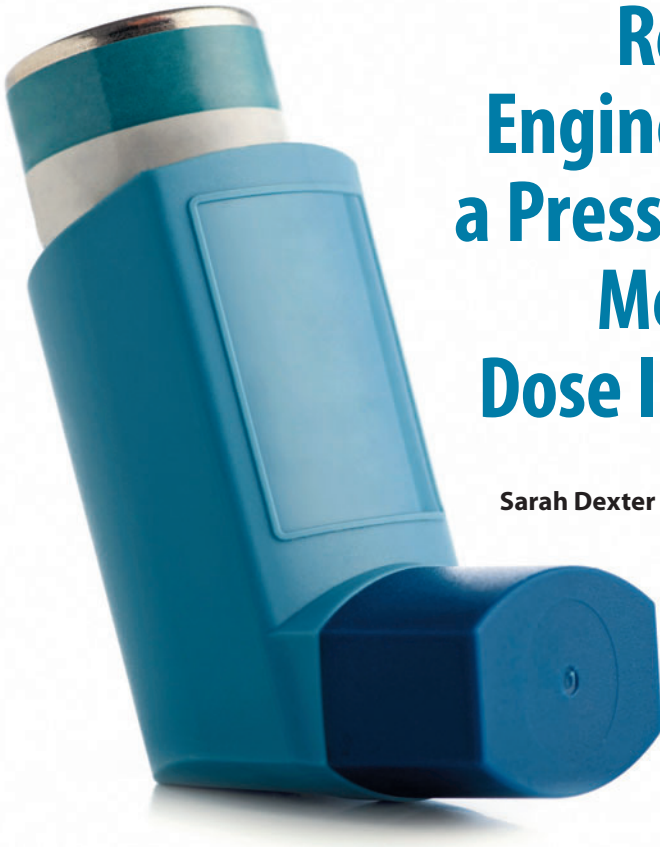

Reverse Engineering a Pressurized Metered Dose Inhaler

Sarah Dexter and Alex Slowey

Understanding the components of a reference marketed pMDI is needed to develop a generic pMDI.

Developing a generic equivalent to a current, marketed pressurized metered dose inhaler (pMDI) product can be challenging. Thorough analysis is crucial to gain a comprehensive understanding of the physical attributes and pharmaceutical performance of the reference marketed product. Many factors need to be assessed, understood, and combined to successfully develop a generic pMDI that will meet the regulatory and quality requirements as an equivalent product in the anticipated target market.

Significant information about the reference marketed product can be obtained from a thorough review of published literature, specifically the summary of product characteristics (SPC) and patient information leaflet (PIL). Additionally, baselining the reference marketed product for pharmaceutical performance offers a working target specification for *in-vitro* correlation that will ensure the smoothest possible path to commercialization and maximize return on investment. Baselining of the reference marketed product is also done to understand batch-to-batch variability and product performance over the stated shelf life to establish targets for critical quality attributes (CQAs), which can be applied to the generic equivalent pMDI.

The development of generic pMDIs must, therefore, use a total system approach to fully design and optimize new products to be safe, efficacious, robust, and reliable during patient use and over the product shelf life. To develop a generic equivalent, a number of elements are required to work together to ensure that the finished pMDIs operate appropriately and meet the appropriate regulatory and quality requirements. These sub-systems can be summarized as the input API, formulation composition, actuator, valve, canister, and secondary packaging.

Although significant information can be obtained from an *in-vitro* perspective, it is often the generation of *in-vivo* clinical data that is required to demonstrate equivalence between a new generic pMDI and the reference marketed product. In Europe, the orally inhaled product (OIP) guidelines describe a stepwise approach that should be employed to develop and gain registration of generic pMDI equivalents to current marketed products (1).

This article considers the various components of a reference marketed product that should be subject to reverse engineering. An understanding of these factors should be established in parallel to determining the pharmaceutical performance of the reference marketed product. The determination of the CQAs should include assessing the emitted dose of the product via dose content uniformity (DCU) or uniformity of delivered dose (UoDD) analysis depending on the target market. The aerodynamic particle size distribution (APSD) of the emitted dose should also be established using appropriate methodology—for example, Andersen cascade impactor (ACI) or next generation impactor (NGI). Analytical methodology for determining such factors should be appropriately developed and validated for this purpose. Testing regimens must be developed with consideration to both the marketed product and development products to ensure no bias in testing.

When selecting reference marketed products for reverse engineering, one should bear in mind that products supplied by the same manufacturer to different markets may not be identical. Some differing product attributes may be obvi-

Sarah Dexter and **Alex Slowey** are both formulation Specialists at 3M Drug Delivery Systems, www.3M.com/dds.

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ous, such as the presence of a dose counter or a particular secondary packaging, while others are subtler and are only discernable with close internal inspection. Product differences may also exist between different product strengths.

Many factors need to be assessed, understood, and combined to successfully develop a generic pMDI that will meet the regulatory and quality requirements as an equivalent product in the anticipated target market.

Formulation

Formulation composition. API concentration(s) should be discernible from the reference marketed product information. Additional excipients should be listed in the published SPCs; however, it is unlikely that the concentration of the excipients or the reason for their inclusion will be specified in the SPCs. Information on additional excipient concentrations may be present in patents, clinical literature, or other sources such as FDA's Inactive Ingredients website. A thorough review of the patent landscape is advised, not only to ascertain if a direct copy is feasible but also to understand the intellectual property (IP) rights and freedom to practice surrounding the manufacture/processing of the API or the pMDI product.

Visual examination of the formulation will determine whether the reference marketed product is a solution or a suspension. It may offer insights into formulation composition and its suspension characteristics. Observing suspension behavior (e.g., the rate of creaming or sedimentation) may be useful for optimizing analytical methodology and developing patient usage instructions. Visualizing formulation suspension characteristics and deposition on the container closure system (CCS) may help to explain any trends in pharmaceutical performance data.

API particle size distribution (for suspension only). Identifying the particle size distribution (PSD) of the API in the reference marketed product enables selection of suitable input raw materials for feasibility studies. This assessment can be determined using appropriate laser diffraction particle sizing methodology. It should be noted, however, that although PSD determination is particularly beneficial for pMDIs containing a single API, it has limitations for a pMDI containing two or more APIs in suspension. For suspension products, selecting an API with a PSD close to that of the marketed product increases the likelihood of matching the *in-vitro* APSD.

Visual examination of the formulation will determine whether the reference marketed product is a solution or a suspension.

Fill weight and number of actuations. Confirming fill weight and number of actuations per unit provides an indication of the required canister size and amount of formulation overage in the canister. Differences in fill weight or canister size between the reference marketed product and generic product may lead to variances in headspace, which can impact pharmaceutical performance.

Actuator

During reverse engineering, the reference marketed product actuator is evaluated for key parameters such as mouthpiece design, spray cone, exit orifice attributes, and expansion chamber geometry. These parameters should be incorporated into the design of the actuator for the new generic product if possible.

Actuator features and outer dimensions. Differences in actuator design and mouthpiece geometry will affect factors such as spray pattern, spray force, and deposition of API on the actuator. The following general attributes should be considered:

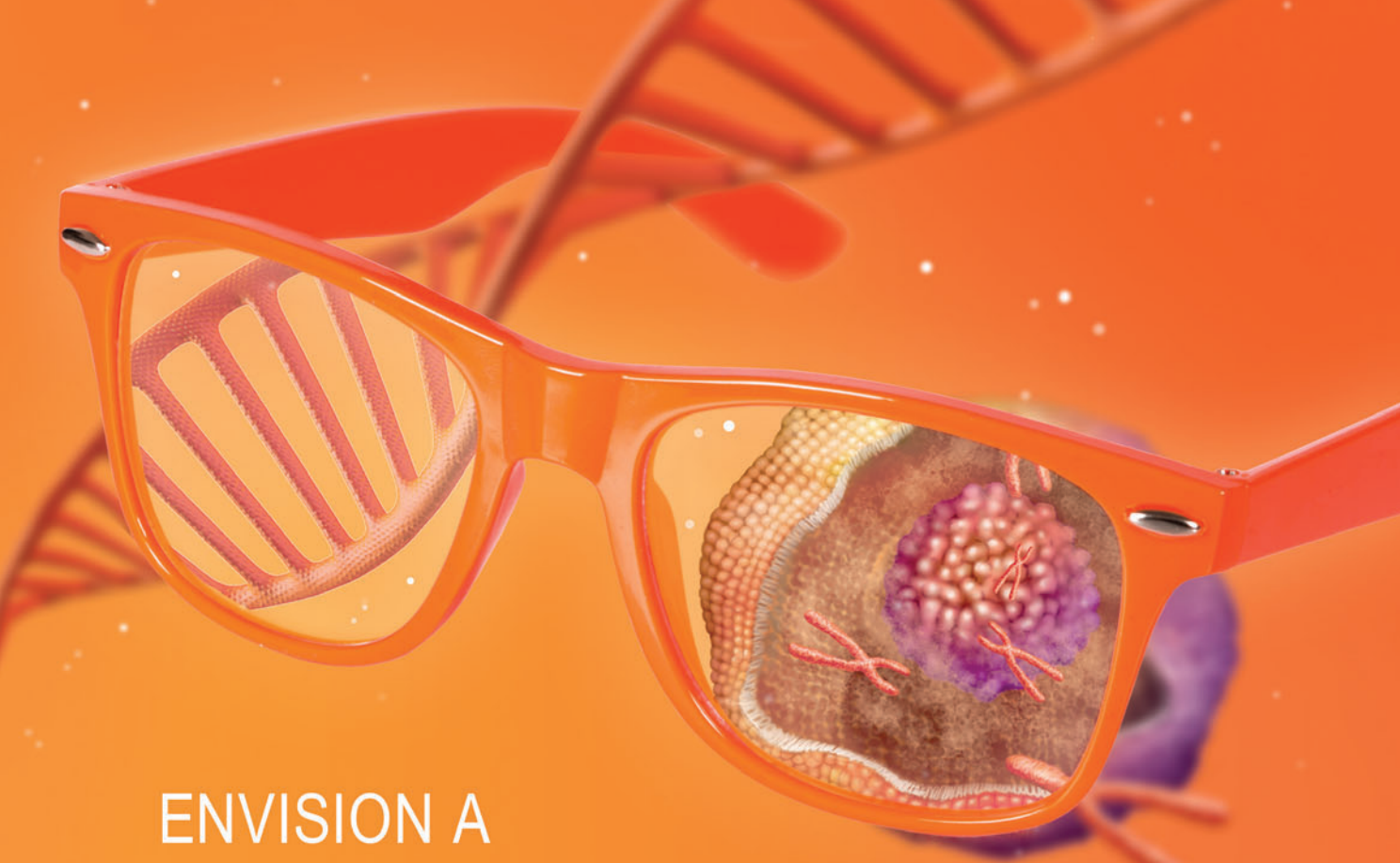
- Mouthpiece shape and actuator dimensions
- Presence of dust cap (tethered or loose)
- Materials of construction.

Other specific details to consider during the development of a generic equivalent product include the following.

Spacer compatibility. Testing with a spacer may be required during pharmaceutical/clinical testing. Ensuring that the generic product is compatible with the specified spacer will improve the probability of matching the reference marketed product from an *in-vitro* and *in-vivo* perspective.

Dose counter. Depending on the intended market, it is likely that some generic new pMDI products will require a dose counter or dose indicator (DC/DI). While it is unlikely that a direct copy of a dose counter will be possible, something functionally and visually similar should be developed to maintain patient recognition. The presence of a DC/DI (particularly integrated) may also affect the pharmaceutical performance of a product.

Spray orifice diameter (exit orifice diameter). The size of the spray orifice affects the APSD of the formulation and is, therefore, a critical parameter when trying to



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match a reference marketed product. Typical spray orifice diameters range from 0.3 to 0.6 mm and can be determined using microscopy.

Generally, the smaller the spray orifice diameter, the finer the spray, which leads to lower API throat deposition and a greater fine particle mass (FPM). However, this FPM may also lead to greater mouthpiece deposition and an increased risk of actuator occlusion.

The quality of the spray orifice finish is also important because a poor quality finish may affect the alignment of the spray, leading to increased API deposition on the actuator and an altered APSD profile.

Spray pattern and plume geometry. Spray pattern and plume geometry are important tests for assessing the performance of the actuator and can be affected by various factors including the size, shape, and design of the actuator; the size of the valve metering chamber and side pierce; canister vapor pressure; and formulation composition. The data from the reference marketed product provide a baseline for screening hardware and formulation options.

Spray force. The force of the emitted spray is closely related to throat deposition. Spray force measurement of the reference marketed product will provide a reference that should not be exceeded to ensure similar deposition profiles and patient perception of the new generic pMDI product. It has, therefore, been suggested that impaction force may provide a better way to evaluate *in-vitro* equivalence in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) for orally inhaled drug products. The belief is that it is more closely related to patient sensation and aerosol deposition than the current parameters (2).

Container closure system

Valve. A clear understanding of the exact composition and functionality of the reference marketed product's valve allows for selection of an appropriate valve for the generic pMDI product. Differences in the valve may affect factors such as formulation compatibility and pharmaceutical performance.

Many valve attributes of a reference marketed product need to be considered prior to generic product development, such as the metering volume, the manufacturer and the materials of construction, and any unusual features of the valve that may need to be understood.

Differences in the valve may affect factors such as formulation compatibility and pharmaceutical performance.

Valve metering volume may be determined from information stated in the SPC or prescribing information. Confirming valve volume through laboratory testing enables selection of the correctly sized valve metering chamber to match the reference marketed product and highlights any differences between different product strengths.

Canister. Information on the canister and/or coating may be listed in the SPC or prescribing information. The presence of a coating on the canister may indicate deposition issues with the API or incompatibilities with the canister material. Identification of the coating is important if a direct match to the reference marketed product is required, otherwise, confirmation of coating presence may be adequate. The height and width of the canister will determine its physical compatibility with various actuators and dose counters.

Secondary packaging. Foil pouches and desiccant may affect product performance throughout the product's shelf life. If foil pouches or a desiccant are present in the reference marketed product, they should be included in feasibility/development studies but they don't necessarily have to match exactly. Attributes to be considered when analyzing secondary packaging include:

- Constitution of secondary packaging (e.g., carton, desiccant, foil overwrap, and PIL)
- Purpose of the secondary packaging, which can be determined through appropriate studies.
- If included, dimensions and composition of foil overwrap and quantity/type of desiccant.

Conclusion

As discussed in this article, the development of generic pMDIs is a technically challenging process that requires significant expertise. The growing market trend towards lower-cost generic products means that companies often need experienced partners to develop robust generic pMDI products that meet the requirements of the current regulatory landscape.

A comprehensive understanding of the physical attributes and pharmaceutical performance of the current reference marketed product through reverse engineering is a key step in the successful generic pMDI product development process because it will enable appropriate *in-vitro* test and reference product matching strategies to be adopted.

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The Search for Practical and Economical Catalysts

Cynthia A. Challener

Researchers develop catalysts that mediate complex transformations under conditions appropriate for commercial manufacture.

As small-molecule APIs become increasingly complex, designing concise, practical, and economical synthetic routes for their commercial production becomes increasingly challenging. There is, consequently, growing demand for cost-effective, highly efficient catalysts that mediate atom-economical, environmentally friendly transformations that can replace traditional, non-catalytic processes that require multiple steps. A summary of selected new catalysts that show promise for pharmaceutical intermediate and API synthesis is presented in the following.

A fortuitous discovery

Silicon-containing compounds are of interest as potential drug candidates because silicon can impart greater stability and lead to compounds with improved solubilities and pharmacokinetic properties. There are two common routes to heteroarylsilanes: stoichiometric reaction of a silicon electrophile with a heteroaromatic organometallic intermediate (prepared via a Grignard reaction) or rhodium- or iridium-catalyzed C–H silylation in the presence of an excess of a hydrogen acceptor. Neither approach is practical on an industrial scale, and both suffer from limited functional group tolerance.

Researchers in the Grubbs and Stoltz groups at the California Institute of Technology fortuitously discovered an attractive alternative method based on the inexpensive base potassium tert-butoxide (KOtBu) (1). When investigating a reaction to convert biomass to chemicals via the breakage of C–O bonds using an iron catalyst, KOtBu, and a hydrosilane as a hydride equivalent, they observed that silylated heteroaromatics were formed in minor quantities in a control reaction using only KOtBu and the hydrosilane. In addition, they noted that the yield of silylated products increased as the reaction temperature decreased.

The cross-dehydrogenative heteroaromatic C–H silylation reaction with hydrosilanes was found to proceed best using a catalytic amount of KOtBu (1–20 mol%) in the absence of an acceptor, with only hydrogen gas as the byproduct. The fact that a common base catalyzes this important reaction was quite surprising, and thus the researchers went to great lengths to confirm that the KOtBu was indeed the catalyst and not some unknown impurity.

The reaction is believed to proceed via a radical mechanism that is completely different from the mechanisms observed with transition-metal catalysts. Its scope is also very broad. Indoles with a variety of substituents on the nitrogen and various positions on the arene ring and many different electron-neutral and electron-rich N-, O-, and S-containing heterocyclic compounds are suitable substrates. Carbonyl groups are generally not tolerated except when protected as acetals. Some groups (bromide, iodide, cyano, and nitro substituents) do hinder the reaction. Interestingly, fluoride, chloride, trifluoromethyl, epoxide, N-alkyl aziridine, pyridine, and tertiary amine and phosphine groups do not.

Notably, even simple arenes serve as good substrates. Substitution affects the regioselectivity; however, ortho-substitution occurs with anisole, while directing-group-free C(sp^3)–H silylation leads to silylated benzyl derivatives with toluene and similar compounds. The researchers are also exploring the reaction of non-aromatic compounds (e.g., aliphatic compounds, alkenes, and alkynes).

The scientists have also shown that the cross-dehydrogenative heteroaromatic C–H silylation reaction is scalable. When run neat using N-methyl indole and 1.5 equivalents of triethylsilane at 45 °C on a 100-gm scale, desired C_2 silylated product was obtained in 76% yield with a greater than 20:1 regioselectivity after simple filtration and distillation.

The researchers also demonstrated the utility of the reaction by silylating the antihistamine thenalidine and the antiplatelet drug ticlopidine in 58–68% yield with high chemo- and regioselectivity, indicating the applicability

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

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of the transformation for late-stage modification of pharmaceutically relevant compounds.

Cooperative catalyst system

Sites of unsaturation (alkenes in particular) are widely present in pharmaceutical compounds and their introduction can be achieved using a variety of methods, such as the elimination of alcohols, halides or other leaving groups, the reduction of acetylenes, and Wittig and Diels-Alder reactions. Dehydrogenation of alkanes is highly attractive because it allows for the flexible placement of alkenes. In addition, when performed under acceptor-less or terminal oxidant-free conditions, only hydrogen is generated as the byproduct. It is, however, a highly endothermic reaction traditionally mediated by expensive noble-metal catalysts at high temperature. Enzyme-based systems do proceed at room temperature, but require the use of a full equivalent of a terminal oxidant, and thus hydrogen recovery is not possible.

Scientists at Princeton University have overcome these issues with the development of a reaction that is noble-metal-free, does not require the use of a terminal oxidant (and thus generates hydrogen), and proceeds at mild temperatures (2). Their approach is based on key aspects of the iron-based desaturase system, which catalyzes dehydrogenation reactions via step-wise hydrogen atom removal. The first hydrogen atom transfer (HAT) occurs from the alkane substrate to a high-valent oxo species, which is much more difficult than the second, which can occur via HAT or electron transfer followed by proton transfer.

In their new approach, the researchers use cooperative catalysis with a dual-catalyst system to achieve the two steps. The polyoxometalate tetra-*n*-butylammonium decatungstate (TBADT) is easy to synthesize and has been shown to mediate HAT reactions of unactivated alkanes under near-UV light irradiation. For the second catalyst, the researchers were interested in cobaloximes because they are known to catalyze radical reactions including the reversible formation of alkenes and cobalt hydrides and have been shown to mediate water reduction under photo-irradiation conditions. Cobaloxime pyridine chloride (COPC) was selected because it is also readily synthesized.

When used together (1.5 mol% TBADT and 0.75 mol% COPC) under irradiation at 323 nm, which is the absorbance maximum of TBADT, cyclooctane was converted to cyclooctene in 23% yield. The researchers also showed that cyclopentane was converted to cyclopentene and cyclopentadiene, while cyclohexane was dehydrogenated to cyclohexane rather than benzene, which commonly occurs under noble-metal catalysis.

The reactivity of ethyl isovalerate was also interesting. Rather than produce the thermodynamically most stable product, which is generally the case with noble-metal catalysts, the dehydrogenation proceeded to form the skipped-enone product. The researchers are also exploring the tolerance for functional groups other than esters.

While the initial results of the cooperative catalysis approach with simple alkanes are not as efficient as reactions with noble-metal catalysts, the researchers believe there is potential to improve the reaction. In fact, when secondary alcohols are used as substrates, the yields increase (i.e., 83% for 1-phenylethanol).

New approaches to C–H activation

Researchers at the Scripps Research Institute (TSRI) developed a catalyst that mediates C-H activation in the synthesis of heterocycles (3). Using an N-methoxy amide group as both a directing group and an anionic ligand, the PdX_2 (X = ArCONOMe) catalyst is generated *in situ* from a Pd(0) source using air as the oxidant. With the PdX_2 species localized near the target C–H bond, the natural preference of the metal to coordinate to the heteroatom is avoided. The catalyst has been used to synthesize a number of different compound types, including furans, benzofurans, benzothiophenes, indoles, pyrroles, thiazoles, pyrazoles, imidazoles, pyridines, quinolines, pyrazines, pyrimidines, pyrazoles, and thiazoles.

Catalysts that mediate other types of C-H activation reactions have also been developed by TSRI researchers. In one case, sequential diarylation is achieved to afford non-natural β -Ar-β-Ar'-β-α–amino acids with diastereomeric ratios of greater than 20:1 (4). These compounds are building blocks for peptide drugs with structural diversity that may make them resistant to enzyme degradation. In the second reaction, palladium-catalyzed enantioselective C–H iodination is used to achieve the kinetic resolution of chiral amines (5). Notably, the reaction proceeds at room temperature and involves only inexpensive and commercially available reagents.

Coupling of heteroatom-substituted olefins

Carbon-carbon coupling reactions have become, in recent years, fundamental transformations for the commercial production of small-molecule APIs. Researchers at TSRI recently developed a new coupling reaction for the preparation of highly substituted, uniquely functionalized compounds catalyzed by an inexpensive iron complex (6). The reaction is also attractive because it is performed open to the air at room temperature.

While typically run in ethanol, the researchers showed that reactions run in vodka, gin, whiskey, tequila, beer, and wine also afforded the desired coupling products. In addition, they demonstrated the broad scope of the reaction by synthesizing more than 60 different compounds, most of which were new chemical entities not previously reported.

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Impact of Quality by Design on Topical Product Excipient Suppliers, Part I: A Drug Manufacturer's Perspective

David W. Osborne

Quality by design (QbD) is a scientific and risk-based approach to product development that begins at the product concept stage. This article will equip the excipient vendor with an understanding of QbD from the perspective of the topical pharmaceutical product manufacturer.

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The US Food and Drug Administration (FDA) began an initiative in 2002 entitled *Pharmaceutical Current Good Manufacturing Practices for the 21*st *Century—a Risk-Based Approach*, which encouraged the pharmaceutical industry to adopt modern quality management techniques (1). As a participant in the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use (ICH), FDA contributed to a number of guidelines such as ICH Q4B (2), ICH Q8 (3), ICH Q9 (4), and ICH Q10 (5). These modern quality management techniques framed in terms of pharmaceutical regulatory concepts have been collectively called quality by design (QbD). QbD can be defined as a scientific, risk-based, holistic, and proactive approach to pharmaceutical product development. It begins at the product concept stage and is applied throughout development and into commercialization.

The QbD paradigm performs a risk assessment during the product concept stage to identify active and excipient attributes having a high likelihood to affect critical quality attributes (CQAs) of the pharmaceutical product. Experimentation is then performed to determine impact of formulation (active and excipient) attributes and processing parameters on pharmaceutical product attributes, and a control strategy is adopted to mitigate risk of CQA failure. By understanding variation of excipient properties as they relate to critical process parameters (CPPs) and CQAs, the pharmaceutical product manufacturer can build robustness and flexibility into their manufacturing processes. Excipients and excipient vendors are of vital importance to QbD, and pharmaceutical product manufacturers are highly motivated to adopt the QbD paradigm. QbD is here to stay and will be embraced by the developers of new drug applications (NDAs) and abbreviated NDAs (ANDAs) for topical products.

From the perspective of a pharmaceutical topical product development scientist, understanding and adopting QbD can be time consuming. It is hard to break the decades-old habit of limiting variability of the excipients so that an "optimized" product conforms to the narrowest specifications possible. The adoption of QbD for topical products prior to 2013 was further hindered by guidance documents often limiting their examples to oral solid-dosage forms. Fortunately for topical product developers, two papers have been published on the topic of generic development of topical

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dermatologic products (6, 7). These publications have made dramatic progress in clearing up misunderstandings about QbD as related to topical products. A third publication (8) describing the performance matrix for a topical cream provides a useful perspective on topical products being qualitatively equivalent (Q1), quantitatively equivalent (Q2), and structurally/functionally similar (Q3). Because QbD is a holistic approach that begins at the product concept stage and never really ends, product development scientists, process engineers, and technical support personnel require a broad understanding of QbD. While familiarity with the full spectrum of QbD is always useful, the excipient supplier can initially focus on QbD concepts specific to pharmaceutical excipients.

The goal of Part I of this two-part series is to equip the excipient vendor with an understanding of QbD from the perspective of the topical pharmaceutical product manufacturer. The topical product scientist will apply these modern quality management techniques not only to products in development, but also to products that have been on the market for years. For excipient vendors to meet the needs of their pharmaceutical customers, it is important that they understand the broader QbD framework used by development scientists. This article will focus on aspects of QbD that are specific to excipients in topical dermatological preparations (both NDA and ANDA) that are meant to be locally active. Part II will discuss what specific information the excipient supplier should provide the development scientist to satisfy a QbD approach for topical product development.

Risk criticality and the quality target product profile

The starting point for QbD is the quality target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics of a drug product that will ideally be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product (9). According to ICH Q8, it (10):

"Could include the intended use in a clinical setting, route of administration, dosage form, delivery systems, dosage strength(s), container-closure system, therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed, and drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product."

The QTPP is different from the product specification because the QTPP should include patient-relevant, product-performance elements such as clinical efficacy/bioequivalence or stability that are not carried out in batch-to-batch release. It provides an understanding of what will ensure the quality, safety, and efficacy of a specific product for the patient and is the starting point for identifying the CQAs, CPPs, and control strategy. The introduction of ICH Q9 (11) states that "…the protection of the patient by managing the risk to quality should be considered of prime importance." The ICH *Quality Implementation Working Group Points to Consider* (12) states: "Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management. Quality attribute criticality is primarily based upon severity of harm and does not change as a result of risk management. Process parameter criticality is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management."

CQAs are product attributes that have the potential to be altered by changes to process parameters or formulation variables during pharmaceutical development. If a product attribute cannot change during the pharmaceutical development process, even though it is an essential element of a marketable product, then that product attribute should not be a CQA. In addition to having the potential to change during development, a CQA must also be directly related to the safety and efficacy of the topical product. Selection of appropriate, product-performance-focused CQAs represents the biggest QbD challenge for topical liquid and semisolid products. A CQA is usually an attribute of the final product, but it is also possible to indicate a CQA of a raw material.

Although it is possible for a raw material to be a CQA, it is much more likely that an excipient will be a critical material attribute (CMA). It is well recognized that excipients can be a major source of variability in topical products. CMAs such as pH, particle size distribution, particle aggregation, or appearance of a single excipient may dominate the analogous CQA of the final pharmaceutical product. Lionberger *et al*. states "Independent critical material attributes (CMAs) are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process" (13). This means that independent CMAs may better define product quality than CQAs. For example, *in-vitro* release testing (IVRT) using a Franz cell for a topical gel product containing suspended drug might seem like the best way to evaluate the manufacturing process. Thus, IVRT is designated as a CQA and is used to evaluate the impact of different mix times and mix speeds used to form the gel and suspend the drug. IVRT results are gathered for 6–10 gels to characterize mixing during manufacturing. This approach is a reasonable way to establish a design space for this product, but is it the best way? The quote from Lionberger *et al.* suggests that the product development scientist should consider defining API particle size and gel rheology as independent CMAs rather than defining *in-vitro* release as a CQA. A potential scenario in which these two CMAs would provide a mechanistic link is when the higher mix speed generates heat that alters particle size. At the same time, higher mix speeds reduce the gel viscosity by lowering the molecular weight of the shear-sensitive gelling agent. The IVRT response surface may be less sensitive to potentially "competing" changes in particle size and viscosity compared to the particle size response surface and viscosity response surface generated from the same 6–10 gel experimental design.

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QbD concerns of topical product development scientists

When focusing on topical product risk and criticality as related to raw materials, typical CQA items are phase separation, rheology, precipitation of dissolved active/excipient or particle changes in suspended active, microbial contamination, pH, assay/impurities, heavy metals, and residual solvents.

Phase separation. Phase separation of a topical product in a multi-use container can result in super-potent dosing for some of the treatment applications and sub-potent dosing for the remaining treatment applications. In the example QTPP for fluorouracil cream (7), this element was labeled "homogeneity and tube uniformity." Phase separation can be most dramatic when the active is found primarily in the dispersed phase of a product that contains little of the dispersed phase (e.g., a hydrophobic drug that is almost completely dissolved in the oil phase of an oil-in-water emulsion that has more than 85% water). If this product is a cream that separates into a half milliliter of oil-rich phase that is at the orifice of the tube, then 90% of the drug may be applied in the first few applications. Alternatively, if the separated oil-rich phase of a lotion creams to the top of a bottle fitted with a pump that has a long dip tube, then 90% of the drug may remain inside the bottle and never be applied. Another example is when a gel containing uniformly dispersed solid-drug particles loses viscosity on storage and the previously dispersed drug falls to the bottom of the container. For topical products that are semisolids or fluid dispersions, assuring content uniformity (i.e., avoiding phase separation) tends to dominate the control strategy.

Rheology. Rheology is the science that characterizes the flow of materials. For topical products, rheology considers the impact of shear on the apparent viscosity of a non-Newtonian liquid. Rheological behavior is directly correlated to microstructure of a topical product formulation. For two products that have the same composition (qualitatively [Q1] and quantitatively [Q2] the same), if they have the same microstructure (Q3), then these two products will have the same bioavailability. The manufacturing process can have a significant impact on the formulation microstructure (6). This means that characterizing rheological behavior as a function of excipient variability, processing parameters, and even active purity or particle size distribution may provide valuable insight with regards to the microstructure of the product. Dramatic change in rheological properties may affect the bioavailability. This impact applies to rheological changes over the shelf-life of the product, lot-to-lot changes in the rheology of the product, and differences in rheological properties between a generic formulation and the reference listed drug.

Precipitation. If the API is completely dissolved in the topical product, then it must remain completely dissolved over the shelf life of the product. Because only dissolved drug penetrates the stratum corneum of intact skin (14), the precipitation of drug is expected to change bioavailability. Formulations that are prone to supersaturation, followed by unpredictable timing for precipitation, are rarely viable commercial products. Likewise, topical products formulated near API saturation that precipitate with relatively small drops in temperature need to rapidly redissolve upon storage at their labeled temperature range to be viable commercial products. Concerns about precipitation midway through stability of a material completely dissolved at product release are not limited to API. A good illustration of the preservative methylparaben precipitating out of a topical gel is provided in the specification and examples of US patent 8,053,427 (15).

Particle changes. If the drug substance is dispersed in the formulation as solid particles, particle size and content uniformity throughout the entire container/closure system will be two critical attributes for the topical drug product. Characterization of segregation and/or aggregation of particles will be necessary, in addition to demonstrating that no changes in the drug substance polymorph occur throughout the stability studies. Particle size of the drug substance throughout the shelf life of the topical product must be determined and may need to be controlled. For particles less than 10 microns, changes in particle size and/or morphology of suspended drugs in topical products are presumed to change bioavailability (14, 16).

Microbial contamination. It is important that products applied to the skin are not contaminated by bacteria or fungi and for this reason, topical products, especially products packaged in multiple-use containers, are usually preserved. Healthy skin provides a reasonably effective barrier against microbes, but this barrier is often compromised in skin conditions that are treated with topical products. Products applied to the face will eventually find their way into a patient's eyes, which is another reason that even vehicle controls must be adequately preserved to assure patient safety. For topical products, passing *United States Pharmacopeia* (USP) <51> Antimicrobial Effectiveness Testing (AET) over the entire product shelf life is sufficient to assure that if contaminated, the product will not support growth and be a risk to the patient (17). AET testing assumes that incoming raw materials will not have significant lot-to-lot differences in the level of bacteria/fungi contaminating the API or excipients that are used to make the product.

pH. Most topical formulations will be adjusted to a specified pH at some point during processing. If the pH remains stable over the shelf-life of the product, then an appropriate control strategy can be put into place to keep pH as a very low risk, non-critical quality attribute. However, some actives degrade into weak acids (e.g., benzoyl peroxide degrading into benzoic acid) and if the product is not buffered (or insufficiently buffered), then the pH steadily drops over the shelf life of the product. If the active has pH-dependent solubility or a dissociation constant near the product pH, then it is likely that bioavailability may change with changing pH (8). The acid/base properties of some excipients can significantly impact the initial pH of the formulation. Lot-to-lot variability of excipients that can shift pH should be a risk mitigation focus for APIs that carry charge.

Assay and impurity tests. Assay tests that are specific, accurate, and precise are mandatory to quantify the amount of API present (per unit weight or volume) in the topical drug product. Likewise, impurity tests are required for specified impurities as justified by ICH Q3B (18) qualification threshold and unspecified impurities as justified by the identification threshold based on the maximum daily dose for the drug product (7). Excipients must be compatible with the API, and drug–excipient incompatibility is usually noted early in development and the formulation modified to assure an adequate shelf-life. A much more difficult problem is when trace level substances (e.g., catalysts, heavy metals, unreacted reagents) contained within an excipient are incompatible with the API. Degradation of the API may be rapid and limited by complete consumption of the trace levels of the excipient impurity. Usually this degradation of the active will be viewed as a processing loss and be ignored (if less than 1%) or corrected by use of an overage. However, if this reactive trace excipient impurity has significant lot-to-lot variability or is not uniform throughout the excipient batch, then the drug product may risk occasional lots failing on stability.

Residual solvents and heavy metals. The drug product manufacturer will always be concerned about complying with *USP* General Chapter <467> Residual Solvents (19) and *USP* General Chapter <232> Elemental Impurities-Limits (20). The requirements include not exceeding limits for the finished drug product by controlling the elemental impurities and residual solvent of excipients. It should be noted that topical products may contain a significant amount of solvent (e.g., ethyl alcohol) and for these products, the solvent used is counted as an excipient, not a residual solvent (6).

Conclusion

The goal of Part I of this series is to familiarize the excipient supplier with some of the QbD concepts and terminology specifically related to topical pharmaceutical products. The pharmaceutical industry is embracing QbD for topical products for both NDA and ANDA products. With this understanding of QbD, it should be possible to build more effective partnerships between topical product development scientists and topical excipient vendors. QbD is truly the new paradigm in topical product development and is providing patients with more robust treatment options. Part II will propose reasonable customer expectations regarding excipient sample requests and specific information about excipients needed for the QbD approach.

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Ophthalmic Drug Packaging: Safety Risks and Patient Acceptability Issues

Karen A. Bernard, Avin S. Lalmansingh, Anurag Sharadendu, Rajendra Uppoor, Paul Schwartz, Bing Cai, Wiley A. Chambers, and Andre S. Raw

The authors describe some cases of container closure design flaws and actions taken by FDA to mitigate safety risks and increase patient acceptability.

Many ophthalmic diseases and eye irritations are treated with topically administered drug products. More than 70% of ophthalmic drug products are simple solutions supplied in multi-dose plastic container closure systems (CCS), which generally contain a month or longer supply of the drug. These products may be intended for the treatment of acute or chronic conditions. The typical multiple-dose CCS for liquid ophthalmic drug products is comprised of a bottle, a drug-dispensing tip, cap, and overseal or other tamper-evident feature. These packaging components are regulated by FDA's Center for Drug Evaluation and Research (CDER) (1). They function together to protect the quality of the drug product, maintain product sterility through initial breakage of seal by patient, aid dosing and administration, and minimize product contamination throughout the duration of its use. As a result, ophthalmic drug product packaging is considered to be relatively more crucial to product performance and safety than the packaging used for solid oral drug dosage forms.

Many CCS manufacturers and suppliers offer designs with unique features (which, in some instances, are patented), which adds to the complexity of ophthalmic product packaging. Due to these differing CCS designs among manufacturers, substitution of a brand-name or Reference Listed Drug (RLD) by a generic drug, or switching between different generic versions of a drug product, can lead to unnecessary confusion and patient risk. This article examines five case studies illustrating these issues. The first two involve patient safety, due to a risk of localized, external eye injury from particular packaging design flaws. The others show difference in patient acceptance, due to differences between the RLD and the substituted generic-drug packaging performance with respect to bottle/cap torque specifications, piercing of the dropper tip, and consistent delivery of the intended drug dosage/volume.

Case study one: Tamper-evident ring feature

One recent safety concern discovered during post-market review involved the use of non-retaining plastic tamper-evident rings (i.e., collar or band) to seal the bottle and cap (**Figure 1**). When the patient twists off a new bottle cap for the first time, he or she breaks the connections between the ring and cap, thereby providing visible evidence that the bottle has been opened.

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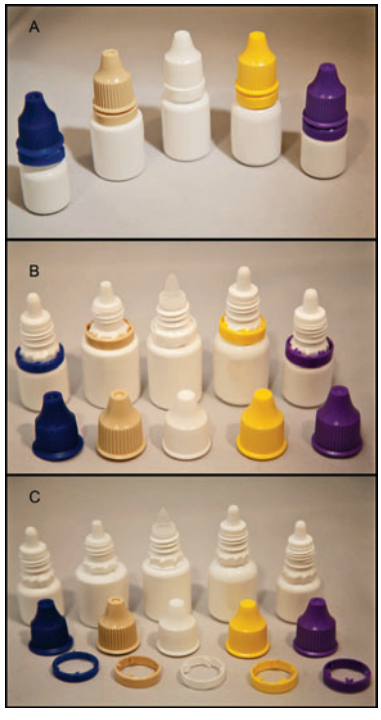
Figure 1: Eye drop bottles with non-retaining tamper-evident rings. (A) Many different container closure venders supply these bottle and cap configurations. (B) The container closure system design is not engineered to secure the plastic ring around the bottle neck. As a result, the plastic rings are likely to slip off the bottle neck on patients' eyes when the bottle is inverted to administer eye drops. (C) The sharp ridges on the rings formed when the seal is broken between the cap and ring can cause corneal abrasions. FDA recommends that these designs of ophthalmic bottles include a positive-retention mechanism to prevent the rings from sliding off during product use.



The plastic tamper-evident ring sits around the base of the bottle neck after the cap has been removed. Unless the bottle has been designed to prevent it from slipping down the neck of the bottle, this loose plastic ring can fall off when the bottle is inverted to deliver the eye drop(s). Consumers have complained to FDA that the tamper-evident ring has fallen on patients' eyes during administration of the drug product, causing eye irritations and injuries. In certain cases, the sharp plastic spikes that result when the bridges between the cap and seal are broken, have scratched patients' corneas.

FDA is in the process of identifying all branded and generic ophthalmic drug products packaged in bottles with non-retaining tamper-evident rings, and has issued a safety alert (2). This alert recommends that applicants either change the CCS design or redesign the bottle neck and ring so that they are similar to those present on disposable plastic beverage bottles such as water or soda bottles, to prevent the tamper-evident ring from coming off the bottle while in use.

In response to the risks of eye injury, some applicants have proposed packaging label changes that would instruct patients to remove the tamper-evident ring from the bottle neck prior to administering eye drops. Such labeling changes, however, are undesirable, because they will promote more manipulation of the product bottle and increase the likelihood that the patient will accidentally touch the drug dispenser tip, leading to contamination of the drug. The proposed labeling change may also contradict other labeling information that instructs patients to avoid contaminating the dispenser tip by touching it with their fingers or allowing it to come in contact with one's eyes, face, or other surfaces.

Tamper-evident packaging is a specific requirement for over-the-counter (OTC) drug products and ophthalmic preparations that are regulated as medical devices (e.g., contact lens solutions) to prevent adulteration of products accessible to the public during retail sale (3). Although prescription ophthalmic drug products have traditionally used a shrink-wrap-type bottle seal for products held behind the pharmacy counter, many applicants have proposed the use of tamper-evident seal technologies for prescription ophthalmic products. It is recommended that, in cases where tamper-evident rings are proposed for ophthalmic products, there should be a positive retention mechanism built into the CCS design to secure the rings.

Case study two: Shedding of plastic particles

Recently, consumers have also complained that foreign particles have entered patients' eyes while applying multiple sterile ophthalmic ointments, which has resulted in such adverse events as eye irritations, pain, ocular discomfort, and superficial eye injury. These types of injuries have been associated with small pieces of plastic or plastic particle shavings from the CCS. In one particular case, unscrewing the cap from the ophthalmic tubes caused the cap to shed plastic particles. Root cause analysis (RCA) by the ophthalmic tube supplier determined that the defect was related to over torqueing or a slight cap tube misalignment during the capping process, which required the tooling equipment to be adjusted. The drug-product manufacturer chose to recall specific lots of affected drug products in response to consumer complaints. FDA's MedWatch system continues to monitor product quality cases like these given the frequency of complaints about particles shedding in patients' eyes when using a variety of ophthalmic drug products.

Case study three: Patient-packaging interface issues with overly tight bottle closures

This case illustrates challenges that patients experienced when opening bottle caps and/or seals in ophthalmic products. Ophthalmic product bottles are significantly smaller than beverage bottles, and extra effort is often required to twist off their caps because of the limited surface area available for gripping and manipulating the bottle and cap. This issue becomes amplified if the drug product is intended for use by elderly patients or patients with reduced dexterity.

In one particular case, there were numerous consumer complaints that caps had been screwed too tightly on ophthalmic bottles. Post-marketing

ALL FIGURES ARE COURTESY OF THE AUTHORS.

evaluation studies confirmed the difficulty in opening the bottles, and FDA asked the manufacturer to revise the torque specifications for the drug product CCS to enable easier cap opening. The applicant's initial strategy was to decrease the number of bridges between the cap and the sealing ring to reduce the torque for bottle opening. This approach failed, however, because the bridges prematurely broke during the capping process, deactivating the tamper-evident safety seal mechanism. The applicant responded by using a different plastic resin to make the cap, and conducted a mechanical bridge breakage torque investigation, followed by human in use qualification studies on bottles that had been fitted with caps manufactured with the new resin. Use of the new cap resulted in an easier, more patient-friendly cap-opening process that required less torque force to break the seal. The new cap resin was applied to the applicant's entire ophthalmic product line, which successfully mitigated the patient/packaging interface issues associated with excessively tight bottle caps.

Case study four: Spike designs for piercing dropper tips

Also problematic are CCS designs that require multi-step procedures for piercing ophthalmic dropper tips. These designs appear to confuse patients. In one set of cases, a serious flaw in the CCS design featured a sealed bottle and a screw cap with a spigot (spike) on the inside of the cap. This design required that the patient or caregiver employ a multi-step process to deliver the eye drops (see **Figure 2**). First, they twist the cap, breaking the seal, and then the plastic ring is removed so that when the screw cap is returned to the bottle and tightened, the spike underneath the cap is positioned to pierce the dropper tip and create an aperture.

Due to the complexity of this multi-step piercing procedure, however, patients were confused about which procedure was required to create an aperture of the appropriate size. As a result some patients used knives and scissors to puncture the tip, which increased the risk of injury from use of these household tools. In addition, this design led to highly variable aperture sizes and significant differences in eye drop size and the volume of medication delivered to the eye. This variability also contributed to complaints that the drug product did not last through the prescribed period of use.

In an effort to mitigate this risk, the applicant revised the product labeling to include more explicit instructions and schematics on the carton and package insert so that users would create the aperture properly. These steps, however, did not solve the problem, and consumers, and prominent ophthalmology organizations, continued to note problems with the design. The applicant then redesigned the CCS, using a more traditional and intuitive approach (i.e., a single-step process for opening that does not require removal of the cap).

As a result of such cases, information requests are now typically issued to inquire whether or not the container closure tip

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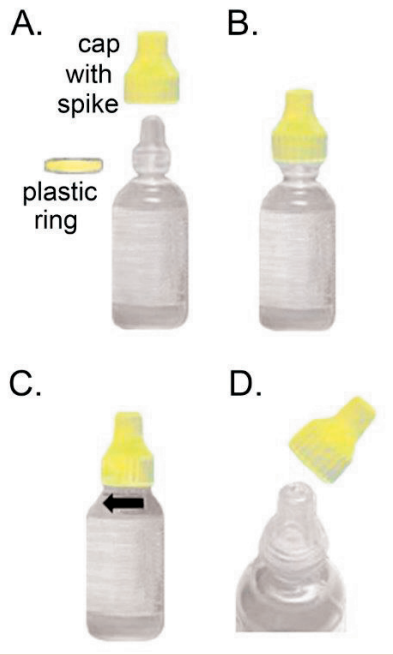
Figure 2: Multi-step process for opening the bottle and piercing the dropper tip. (A) This bottle/cap design features a spike on the inside of the cap used to pierce the dropper tip. The cap is unscrewed initially and the plastic ring is removed. (B, C) The cap is then returned to the bottle and tightened to allow the spike to pierce the dropper tip. (D) Removal of the cap reveals the aperture on the dropper tip. The procedures for piercing the bottle tip are confusing to the patient population and result in variable aperture sizes and lack of control in the drug dose delivered. FDA recommends that this type of spike design not be used for ophthalmic drug products.



is sealed until activation, on first opening by the patient. In cases where the seal tip is opened by activation, multi-step procedures that require removal of the cap are discouraged. Single-step procedures that involve simple, intuitive twisting without removal of the cap are generally preferred.

Case study five: Differences in volume of drug delivered

As mentioned earlier, proper sizing of the eye-dropper aperture is crucial in order to control the eye-drop volume and rate of eye drops dispensed when the bottle is inverted and gently squeezed. In a particular case related to eye-dropper performance, there were numerous patient complaints that the drug product did not last through the prescribed period of use. The generic-drug packaging was observed to release larger eye drops to the eye than the packaging that had been used for the RLD. Samples of the marketed drug products were tested, and the results showed that the generic product had a significantly larger eye drop size compared to the RLD (49.2 microliters versus 34.1 microliters). Generally, the average eye-drop volume for ophthalmic solutions is approximately 28 to 32 microliters. Although the generic product released significantly larger drop sizes than the RLD, this did not result in excessive drug exposure, because the volume exceeded the level that can be held in the *cul-de-sac* of the eye without overflowing, which is approximately 30 microliters (4). The excessively large drop size of the generic, however, did result in consumer complaints of inadequate supply, associated with the drug product not lasting through the month-long prescribing period.

Generic ophthalmic drug products are required to be pharmaceutically equivalent to the RLD, and, as part of this requirement, applicants of a generic ophthalmic product are expected to show that the drop size is not significantly different from that of the RLD. This is in line with a 2008 Citizen Petition response (5) stating that FDA reviews "drop size as part of the quality review to ensure that, when used by the consumer, the generic product will have comparable delivery characteristics [to the brand-name product]." Based upon these requirements and expectations, the applicant in this case agreed to replace the dropper tip to correct the differences in the dropper performance between the two CCS designs, resulting in a more comparable eye drop size to the RLD product. As a result of cases concerning differences in eye drop volume between the RLD and generic, it is FDA's position that the drop size of the proposed drug product should not significantly differ from that of the RLD.

Conclusion

FDA/CDER's Office of Pharmaceutical Quality (OPQ) focuses primarily on the quality review of container closure systems from the perspective of how the packaging components impact drug product's critical quality attributes from the time of packaging through patient usage and treatment. In an effort to better manage patient risks and acceptability issues, FDA has been increasingly assessing the effects of patients' handling or usability of the drug product until the last labeled dose is delivered by the CCS. FDA recommends that applicants consider the intended patient population when designing ophthalmic packaging, especially since the intended patient may be elderly with motor coordination difficulties, or may have certain medical conditions associated with impaired vision. This patient-centric focus is in line with broader FDA goals to link drug product quality attributes to patient acceptability in terms of objective and measurable outcomes.

The cases presented herein are general examples of container closure design flaws that may affect branded and generic drugs. In many cases, safety signals such as eye irritations, discomfort, and superficial eye injuries as a result of CCS quality defects are reported to the drug product manufacturers as adverse events. When drug manufacturers receive these market complaints concerning drug-packaging performance, they often propose revisions to labeling instructions to correct the noted issues with packaging. While this strategy may be quicker and easier to implement, labeling revisions are generally not appropriate substitutes to remedying packaging design flaws and should only be considered as temporary solutions under certain conditions. A more effective strategy should be a redesign or replacement of the faulty CCS components as part of the corrective action and preventative action (CAPA) plan.

Careful consideration of ophthalmic packaging performance attributes is crucial given the complexity of the CCS and the inherent risk of harm to the eye. Per FDA guidance on drug product container closures (6), packaging components with 'special' functions should be qualified to show that they perform the intended function(s) properly. These include tamper-evident collars, specialty seals, and drug-delivery components, all of which are considered 'special' function components. FDA recommends that when a newly proposed or novel CCS is being submitted as part of the data package for a new drug application (NDA), abbreviated new drug application (ANDA), or supplemental NDA or ANDA, appropriate qualification is performed and data are provided for FDA review to support the usability and to assess risks with the proposed packaging components. This helps to ensure safety and consistency in packaging performance among the various CCS designs used for packaging of ophthalmic drug products marketed.

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Disclaimer

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Chasing a Moving Target for Counterfeiting and Illegal Diversion

Agnes Shanley

As criminals duplicate the latest overt security technologies, pharmaceutical manufacturers are evaluating covert and layered approaches to fight counterfeiting, theft, and illegal product diversion.

Although they receive less press than illegal drug trafficking, pharmaceutical diversion and counterfeiting remain huge, growing, and largely undocumented, problems (**Sidebar**). A report by the World Economic Forum, released in 2011, found that fake drugs have a $200-billion-per-year impact on the world's drug manufacturers (1). The business costs of illegally diverted drugs may be several times higher than that, says Kent Mansfield, president of TruTag Technologies, which has developed an on-dose covert security solution that is now in pilot and trial programs with pharmaceutical manufacturers and film coating providers.

"The companies we work with don't tend to separate counterfeiting and diversion. They may have different teams working on each problem, but they don't split out the numbers. Instead, they'll typically say 'This [problem] is costing me X million,'" says Jim Sinisgalli, director of marketing development at Systech International, LLC. "Generally, if a client has a good understanding of the extent of a product's illegal diversion, they can better assess and address the entire [security] problem," says James Lee, Systech's vice- president of product management.

Recently, researchers have called for better labels to distinguish between all the possible forms of counterfeiting and diversion (2). Both counterfeit and diverted drugs hurt the public, when, for example, people abuse and become addicted to drugs intended for legitimate therapeutic uses, or take products that have expired or been improperly stored or labeled, says Mansfield. Both worlds collided recently in investigations into the death of the musician, Prince, which some reports linked to diverted opioid pain killer as well as a counterfeit generic drug (3).

Serialization and track-and-trace efforts promise to give manufacturers more control than ever in preventing illegal diversion, and they can help in anticounterfeiting efforts, but, by themselves, are not enough to prevent counterfeiting. Covert and overt brand protection technologies are also needed. All solutions must work in concert to achieve the three goals of protection, detection, and prosecution, says Shabbir Dahod, CEO of TraceLink, whose cloud-based platform is being used in many pharmaceutical serialization and traceability programs. "Security is a continuous battle, and, no matter what we do, criminal organizations are using sophisticated methods. We must continually raise the bar," he says.

Drawbacks of overt technologies

One of the vulnerabilities of overt, visible anticounterfeiting technologies for pharmaceuticals is that they are packaging-based, and easily duplicated. Criminals have become adept at mimicking not only logos, but color-shifting inks, and holographs. As a result, the use of each of these technologies tends to be short-lived before tweaks and updates are needed.

"Overt technologies are only good for a certain period of time until counterfeiters figure them out. They can only be expected to last so long, and they tend to be expensive," says Lee, who sees the need for a layered approach to preventing both counterfeiting and diversion.

"If a company is relying on a hologram to demonstrate authenticity, then both the supply chain inspector and/or the consumer need to know what

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Tracking a Global Problem

A number of organizations have analyzed and estimated the size of pharma's counterfeit and diversion problem. The Pharmaceutical Security Institute (PSI), established in 2002 by security professionals who work for pharmaceutical companies, examines it from that point of view, and from the law-enforcement angle. The non-profit group is based in the Washington, D.C. area with operations in the United Kingdom and Hong Kong, and currently has 33 global members. CEO Thomas Kubic was previously deputy assistant director at the US Federal Bureau of Investigation (FBI), in charge of the white collar crime and corruption programs.

PSI's Counterfeit Incident System database uses both public and proprietary information to track incidents of illegal diversion and major theft (i.e., cases involving more than $100,000), as well as counterfeiting. Some of these data are summarized in annual Enforcement Statistics and Situation reports on the organization's website, www.psi-inc.org.

Numbers of incidents as well as confiscations are trending upward, Kubic says, noting the scarce resources that the world's governments are devoting to anticounterfeiting efforts. Even in the US, where anticounterfeiting efforts are well advanced, only about 50 agents in FBI are working on counterfeiting of all types of products, not only medicines.

In 2015, he says, PSI found that there were 3002 new incidents, up 37% from the previous year. Of these, 1689 involved counterfeits, 1106 were diversions, and 207 were major thefts.

Seizures were up 33%, mostly due to improved customs operations and the discovery of major counterfeit sources in Cambodia and Vietnam. Kubic says he is seeing a smaller number of big-time seizures, and an increase in counterfeit injectable medicines, a very worrying trend.

In 2015, PSI data showed an increase in diversion, theft, and counterfeiting of dermatological medicines, which were up by 57%; incidents involving central nervous system therapies were up by 29%; and cardiovascular drug incidents, 30%. Erectile dysfunction treatments remained a targeted medicines focus for counterfeiting and diversion. In all, 1100 different types medications were seized in 2015, up from 680 in 2014, Kubic says.

Previous analysis of PSI data (1) noted a number of trends, with criminal groups in China implicated as the source in nearly 28% of reported pharmaceutical counterfeiting and diversion.

Kubic sees less traditional or hieratical organized crime involvement in counterfeiting, at least in developed countries. In the early 2000s, this was clearly seen when Dora Akunyili, then director of Nigeria's FDA, NAFDAC, took a hard line in dealing with drug counterfeiters, facing death threats, narrowly missing being shot, and having her laboratories burned down. Her stance inspired a number of others in other developing nations.

Even though their government representatives may have signed on as participants in global anticounterfeiting programs, says Kubic, there is rarely any consistent follow up. "In some cases, criminals are suspected of making payoffs to the authorities," he says. For example, this year, in Kenya, a whistleblower accused the nation's Pharmacy and Poisons Board of allowing fake and substandard drugs from unregistered suppliers into the country, issuing fake permits between 2005 and 2011 (2). In general, throughout the world, Kubic says, "We need to see more effective coordination between regulators, customs, and the police."

At the same time, in the US, illegal operatives have shifted from an emphasis on unauthorized online pharmacies, which were a major threat to public health a few years ago, especially during periods when key drugs were in short supply (3).

Since then, they have increased their efforts at direct-to-clinic sales of diverted or counterfeit drugs, Kubic says. This was first seen in the counterfeit Avastin case, when tainted materials reached the legitimate supply chain after clinics bought directly from illegal sources. "Marketers are targeting retirement homes and clinics," he says, where diverted oncology drugs are offered at up to 40% off list costs.

FDA's Office of Criminal Investigations (OCI) has been stepping up investigations of physicians, clinics, and other groups suspected of buying diverted pharmaceuticals. However, a September 2016 report (4) questions its methods. In some cases, author Sarah Lynch found, healthcare professionals had unknowingly purchased the materials; in addition, she alleges that aggressive tactics failed to result in prosecutions or other tangible results.

PSI's Kubic believes that an outreach and education effort yields better results than aggressive enforcement alone. "It's more important to educate potential buyers than to try to put the genie back in the bottle," he says. Public outreach is also important, he says, citing the International Federation of Pharmaceutical Manufacturers and Association's (IFPMA's) Fight the Fakes program, which features real-life stories of counterfeiting and effective response, as an example of an information program that's being done right.

Although counterfeiting harms the public, it is still considered intellectual property theft and prosecution is handled that way. Generally, penalties are fairly lax. Nigeria currently imposes life imprisonment, while Israel recently increased its penalty from six months to three years.

Complicating the picture has been the blurring of distinctions between diverted and counterfeit pharmaceuticals, and economically motivated adulteration. After the first Gulf War, Kubic says, security agencies learned that Saddam Hussain had looked into adulterating medicines and cosmetic products being sold to the US and Europe. However, he notes that most counterfeiters and adulterators are in the business for the money but don't wish to harm people. "They don't use poisons, although their placebos kill," he says, and proving a link between patient deaths and counterfeit or diverted product can be extremely difficult.

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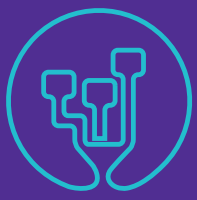

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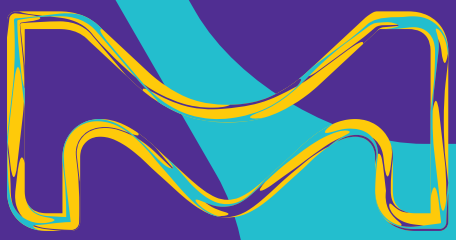

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the real hologram looks like, so that they can effectively spot the difference between a fake and an authentic one. These days, this [differentiation] is becoming much more difficult to do," says Mansfield.

One of the vulnerabilities of overt, visible anticounterfeiting technologies for pharmaceuticals is that they are packaging-based, and easily duplicated. Criminals have become adept at mimicking not only logos, but color-shifting inks and holographs.

He recalls situations in the past where drug companies were using scratch-off codes that could be authenticated by texting the revealed numeric code to a security database or calling the number through a special hotline. Within six months, he says, fakes were discovered where either a false hotline phone number was used, or a single authentic number was duplicated multiple times. "In the latter cases, counterfeiters copied one real code for use with multiple fake packages, knowing full well that only a small percentage of consumers were actually participating in the program," says Mansfield.

Taggants for product identification

Although overt technologies remain important and are being improved, a number of anticounterfeiting techniques are focusing on covert, invisible approaches. One way of doing this is by incorporating taggants, tiny markers that identify the product, into its formulation.

This approach has become more attractive to pharmaceutical companies since 2011, when FDA published its final guidance on physical chemical identification markers (4). The guidance mandates that the material already be an approved ingredient that is generally recognized as safe (GRAS) and present in extremely small amounts in the overall formulation. Providing that all requirements have been met, all that manufacturers need to do is to complete dissolution testing to ensure the release profile or stability of the drug is not affected, and to report use of the material on their annual report to FDA for the product, says Mansfield.

A number of companies are working on taggants that would be added directly to the drug to allow for product authentication. So far, these taggants only work on pills, and some can also be used on labels or packaging, while research is evaluating their use in other dosage forms in the future.

Applied DNA Sciences, for instance, uses a plant-based DNA marker that can be embedded in the pill's coating or packaging. Micro-Tracers, which has sold tracers for use in coding animal drugs for more than 55 years, has taken a different approach. Utilizing technology from the semiconductor industry, the company offers SECURtracers, edible particles 50–150 microns in size that can be embedded into pills, capsules, and labels. Each particle is comprised of GRAS chemically inactive materials, fluoresces under UV black light, and contains lettering 10–20 microns in size.

To confirm authenticity, pills or packaging can be viewed under a simple, inexpensive microscope to read the lettering on the tracer particles. The process requires less than 30 seconds and can provide such information as manufacturing company name, lot number, production date, and expiration information.

If tracer particles are included within pills or capsules, the dosage forms would be ground to powder, and the particles isolated magnetically before being read under a microscope. Particle design is customizable, with x and y dimensions of 50 microns or larger in size. Letters can be etched in sizes as small as 2 microns wide and 10 microns long.

Also working on taggants is TruTag, whose On-Dose authentication solution for oral solid-dosage forms grew out of US Army medical research from 2009–2011, and work by the company's Chief Science Officer Michael O'Neill. It features three key elements:

- Microscopic silica particles, each featuring a unique spectral code that can be used to link provenance data from a product to authenticate it, show dosage and packaging information and lot or batch numbers on the scanner's high-resolution screen.
- Scanners designed to analyze a pill and decode and authenticate microparticles in the product, either within the excipient blend or the coating.
- Data management and storage for analyzing results.

The solution allows for verification directly from the dosage form and would complement serialization and track-and-trace technologies. TruTag has run more than 100 pilot tests, evaluating the technology with multiple APIs via a broad number of common pharmaceutical film coatings, as well as in blends. In addition, the taggants' impact on stability, dissolution, and efficacy have been verified, says Mansfield, who expects full-scale commercialization later this year.

TruTag has been working on film coating application testing, using various active ingredient solid-dose products, with multiple pharmaceutical manufacturers. The company is also involved in technical collaboration

with leading pharma film-coating suppliers and is about to publicly release the results of these studies to industry. Additionally, the contract research and manufacturing company, WuXi Apptec, has invested in the company and is promoting the on-dose technology.

A second layer for added security

Systech International, LLC, which is actively involved in serialization and track-and-trace efforts, has also developed a covert security technology, Unisecure, which clients are evaluating and using as a second layer of protection.

The technology uses machine vision to derive unique fragments from machine-generated universal product codes (UPCs), based on imperfections caused by the paper, the printer, or other conditions. "No two labels are exactly the same," says Lee. Mike Saborski, a vision software specialist at Systech, was able to find a way to leverage the unique imperfections inherent in any installation to come up with identifiers for each product.

Unisecure is being added as an additional layer above serialization, Lee says, with the ultimate goal to add traceability as well. "If you have two identical serial numbers, you cannot distinguish between them, but if you look at the signature fragments for each, you'll see differences between the two. This way, when you scan the UPC code for tracking and authentication history, you know it's the right item in the right market," he says.

Using the technology does not require any special equipment, just a standard camera mounted on a production line, Lee says. Users capture the image and device fingerprint for each product, and then move on to the next.

One pharma company that had already serialized has added Unisecure as a second brand-protection layer. After pilot testing the combined approach in April 2016, the firm now plans to deploy it on serialized lines for high-cost drugs, Lee says. Another company is evaluating it for a mix of different products, both pharmaceuticals and consumer products, he adds.

Systech, half of whose business is in Europe and the US, has been expanding in Asia. A few years ago, the company set up an office in China, and in September 2016, it launched an office in India.

While developers continue to improve brand-protection technologies, pharmaceutical manufacturers and their partners are making progress on serialization and traceability efforts, now mandated in much of the world. "Since January 2016, we've seen a tenfold increase in the number of contract manufacturers embarking on serialization programs," says Dahod.

In general, he says, the technology required for brand-protection already exists. "The challenge will be integrating it into one single source to disseminate information that can be easily accessed."

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Protein Impurities Pose Challenges

Cynthia A. Challener

Multiple methods are required for detecting and removing protein impurities.

Residual undesired proteins—host-cell proteins (HCPs) and high-molecular-weight (HMW) and low-molecular-weight (LMW) species—have the potential to affect the safety and efficacy of biopharmaceuticals. As a result, the levels of these protein impurities in biologic drug substances and drug products must be controlled and are typically considered as critical quality attributes. The properties of the different contaminants vary significantly. In addition, the identification and quantification of some of these residual proteins, particularly in the presence of large concentrations of the product protein, can be challenging.

Use of multiple orthogonal analytical methods and purification techniques is often required. Advances in mass spectrometry are, however, enabling more detailed analyses and thus improved monitoring of residual proteins during downstream processing.

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

The most common protein-based impurities that downstream processes are developed to control include high- and low-molecular-weight species, charge-variants, and host-cell proteins.

HMW species include dimers, trimers, tetramers, etc., formed of monomers that can be either covalently or non-covalently linked, according to John Moscariello, vice-president of process development for CMC Biologics. "Often, these large protein impurities consist of misfolded monomers in which surfaces of the monomer are exposed that typically would not be in the monomeric form. They are believed to primarily impact safety, but also can impact efficacy," he says. He does note, however, that there are data suggesting that some aggregated species are well tolerated. Even so, regulatory agencies expect biopharmaceutical manufacturers to control HMW species through specifications for the drug substance, drug product, and end-of-shelf life.

LMW species, which include clipped species and half molecules for compounds that are intended to be dimeric, such as monoclonal antibodies and bispecific antibodies, must also be controlled during downstream processing. These molecules can impact both safety due to the potential to cause immunogenicity responses and efficacy as the result of missing structural features, such as complementarity determining regions, which play a role in determining the antigen-binding specificities of antibodies and T-cell receptors, according to Moscariello.

HCPs are generated during the production of recombinant proteins. The host cells used for fermentation/cell culture produce HCPs necessary for the cells to function (growth, gene transcription, protein synthesis, etc.) and during cell death. They must also be controlled during downstream processing because they have the potential to elicit an immune response in patients due to the use of non-human cell lines (typically Chinese hamster ovary or CHO cells) for production. Some HCPs can also affect drug product stability. "Regulatory agencies expect robust control of these species through drug substance release testing," Moscariello observes.

Multiple analytical methods

The properties of the different types of residual protein contaminants in biologic drugs vary significantly, leading to the need to use different analytical methods to detect and monitor each. The presence of HMW species, for instance, is frequently determined using size-exclusion chromatography (SEC) coupled with high-pressure liquid chromatography (HPLC) or ultra-high performance liquid chromatography (UHPLC), while LMW species are detected using a capillary electrophoresis–sodium dodecyl sulfate (CE–SDS) (reduced and non-reduced) technique. HCPs are typically measured using enzyme-linked immunosorbent assays (ELISA).

"SEC–HPLC (or UHPLC) is a very robust assay and typically has very good resolution for HMW species, but it is often difficult to resolve LMW species," Moscariello says. As a result, CE–SDS is used for the detection of LMW protein

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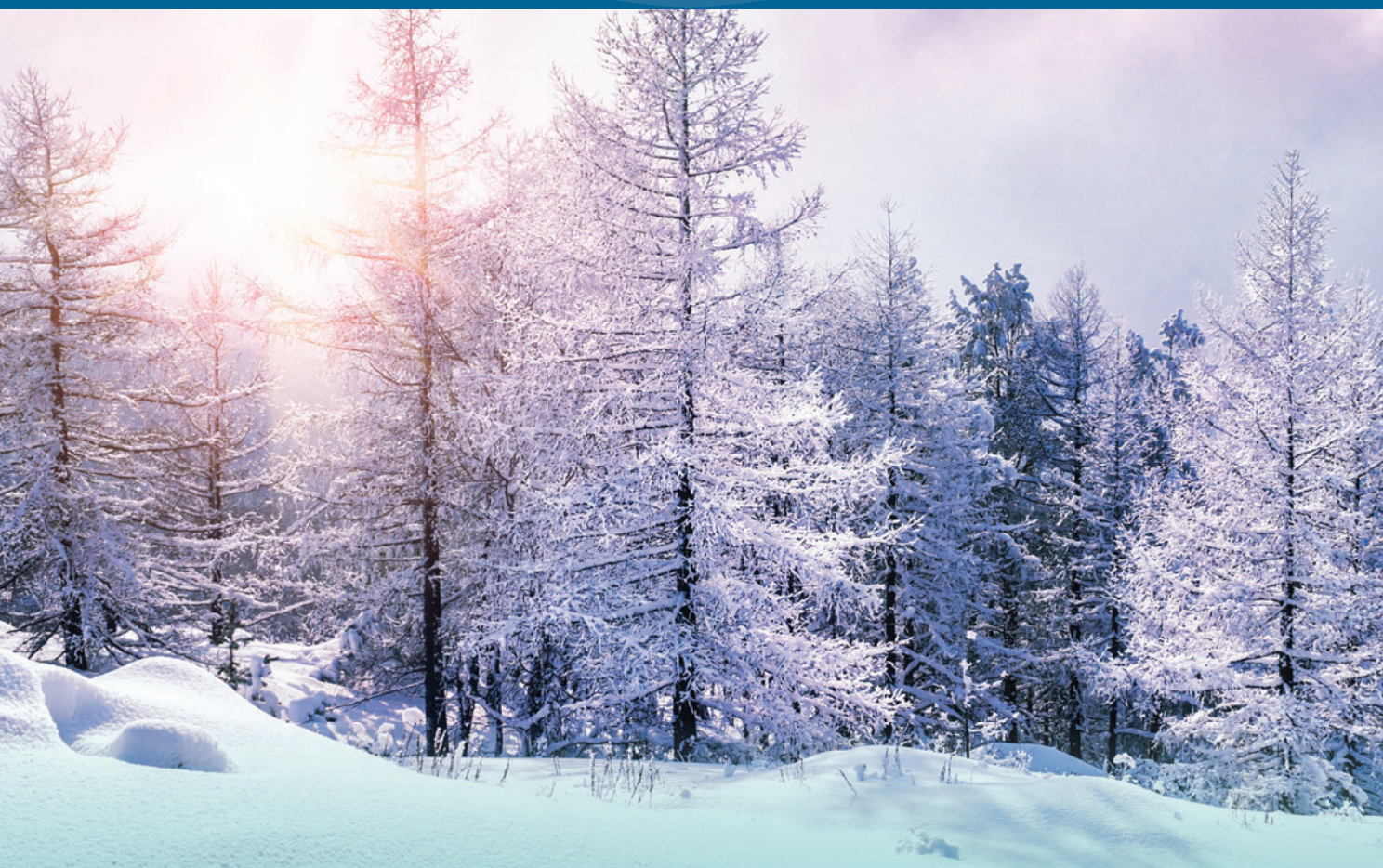

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impurities. The SDS denatures the protein, and if needed a reducing agent can be added to break any disulfide bonds. As in SDS–PAGE (polyacrylamide gel electrophoresis), the LMWs are separated based on size. For monoclonal antibodies, when running a reduced CE–SDS, typically highly resolved intact heavy and light chains, as well as any clipped species or non-reducible HMW species (i.e., covalently linked compounds) can be observed, according to Moscariello. To detect half-antibodies, however, non-reduced CE–SDS is frequently used because they are difficult to detect when using a reducing agent.

Advances in mass spectrometry are enabling more detailed analyses and improved monitoring of residual proteins during downstream processing.

Although ELISA is the most common technique for monitoring HCPs, the selectivity of this method is dependent on the antibodies used in the ELISA kit, and consequently some HCPs can potentially be missed, according to Peter Levison, senior marketing director, downstream processing with Pall Life Sciences. HCP ELISAs employ a polyclonal mixture of anti-host cell proteins, but often do not provide complete coverage for all of the HCPs expressed during a specific process. This situation is particularly true for commercial kits. "While these kits allow for off-the-shelf detection of a wide range of HCPs for various cell lines, including CHO, they likely have significant gaps in HCPs for each specific process. As a result, ELISAs are known to show significant variability and it is difficult to get accurate values," Moscariello comments. On the other hand, he notes that the development of product-specific HCP assays with high coverage is costly and time consuming.

Better detection

Most companies are exploring more advanced techniques for the detection of HCPs and other protein impurities that are designed to overcome the limitations of existing methodologies. In particular, Moscariello notes significant investment in process analytical technology (PAT) tools for online or at-line monitoring of HMWs and other contaminants. For instance, he points to the use by Amgen of multi-angle light scattering (MALS) to monitor protein aggregates at the effluent of a cation-exchange column.

Several advances in detection techniques for HCPs are also being made. Use of isotope tags for relative and absolute quantification (iTRAQ) HPLC technology can enable better detection of host-cell proteins, and when coupled with comprehensive genome sequences, can enable better identification of HCPs using established mass spectrometry (MS) databases, according to Levison. Data obtained from techniques such as surface-enhanced laser desorption/ionization-time of flight (SELDI–TOF) MS in combination with ELISA results are also allowing semi-quantification of total HCPs.

Improved purification

The first step in the purification of bioprocess fluids taken from bioreactors is clarification. In this step, the biologic-drug substance is separated from cell debris and turbidity is removed, leaving a clear harvested cell-culture fluid. This step is typically achieved via depth filtration or centrifugation and does also lead to the reduction of undesired protein impurities. Pall Life Sciences introduced the Cadence Acoustic Separator technology in April 2016—an alternative clarification method for cell-culture bioprocess fluids, including those from continuous perfusion processes—based on acoustic wave separation technology licensed in 2015 from FloDesign Sonics (FDS).

Following clarification, orthogonal chromatographic steps during protein purification are generally used to further reduce HCP, HMW, and other contaminants to acceptable levels, according to Levinson. "The most powerful step to remove HCPs is affinity chromatography," asserts Moscariello. There are issues with this method, however. While almost universally adopted for monoclonal antibodies, this method is often not applicable for non-fragment-crystallizable (Fc)-region-containing products. There are significant product-HCP interactions with antibodies. It is common to try to disrupt these interactions with harsh washes, particularly on affinity resins, which requires that they be salt-tolerant. Levison adds that the introduction of new mixed-mode modalities has provided additional selectivities that are providing improved HCP clearance.

There is also a lot of work being done with precipitating and flocculating agents, according to Moscariello. He notes that caprylic acid has been shown to significantly remove HCPs from product streams without significant loss of product.

Further advances expected

Advances in detection technologies are having an impact on the capability of downstream processing to remove undesired protein impurities, according to Moscariello "The ability to identify specific HCPs using state-of-the-art MS techniques has allowed downstream development scientists to assess the charge, size, and hydrophobicity of these HCPs and exploit their differences from the product of interest and develop more robust processes," Moscariello adds.

"Improvements in analytics and genomic/proteomic analyses may well provide better awareness of the presence of contaminants and therefore facilitate their clearance," Levinson concludes. **PT**

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Issues with glass (the traditional material for parenteral containers) and the complex needs of the rapidly growing biologics market are spurring developments in parenteral packaging. "Ease-of-use for the patient is another concern due to an increasing trend toward self-medication," says Christopher Cassidy, vice-president of sales and marketing, North America for Schott Pharmaceutical Packaging.

Quality continues to be imperative. " … the main and most important concern of the pharmaceutical packaging market has always been the integrity of the drug and how to avoid any interaction between the glass and the drug," says Paolo Golfetto, director of technical and business external relations at Ompi. He reports, "In recent years, with several recalls spurred by container or closure defects (… loss of sterility) or particle contamination, attention has intensified."

Dr. Nicolas Brandes, director, Market Development at West Pharmaceutical Services, agrees. He says, "From a regulatory perspective, we are seeing increased scrutiny on quality. It's essential to build in quality from the start."

The steady rise in biologics poses additional challenges. "Biologics often require specialized containers," notes Brandes. Products often are highly concentrated, more viscous, and sensitive to packaging materials such as glass, polymers, elastomeric stoppers, coatings (such as silicon oil), and the traces of tungsten left behind during the syringe manufacturing process.

The higher viscosity and higher volume of many biologics that will be entering the market may not be compatible with some formats, especially auto-injectors and prefilled syringes. Steven Kaufman, global business development lead at Bespak, explains: "In the past, a fill volume of 0.2 mL to 1 mL, using a 1-mL prefilled syringe with a 27-gauge needle was typical. That's changed. In addition to the 1-mL prefilled syringe, primary containers have grown to include the 2.25-mL prefilled syringe, and needle gauges have diminished in size to 29 gauge. This combination poses a big challenge for injection time and, more importantly, for ensuring completeness of injection. With high viscosity comes concern about the force placed on a glass syringe to achieve a target injection time and guarantee conpleteness of injection. Glide force also must be considered, along with injection time and the risk of breakage. Major suppliers have addressed these needs with biotech-ready prefilled syringes, which offer better dimensional control and siliconization. Many pen systems have difficulty handling formulations above 10 centipoise (cp), but Bespak's VapourSoft-based auto-injectors and our latest amplification system can easily handle several 100 cp with minimal risk of glass breakage." In addition, Kaufman says, "Shipping testing and transport are critical parts of any device manufacturer's program. When delivering high-value biologics, the appropriate level of robustness must be built into the device itself. ISO standards must be followed and tested against to ensure there's no variability and that key specifications are met. Now, more than ever, the importance of auto-injectors and similar devices such as wearables is increasingly clear."

Glass innovations

Glass, a well-established material for vials, syringes, cartridges, and ampuls, has experienced quality issues such as particulate contamination, interaction with high pH products, and subsequent delamination. Glass also has the potential to break and may not be compatible with the cold temperatures some biologics and other novel applications, such as cell therapy, require. "Extremely cold temperatures pose a challenge to container closure integrity," explains Brandes.

Suppliers of glass containers for parenterals have improved manufacturing processes to reduce chances of delamination and particulate generation and upgraded testing to provide earlier detection of problems. Ompi, for example, has "completely redesigned manufacturing equipment and introduced new process steps to drastically reduce … particles," Golfetto reports. He adds, "We operate with a continuous improvement mindset, with a special focus on manufacturing

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process capability and product quality." In fact, the company's quality targets have moved from an acceptable quality level approach to a more stringent parts-per-million defect level.

Cassidy emphasizes the importance of making process improvements within existing validation frameworks. For example, he says, "With Vials DC, we have optimized an established production process [to minimize chances of delamination]." Produced from high-quality Fiolax glass tubing, Vials DC containers undergo an optimized hot-forming process. The result is vials with highly homogeneous inner surfaces. Tests based on *United States Pharmacopeia (USP)* <1660> showed no delamination or pre-indicators for delamination. He recommends, however, "performing screening studies for each individual case."

Measures are also being taken during manufacture, fill/finish, and final packaging to minimize glass-to-glass and glass-to-machine contact, which can flaw a container or cause breakage. The expanding use of ready-to-use nested vials, now available from multiple suppliers, prevents containers from coming into contact with each other or the equipment. Nested vials also streamline the fill/finish process. "Ready-to-fill packaging eliminates the need for washing and sterilization by the pharmaceutical company or third-party filler," says Brandes. Users can load tubs directly onto filling lines. The streamlined, contact-preventing process reduces reject rates and preserves the cosmetic quality of the vials.

Dual-chamber cartridges

Nested vials are not the only recent innovation in glass packaging for parenteral products. Double Chamber cartridges from Schott combine liquids with liquids or liquids with lyophilized drugs to provide stable storage, reliable reconstitution, and convenient and safe administration versus the traditional, multi-step dual vial (drug, diluent) and syringe administration process. "The risk of error, such as a possible contamination of the substances, increases with the number of steps," observes Cassidy. "In addition, there is the risk that the patient could miss the right mixing ratio or inject the wrong dosage. A Double Chamber cartridge solves this problem because it carries out mixing and application in one go."

The dual-chamber design addresses approximately 25% of new injectable drugs, vaccines, and biologics that are freeze-dried and have to be reconstituted prior to injection. The Double Chamber cartridge stores drug and diluent in consecutive chambers separated by a plunger (see **Figure 1**). A bypass in the glass barrel allows the contents to mix before the drug is injected. Turning the pen lock pushes the plunger, leveling it to the bypass and forcing the diluting liquid through a 0.1-mm opening and into the second chamber; the liquid then reconstitutes the drug. Now, the exact dosage of the drug can be injected without risking contamination.

Medical professionals and patients favor dual-chamber cartridges because they're simple to operate. Plus, high dosage accuracy makes the system safe and convenient for patients, especially if a highly concentrated drug is involved. The cartridges are compatible with common pen systems and can be customized. Several major pharma/biotech firms have already adopted the format for a variety of products including human growth hormone.

Polymeric options

Although glass continues to dominate parenteral packaging, it's not suitable for all products. In those situations, polymeric options are being specified. The most common materials, cyclic olefin copolymer (COC) and cyclic olefin polymer (COP), are tungsten-free and do not leach alkali-ions such as sodium, which can cause the pH-value of the drug to shift. "In severe cases this pH shift may affect the stability of the drug," notes a Gerresheimer spokesperson.

"COP reduces the risk of breakage and is proven for low temperatures," says Brandes of West, which offers Daikyo Crystal Zenith COP vials. West licenses this technology from Daikyo Seiko. A clean material, Daikyo Crystal Zenith systems provide very low extractables. As a result, he adds, COPs "help reduce chemical interactions, delamination, protein absorption, and aggregation." He notes that the material can be formed in custom shapes and designs, which are not possible with glass. "In a crowded market, there's a need to differentiate products.

Figure 1: Double Chamber cartridges from Schott store drug and diluent in consecutive chambers separated by a plunger.

FIGURE 1 IS COURTESY OF SCHOTT

Ready-to-use vial trends

According to Gerresheimer, the shift to ready-to-use vials depends on:

- End users focusing more on core competencies, such as drug product development
- Producers of primary packaging components evolving into system suppliers
- A shift from blockbuster drugs to products with smaller batch sizes, which makes current vial filling lines less efficient
- Growth in personalized drugs, for which volumes are too small for traditional equipment
- Development of technology to allow filling, stopping, and crimping of nested vials
- Expansion in the sizes available.

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Benefits of ready-to-use vials

According to Ompi, the benefits of ready-to-use vials include:

- Eliminate glass-to-glass handling throughout the supply chain and improve quality and safety
- Streamline fill/finish process (no washing, drying, depyrogenation, sterilizing on the packaging line)
- Increase flexibility in fill/finish operations
- Reduce total cost of ownership due to streamlined fill/finish process
- Cut time to market and lengthen patented product lifecycle (e.g., one validated line can run nested vials for clinical trials and nested syringes for commercial operations, so there's no need for process requalification from trial to commercial).

Custom containment and delivery systems could deliver that differentiation."

Gerresheimer has offered a range of ready-to-fill COP syringes manufactured by its longstanding partner, Taisei Medical, in Japan. In collaboration with Taisei, Gerresheimer has expanded its ready-to-fill COP syringe portfolio and production capacity by beginning to manufacture the Gx RTF ClearJect syringe at its Gerresheimer Medical Systems plant in Germany. The first Gx RTF ClearJect product to be manufactured is the 1-mL long syringe with staked-in needle. "The Gx RTF ClearJect syringe … allows the use of standard components like plunger stoppers, backstops, and plunger rods," says a Gerresheimer spokesperson. Under development for approximately 18 months and now in a prelaunch phase, the Gx RTF ClearJect syringe will be available in 2018.

Schott offers a prefillable COC syringe for sensitive drugs. The Schott TopPac SD syringe with pure elastomer components features a reduced extractables and leachables profile. Careful component selection and an optimized processing method result in a significantly reduced level of impurities and decrease the chance of drug/container interaction. Cross-linked silicone for barrel lubrication reduces the amount of subvisible particles while providing optimal functionality. Sterilization with ethylene oxide instead of irradiation further reduces extractables and leachables.

Multilayer containers

Polymeric containers may also be multilayer. The Gerresheimer MultiShell COP/polyamide/COP vial combines excellent barrier properties and glass-like transparency to protect contents from oxidation and water vapor and increase shelf life. A commercial production line manufactures vial sizes from 2 mL to 100 mL. An automated packaging line packages ready-to-use vials or bulkware. Applications include oncology

drug products, monoclonal antibodies, osteoporosis treatments, and specialty injection solutions with high pH-value and significant sensitivity to oxygen.

Another multilayer polymer-based container, Wheaton's DualFusion vial, addresses delamination and leachate concerns. "There are two Fusion layers. The first layer is what we call a 'protective layer,' which is an inert organosilicate layer that protects against high or low pH products that can cause delamination via a silicon network hydrolysis," explains Wayne Brinster, president and CEO of Wheaton. "The second layer is the 'barrier layer,' which is a silica layer that is covalently bonded to the COP shell *via* a plasma-enhanced chemical vapor deposition technology. These layers are less than 500 nm in thickness, so they are not seen with the human eye. When these two Fusion layers are combined with a COP shell it is known as a new material called a 'Fusion material.'" The outer COP shell provides mechanical strength, protects against breakage, and can withstand a temperature range of -196 °C to 121 °C without cracking. The inner layer prevents permeation of water vapor, oxygen, and other gases; protects against delamination; and eliminates concerns over leaching of metal ions. Since the lining is so thin, transitioning to the new container would be reportable, but would not require new trials. "It would be a drop-in replacement," says Brinster.

The base of each ready-to-use, ready-to-sterilize DualFusion vial is laser-etched with a unique DataMatrix barcode for rapid and easy traceability. "This is extremely important when combating the ongoing concern of counterfeit drugs," says Brinster. In addition, batches can be matched to run size.

Applications include highly toxic drugs like chemotherapy doses where breakage would result in hazardous conditions and an arduous cleanup. Brinster reports, "We are already seeing a shift toward the DualFusion vial in the pharmaceutical industry, specifically in the biological segment. ... There is always a concern with leachates when packaging large protein molecules. For example, if a chemical molecule migrates from the primary packaging component into the end product, it can cause the protein to fold and change its form; this occurrence would result in a drug efficacy [concern]. For example, the folding of the protein will cause the end product to become less potent or even cause it to become dangerous to the patient." The organosilicate inner lining of the DualFusion vial reduces the concern for leachates because of the high purity of the material. "We are also seeing a shift toward the DualFusion vial in the traditional chemical-synthesized segment due to its protection against delamination. ... The inert organosilicate layer ... protects against delamination from silicon network hydrolysis, which is common for drug products that are in a pH range of 3 to 11," he concludes. **PT**

DANLEAP/GETTY IMAGES

Improving Feeder Performance in Continuous Pharmaceutical Operations

Sharon Nowak

Designing loss-in-weight feeders for accurate and consistent refill is crucial to a continuous solid-dosage process.

The recent milestone of FDA approval of two solid-dosage formulations produced through continuous manufacturing has brought attention to the merits of continuous manufacturing to the entire global pharmaceutical community. As this industry continues to investigate and use continuous manufacturing practices, the roles of loss-in-weight (LIW) feeders and the subsequent accurate and consistent refill of these feeders are critical. The importance of the method of refill, refill control algorithm, reaction time of the refill device, and also the size of the refill hopper are all critical variables that often get overlooked when designing a continuous manufacturing system. This article outlines a number of important considerations in refill operations and investigates their influences not only on LIW feeder accuracy, but on the overall continuous manufacturing process.

Loss-in-weight feeding

A typical LIW feeder achieves rate control by weighing the entire feeder, hopper, and the material contained in it (see **Figure 1**). The speed of the metering device is controlled to result in a per-unit-time loss of system weight equal to the feed rate. As an integral part of loss-in-weight feeding, the weighed hopper must be resupplied with material. Several pharmaceutical operations are dependent upon this refill of feed principle. These operations include continuous extrusion (both hot-melt and wet-granulation extrusion), continuous direct compression, and continuous wet granulation.

Refilling the feeder hopper. The feeder hopper can be refilled with either a manual method or an automatic method. The manual method implies that a quantity of bulk solids is tossed into the feeder hopper by the plant operator, and the process continues. The automatic method implies that dosing machinery under control of the feed system will add material to the feeder hopper from an upstream supply.

In the past, the traditional method of maintaining feed was to simply use a constant metering speed throughout the refill phase—a speed corresponding to the metering speed associated with gravimetric control just prior to entering the refill phase. If, for example, the metering speed averaged 60 RPM just prior to the system sensing the need to refill the supply hopper, the screw speed would be maintained at that 60 RPM for the duration of the refill operation. After refill is completed, material has settled, and the feeder senses an appropriately declining system weight, the feeder is returned to gravimetric operation where metering speed once again becomes the parameter of control.

There are two problems associated with this technique. First, during refill, the feeder only acts as a volumetric feeder. Second, upon re-entry to true LIW control, abrupt changes in feeder speed can occur, resulting in a sometimes extended period of off-spec mass flow until the feeder settles into the new proper speed.

Figure 2 plots the hopper weight versus time and shows the declining weight signal, the slope of which is the feed rate (change in system weight per unit time). Note that the hopper does not empty completely before the refill phase is triggered, primarily to assure

Figure 1: Coperion K-Tron loss-in-weight feeder mounted on a platform scale.

ALL FIGURES ARE COURTESY OF THE AUTHOR.

Sharon Nowak is global business development manager, Food and Pharmaceuticals at Coperion K-Tron, www.coperionktron.com, snowak@coperionktron.com.

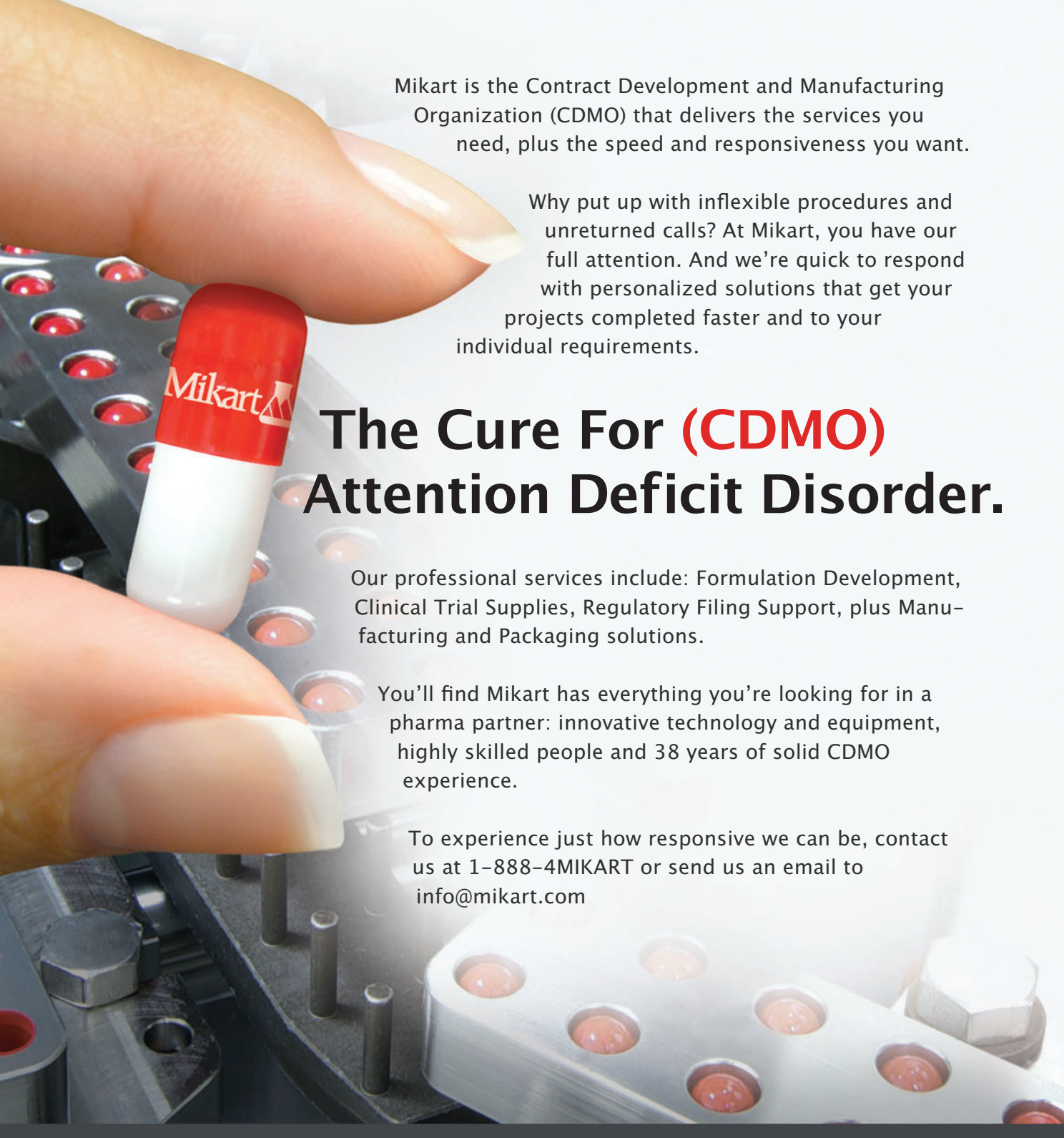

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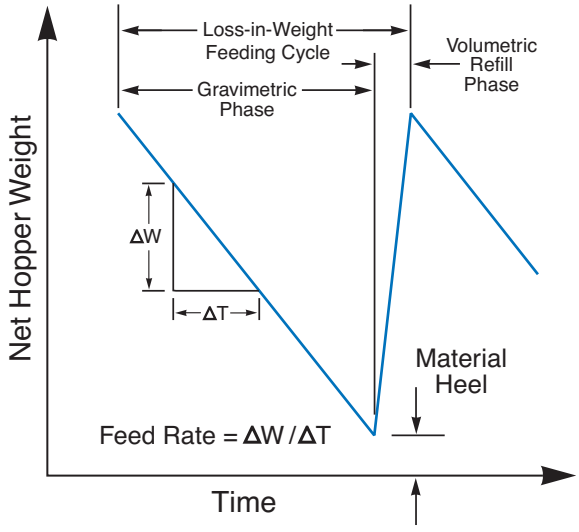
Figure 2: Loss-in-weight operating principle.



an ever-present supply of material at the metering device so feeding may proceed without interruption. Additionally, if a sufficiently large material heel is not present, the increasing pressure applied by the impact of the incoming and possibly aerated material during refill may cause uncontrolled flooding through the feeder.

Even with an insulating heel of material in place, density within the metering zone will rise somewhat as the hopper fills. Given a constant metering speed during refill, this increase in density causes aggressive degradation (overfeeding) in feeding accuracy as more and more material enters the hopper and compacts the material into the hopper's lower regions.

How severe is this accuracy? The answer hinges on hopper size/geom-

Smart Refill Technology

Sidebar Figure 1 illustrates the Smart Refill Technology (SRT) approach. The graph at the top plots net hopper weight versus time. Beginning with a full hopper (where net hopper weight equals refill complete weight) gravimetric operation is in effect, and the feeder operates normally. As net hopper weight declines, the controller also determines and stores a set of up to 100 feed factors, each of which is the index of the average density of material discharged at the hopper weight associated with the feed factor. A low feed factor indicates that a higher number of screw revolutions were required to discharge a given weight, implying a reduced material density. Conversely, a higher feed factor reflects higher density because fewer revolutions were required to deliver the same material weight.

The middle plot of **Sidebar Figure 1** shows motor speed versus time. During the early portion of the gravimetric feeding phase, motor speed is relatively constant because density within the metering zone of the feeder, while higher than at later times in the feeding cycle, does not vary substantially. This is because material in the upper portion of a typical hopper is largely supported by the material below, and, in turn, the tapering walls of the lower portion of the hopper. As feeding proceeds and hopper level declines, headload in the metering zone begins to lessen, resulting in a reduction in density and a corresponding increase in motor speed required to maintain feed rate. When hopper weight reaches the refill request threshold, the refill phase begins. During refill, SRT begins with the motor speed that was in effect at the time of the refill request, and then modifies that speed by applying the corresponding feed factor as each hopper weight "slice" is encountered.

By taking this more sophisticated approach, it is possible to smoothly exit the refill phase and return to true gravimetric operation. Additionally, by controlling feeder speed during refill based upon the most recent performance history, reverting to volumetric performance is avoided and gravimetric accuracy is essentially preserved.

Sidebar Figure 1: The smart refill control concept.

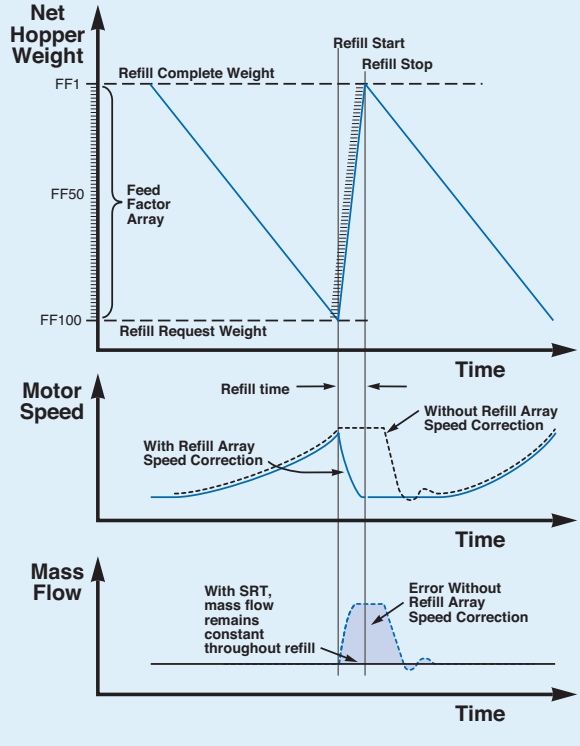


FIGURE IS COURTESY OF THE AUTHOR.

etry in addition to the compactability of the material itself. Laboratory tests and field experience involving many hundreds of materials show that, in practical terms, headload-related LIW overfeeding may range between +/- 1% for relatively constant-density materials. For powders and other materials whose density can vary substantially, however, this variation can be as high as +/- 10–15%. When dealing with compressible pharmaceutical powders in continuous operations, this variation can significantly affect accuracy.

Using a smart refill algorithm. A controlled method of storing and trending the weight-to-speed relationship was developed to avoid these problems. This method, referred to as Smart Refill Technology (SRT), discards the approach of maintaining a constant metering speed. Instead, during automatic refill, the feeder control system switches to volumetric control, relying on the trending data obtained while the hopper was emptying of product. As the hopper is emptied, the corresponding speed of the motor is trended. When the refill is occurring, this same speed is used for the corresponding hopper weight (see Sidebar).

The refill window must be evaluated for the material being fed and its properties.

SRT enables metering speed to be gradually lowered during refill to precisely counterbalance the effects of increasing material density occurring within the metering zone as the hopper weight increases. In this way, gravimetric feeding accuracy during the brief refill may be maintained.

Determining refill interval

As a rule, the refill period should be approximately 6–10 seconds. This duration ensures positive control over the incoming material but is so short that minor flow variations should not perturb the downstream processes. For many pharmaceutical operations, however, the refill window can be much smaller, due to the shorter overall time span of the operation. Because it is important to keep the feeder in gravimetric control over the majority of the continuous operation, often more frequent and shorter refills are used, typically using approximately 60–80% of the refill hopper volume. This refill window can be crucial to the overall operation of the feeder and must be evaluated for the material being fed and its properties.

For this reason, it is imperative to study the bulk solid properties such as bulk density, particle size, compressibility, angle of repose, gas permeability, particle morphology, and angle of friction when

dealing with any type of material feeding operations, including refill. Each of these material characteristics will greatly affect not only the flow out of the hopper to the feeder but also how quickly the hopper is refilled. For example, if the bulk material has a high gas permeability (i.e., if gas can escape rapidly from the solid), the refill can occur as rapidly as is feasible. On the other hand, if the bulk material has a low permeability rate (i.e., the gas expands the bulk material and doesn't quickly escape to return the solid to its resting condition), care must be taken during refill, for often these materials become floodable in this condition or at least suffer significant bulk density changes.

For example, if flooding of the bulk solid begins during refill, the product could easily flush out of the LIW feeder. At a minimum, air entrainment effects resulting in underfeed conditions during and immediately after refill can significantly alter bulk density, because the control system is using control data from earlier in the run, when the product density was much higher. Air entrainment comes from rapidly refilling the feed hopper, such that air, being unable to quickly escape, passes through the incoming material to the region of lower pressure in the refill hopper. Venting of the weighed hopper can minimize the problem, but now dust collection and, in the case of active materials, filtration, must be arranged. Adequate venting will assist in material settling and aid in a quicker return to true gravimetric operation.

Selecting the refill device

There are several choices of refill devices used above the feeder hopper. Options include modulating butterfly valves or, in the case where extreme control is required, the use of alternate metered devices, such as volumetric screw feeders. In addition, the use of pneumatic loaders above the butterfly valve is often employed to transfer the material to a receiver above the feeder hopper.

It should be noted that problems may arise when the refill system does not take into consideration the capacity of the feeder hopper, the flow properties of the bulk sold, and the distance

If the bulk material has a low permeability rate, care must be taken to avoid flooding.

and potential storage volume of the bulk solids that can occur between them. For example, in refilling a feeder hopper from an intermediate bulk container (IBC), the volume of the product in these vessels will often exceed the volume of the feeder hopper. Clearly, it is impossible to control the refill without overfilling the feeder hopper, unless a time window is established for the opening and closing cycle of the refill valve. This time window can be calculated based upon bulk density of the material, the angle of repose (which dictates the settling level in the feeder hopper), and the flow rate through the refill device. When discharging from bins or IBCs, which may be equipped with flow aid devices (e.g., vibrators or live bottom bins), special care must be made to isolate the vibration of these devices from the feeder hopper to ensure that there is no interference on the LIW feeder weight-measuring device.

As stated previously, the flow rate from the refill device must be sufficient to avoid exceeding the refill time limit. Additionally, the flow cutoff action of the selected device must be quick. A slow tapering off of the refill flow needlessly lengthens refill time; any leakage of the refill device may cause an unavoidable measurable weight disturbance, but will always result in a flow error in the positive direction.

Pneumatic vacuum receivers as refill devices. Pneumatic receivers, which operate under a dilute-phase vacuum transfer principle, are often used as re-

fill devices, particularly for continuous operations. The pneumatic receiver can have a butterfly valve at its outlet, or it can be part of the volumetric feeder, which includes a valve at the outlet. The pneumatic system uses negative pressure to draw the material into a separately mounted and supported vacuum receiver. The receiver is filled to a determined level and then holds this material charge until the feeder below requests a refill. The level of fill in the receiver is determined by level sensors. At the point of the refill request by the feeder, the discharge valve opens and the receiver contents are discharged into the feeder hopper. At the same time of this release, a gas pulse is sent through the filter housed in the vacuum receiver to release any entrained particulate or material that may have settled on the filter. Filter material options include a laminated membrane-type material for quick release and easy-clean properties.

After dumping the material into the feeder hopper below, the valve is shut again and the receiver vacuum cycle immediately begins, so that the pneumatic receiver will be instantly ready for the next refill request. The use of pneumatic receivers as refill devices allows for an uninterrupted source of refill from a bulk container.

The refill method and the control of the refill algorithm are important for a highly accurate continuous manufacturing system.

A pneumatic receiver avoids possibly overfilling the feeder hopper. It should be noted, however, that in some cases, refill by gravity (not pneumatic transfer) is preferred. Gravity refill typically uses an IBC above the feeder hopper, and this system should use a modulating control valve tied directly to the required feeder refill levels to avoid overfill, as previously discussed.

Summary

The refill method of the LIW feeder and the control of the refill algorithm are important processes in the optimal performance and design of a highly accurate continuous manufacturing system. Through careful evaluation of the feeding process, system layout, and material characteristics, a continuous feed and refill system can be optimized. **PT**

Fill/Finish Outsourcing

Eric S. Langer

This key bioprocessing segment is expecting continued growth.

SVETA DEMIDOFF/GETTY IMAGES

PharmTech.com/ptoutsource

Fill/finish operations have traditionally been among the most commonly outsourced biopharmaceutical manufacturing activities. Biologics final formulation and dose filling processes require rigorous attention because they occur at the end of costly biologics manufacturing where product safety value is highest. Traditional filling involves stainless steel equipment connected through reusable valves, tubing, and piping. And because of the need for specialized equipment, expertise, and care, much of this work has been outsourced.

Stability and caution are hallmarks of this segment, and fill/finish operations are not typically characterized as part of the more rapidly changing segments. However, according to BioPlan Associates' *13th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (1), this segment remains an actively evolving area where innovation and new technologies are improving product safety and cost of goods.

Outsourcing and other fill/finish trends

To determine how the rapid advances in other bioprocessing manufacturing sectors compare to fill/finish segments, respondents to BioPlan's survey identified the following as the most important trends in fill/finish today:

Eric Langer is president of BioPlan Associates, tel. 301.921.5979, elanger@bioplanassociates.com, and a periodic contributor to *Outsourcing Outlook*.

- Adoption of single-use/disposable equipment was the top trend in fill/finish activities, cited by 64% of respondents (down from 75% in 2015). Aseptic suites for final filling operations that use disposable technologies can reduce cleaning requirements and minimize risks of cross contamination. They can also be used for bulk storage containers, filters, connectors, and manifolds to minimize contamination risks and reduce downtimes.
- More multi-product-use-oriented facilities was the next-largest trend, with many also pointing to the introduction of a restricted-access barrier system (RABS) and isolator as well as more innovation for fill/finish equipment.
- Outsourcing of fill/finish may be flattening out. Respondents may have maxed out their enthusiasm for outsourcing of fill/finish as a trend. But the study indicates they will increase outsourcing to contract manufacturing organizations (CMOs) in the future.
- Smaller-footprint operations can be expected as smaller companies access new technologies and automation. Some may be able to manage more work in-house, despite the need for these smaller operations to address issues such as reducing waste.
- Robotics and automation continue to advance, as automation in filling operations further reduces risks of contamination. Most systems today, except for small manual operations, tend to be highly automated, with as few human interactions, such as loading raw materials, system changeovers, and cleaning, as possible.
- New delivery devices, such as prefilled syringes, have expanded and require changes in filling operations.

Fill/finish outsourcing may not be buzz-worthy

Outsourcing of fill/finish operations today remains a key fill/finish trend, but the percentage increases have flattened. Data indicate that almost three-quarters (74.2%) of biomanufacturers today are outsourcing fill/finish activities to at least some degree (1). This is the continuation of a steady trend of more widespread outsourcing of fill/finish dating back to 2010, when 6 in 10 respondents reported outsourcing at least some fill/finish activities. This year, fill-finish places fourth on a list of 24 outsourced activities, trailing only analytical testing of bioassays (89.7% outsourcing), plant maintenance services (80.4%), and toxicity testing (76.3%).

Further evidence of the strong state of outsourcing in the fill/finish market is also available. Respondents were surveyed concerning the average percentage of outsourcing done today (**Figure 1**). As expected, on average, respondents estimated outsourcing fill/finish operations to the largest degree. Indeed, the data indicate that more than one-third (35.6%) of this activity is outsourced. This figure is within the 32–27% range witnessed this decade. It also makes fill/finish easily the most heavily outsourced activity of the lot, far ahead of the next one on the list, analytical testing of bioassays (27.4% of activity outsourced).

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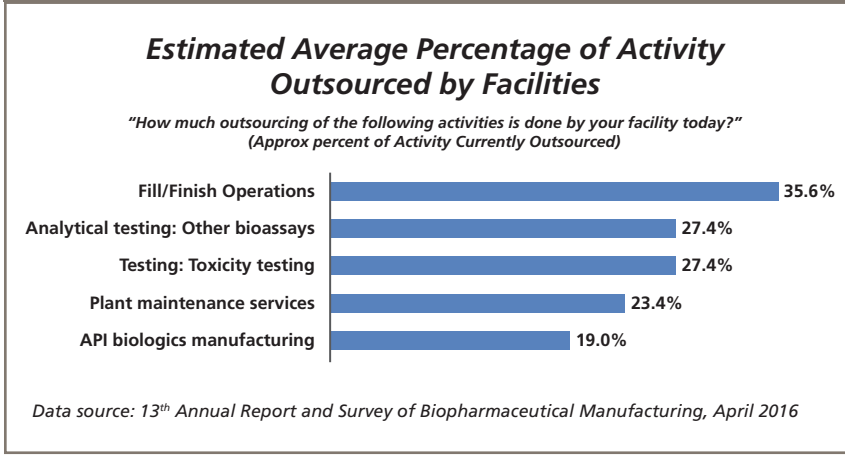
Figure 1: Top five activities by average percentage of activity outsourced today.



Data source: 13th Annual Report and Survey of Biopharmaceutical Manufacturing, April 2016

Outsourcing of fill/finish activities is clearly commonplace and no longer considered part of the critical trends that make up the bioprocessing market. While this may change, as more innovative single-use processes and isolator technologies are introduced, filling will remain a conservative segment.

Expect more fill/finish outsourcing in the years to come

There's reason to believe that the industry will see even more outsourcing of fill/finish activities to CMOs. Survey data demonstrate that a sizable share of the industry is planning to significantly increase its outsourcing of fill/finish operations (1).

Specifically, one in four respondents (25.4%) expect to outsource fill/finish operations at "significantly higher levels" in the coming 24 months. That figure is up from 19.7% in 2015. Still, relatively speaking, fill/finish operations are set for bigger increases than virtually any other activity measured. The only area respondents expressed greater enthusiasm about the future outsourcing was for analytical testing of bioassays, where close to one-third (31%) plan to significantly expand. Fill/finish operations even nudged API biologics manufacturing in planned increases, despite the latter's multi-year upward trend on this measure.

But why outsourcing if in-house capacity is sufficient?

It's interesting to view the extent to which fill/finish operations are outsourced within the context of in-house capacity. To this end, there is sufficient in-house capacity for current biophar-

maceutical products, even without adding shifts or additional equipment. That view may not be held by some small-molecule fill/finish facilities, which have been operating at near-capacity due to consolidations and regulatory actions.

BioPlan estimated capacity utilization by looking at current usage against maximum capacity per shift using respondents' current configuration for number of shifts and equipment set-up and found that capacity utilization averaged:

- 48% for vialing, down slightly from last year (50%)
- 41% for pre-filled syringes/cartridges/devices, fairly even from last year (40%)
- 58% for lyophilization, up from 52% last year.

The basis for these estimates excludes CMOs, who are major players in this industry, such that these estimates relate to in-house capacity only. This suggests that outsourcing of fill/finish activities isn't being driven primarily by a need to expand capacity. Specialized CMOs, instead, may be viewed as having more sophisticated techniques and newer technologies. Those with newer technologies may have a competitive advantage, particularly considering that more than one-third of fill/finish respondents this year don't plan to add any new technologies during the next 24 months.

Conclusion

The industry's desire for improvements in fill/finish services has eased a little this year, after growing in years past. Additionally, increased outsourcing to CMOs is not seen as the key trend that it was last year.

Fill/finish activities and operations are the most heavily outsourced of any biomanufacturing activity, and each year more respondents report outsourcing fill/finish activities to at least some degree. Moreover, many respondents see significant increases in fill/finish outsourcing on the horizon. Outsourcing of fill/finish activities is certainly entrenched, even if there is ample in-house capacity. That doesn't mean it won't be a competitive environment for CMOs, who may well be expected to adopt or already be using technologies such as closed-vial filling and single-use fill-finish devices. All in all, outsourcing may not be buzzworthy for fill/finish this year, but the state of fill/finish outsourcing remains quite healthy.

Reference

1. BioPlan Associates, *13th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (BioPlan Associates, Inc. Rockville, MD., April 2016). **PT**

GE Healthcare Invests in Ireland Biopharma Manufacturing Campus

GE Healthcare will invest €150 million (167.5 million USD) in a new biopharmaceutical manufacturing campus on Industrial Development Agency (IDA) Ireland's strategic site at Loughbeg, Ringaskiddy, County Cork.

GE BioPark Cork, subject to contract and planning approvals, will hold Europe's first four KUBio, prefabricated, off-the-shelf bio-manufacturing facilities, owned and run by GE customers. GE will run centralized, shared utilities and site services.

To further develop biopharma manufacturing skills and expertise in Ireland, GE and the National Institute for Bioprocessing Research and Training (NIBRT) also announced today their plan to create a NIBRT-GE Single-use Centre of Excellence at NIBRT's Dublin facility. NIBRT expects to train up to 1500 bioprocessing professionals annually on next-generation biologic manufacturing technologies that will be used in GE BioPark Cork's manufacturing facilities.

GE BioPark Cork is expected to be home to more than 500 new jobs when fully operational; 400 with biopharma companies and a further 100 employed directly by GE. The construction phase, subject to planning approvals, is expected to begin by mid-2017 and create up to 800 construction jobs. The project is supported by the Department of Jobs, Enterprise, and Innovation through IDA Ireland.

GE's KUBio enables pharmaceutical companies to quickly deploy new biologics manufacturing capacity and bring medicines to market faster. KUBios increase manufacturing flexibility and are between 25 and 50% more cost-effective to build than comparable traditional facilities. Carbon dioxide emissions can be reduced by 75% and water and energy use by approximately 80%. Build time can be shortened to 18 months from the usual three years.

Catalent to Acquire Pharmatek

Catalent Pharma Solutions announced its plans to acquire Pharmatek Laboratories, a California-based manufacturer of oral, injectable, and topical products. No financial terms of the agreement have been disclosed.

The acquisition of Pharmatek will add spray drying to Catalent's portfolio of drug formulation and delivery technologies and expand their capability for handling highly potent compounds. Pharmatek offers a drug-development platform including formulation screening, formulation development, analytical services, and finished-dose-form manufacturing for clinical supply. The company also offers solutions for poorly soluble compounds, controlled release formulations, and facilities for potent compound handling.

Pharmatek's San Diego facility contains two analytical and two formulation laboratories, four engineering rooms, and nine certified ISO Class 8 manufacturing suites. Catalent says they expect the transaction to close within the new few weeks and that the company will pay all cash in the acquisition.

Capsugel Announces Expansion at Quakertown Facility

On Sept. 7, 2016, Capsugel announced that it will be expanding its Quakertown, PA facility to meet demand for micronization services for clinical and commercial manufacturing. The expansion will double the size of its current pilot-scale capacity for clinical-trial quantities and increase the number of suites for commercial manufacturing.

The Quakertown facility, which Capsugel acquired as part of its purchase of Xcelience and Powdersize in January 2016, operates as a full-service provider of particle-size reduction and particle-size control/classification technologies for pharmaceutical customers.

The acquisition expanded the company's suite of bioavailability tools aimed at improving the bioavailability of APIs with either dissolution or solubility challenges. In addition to enabling increased capacity, the added suites will include single-use containment technologies to accommodate potent and highly potent compounds. The new equipment and suites are scheduled to be operational by January 2017.

Merck KGaA Joins the DiViNe Project

Merck KGaA Darmstadt, Germany announced that the company has joined the DiViNe Project, a European consortium of six companies to address challenges facing the development, manufacture, and delivery of vaccines. The objective of the project is to create an integrated cost effective purification program tailored for vaccines that achieve higher yields while preserving product integrity.

Merck KGaA, Darmstadt, Germany will focus on simplifying the process of vaccine purification that typically relies on affinity chromatography. Merck KGaA will provide chromatographic materials and coupling technologies for the project, the company said in a press announcement. The project's purification platform will be tested first with heterogeneous vaccines including glycoconjugates, protein antigens, and viruses. After the platform is validated, the consortium plans to implement the platform in downstream processes for other biologics.

Other members of the consortium include Affilogic (France), Aquaporin (Denmark), GenIbet Biopharmaceuticals (Portugal), and GlaxoSmithKline (Italy). The project will be coordinated by iBET (Portugal) and has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement N° 635770.

BASF Opens PVP Facility in Shanghai

BASF announced on Sept. 27, 2016, the opening of a new plant for the manufacturing of polyvinylpyrrolidone (PVP) at the BASF site in Shanghai, China. The plant will produce PVP K30 powder, a polymer used as a base for several applications including pharma excipients.

The site is equipped with production facilities, a quality control laboratory, and warehousing capacity. The facility operates in compliance with local and international good manufacturing practice standards, including those defined by International Pharmaceutical Excipient Councils (IPEC). The plant expands the company's reach to customers in Asia Pacific, especially in China.

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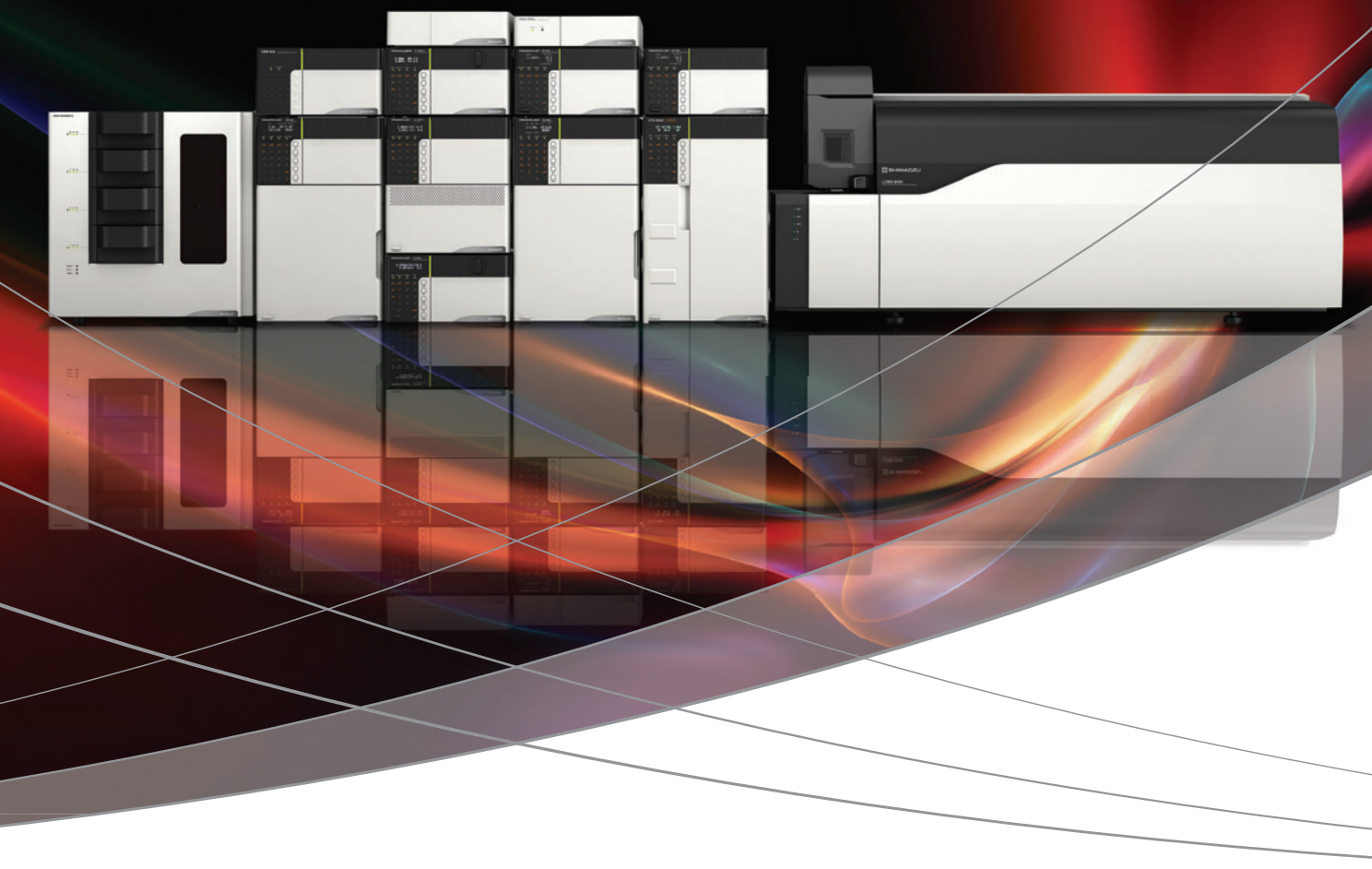

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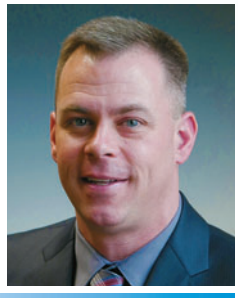
Decontamination and Depyrogenation of an ASEP-TECH® Blow/Fill/Seal System

A Q&A



Andrew W. Goll
Director of Sales and Marketing
Weiler Engineering, Inc.

Weiler Engineering uses nitrogen dioxide rather than steam or conventional methods to sterilize/Sanitize the Grade A filling zone.

Use of Blow/Fill/Seal (BFS) technology is expected to increase for packaging biologics, such as vaccines and protein-based materials. BFS is an automated system that minimizes human contact. Typically, the product-contact path of the BFS process is sterilized with steam, and the entire process takes place in a cleanroom environment. Weiler Engineering recently presented research on NO_2 sterilization and depyrogenation of the fill area in Weiler's ASEP-TECH® BFS systems. *Pharmaceutical Technology* recently spoke with Andrew Goll, the Director of Sales and Marketing at Weiler Engineering, Inc. to learn more about what makes Weiler Engineerings ASEP-TECH® BFS systems suited for packaging injectable products, particularly small- and large-volume parenterals.

Pharmaceutical Technology: How is the critical filling zone or the Grade-A environment cleaned?

Andrew Goll: Typically, under normal operations, customers would use a steam sterilization process to clean the Grade-A filling zone, or there would be a manual process whereby customers wipe down the inside of the Grade-A environment using either hydrogen peroxide and/or isopropyl alcohol. This requires human intervention and actually breaching the Grade-A environment to perform the cleaning process, which is typically frowned upon in the pharmaceutical industry. Fortunately, most of these processes occur prior to an SIP cycle, which adds to the safety and makes it a little more accepted within the industry.

Pharmaceutical Technology: What were the most important considerations when deciding on moving forward with this technology?

Andrew Goll: First, we had to make sure that it was going to be safe because nitrogen dioxide (NO_2) is a gas and not widely used in the industry. That was a key factor. The second consideration was whether the sterilization concept could be completed during a CIP and SIP process. To keep the machine running, uptime is money. So we wanted to turn the machines around and have a quick changeover that required us to sterilize inside the Grade-A environment during both CIP and SIP. Third, we wanted to have the process be completely automated without the need for human intervention. Because it is a true decontamination and depyrogenation of the critical filling zone, we also wanted to make sure that there was little residual and

that we could get three-log reduction for endotoxin during the sterilization process. This is important because a lot of customers will have multiple product lines that will run on one machine. So, quick changeover times between product lines and then sterilization of the Grade-A filling zone was a key consideration for this application.

Pharmaceutical Technology: Why has nitrogen dioxide been the choice in a sterilant?

Andrew Goll: Because it is a non-aqueous gas, NO_2 does not condense in complicated geometries, which is nice because there is very little humidity required for the process. It's a quick aeration phase, which means you don't have to allow for a lot of airflow and air changes. The gas is activated at room temperature– between 18 degrees C and 30 degrees C. Because of the complicated geometries inside a Grade-A environment where the fill system and product pathway are partially housed, you need to penetrate within those geometries to ensure complete sterility assurance.

Pharmaceutical Technology: What were the results of the decontamination and depyrogenation in the BFS nozzle shroud?

Andrew Goll: We varied the cycle parameters, focusing primarily on the NO_2 concentration, the humidity, and the time of exposure during the sterilization cycle. Nine biological indicators with *Geobacillus stearothermophilus* were used as the biological indicators within each cycle. At the end of the cycle, all nine biological indicators were dead. The next step focused on endotoxin reduction. Four endotoxin vials were distributed throughout the nozzle shroud. At the end of 11 cycles, the observed endotoxin reduction was more than 10^3 in each cycle. The process parameters were varied to prove efficacy for time, humidity, and NO_2 gas concentration. As everything was modified throughout the sterilization or validation processes, it proved we had increased the safety and the sterility assurance over manual processes and provided the additional safety of a complete depyrogenation, which resulted in better results than originally anticipated.

Pharmaceutical Technology: Where do you see the industry heading that will require this type of technology?

Andrew Goll: We are getting more inquiries from customers globally who are looking to do biologics, some of which are protein-based and/or are heat-sensitive products, requiring that they be processed under cooler than normal temperatures. Additionally, the injectables and vaccine markets are two of the most advanced markets that we're seeing for Blow-Fill-Seal technology.

Pharmaceutical Technology: Is the industry widely accepting this type of a new technology, especially as it pertains to a completely new sterilization methodology utilizing a gas instead of steam or hydrogen peroxide?

Andrew Goll: People are curious to learn about NO_2 because it is a new gas, but it is gaining notoriety. Typically, in the pharmaceutical industry, we like to stay with things that we know. There is a company utilizing NO_2 to sterilize inside isolators. People are interested and actively pursuing the best methodology for using this technology on their equipment. It's been invigorating to see something new come to light within the industry that offers people a different advantage for their processing. If you can keep machines in production longer–meaning you're processing changeover is quicker–it equates to more money at the end of the day based on uptime.

Weiler Engineering, Inc. is a leading provider of aseptic custom packaging for pharmaceutical and healthcare applications.

Reversed Phase Liquid Chromatography using Surrogate/ Additional Stationary Phases

LIVE WEBCAST: Wednesday, October 26, 2016 at 11 am EDT | 10 am CDT | 8 am PDT

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

EVENT OVERVIEW:

Liquid chromatography is used to identify an analyte or API, to quantitate the amount of analyte or API (assay), and as a preparative method for separating the analyte or API from its related substances. Techniques that can increase the resolution between related substances and the API are vitally needed for establishing the identification, assay, and preparative output.

In this webinar, analytical experts will present data on the use of a surrogate/additional stationary phase (SSP/ASP) bound to C18/ C8 reversed phase media, and the effect on the resolution parameters such as retention factor (k'), efficiency factor (number of theoretical plates (N)), tailing factor (peak asymmetry), and the selectivity factor (α).

Who Should Attend

- Scientists/researchers practicing chromatography in industry and academia
- CMC professionals working in small, mid-size, and large pharma focused on development of peptides
- CMC and regulatory consultants
- Process chemists responsible for development and manufacturing of peptide APIs key starting materials
- R&D leaders
- Project managers responsible for clinical stage compounds (peptides and complex small molecules)
- Professionals responsible for quality control, quality assurance, and regulatory affairs

Presenter

Mohmed (Mike) K. Anwer, PhD
Vice-President and Head
Neuland Laboratories Limited, Hyderabad, India

Christopher M. Cimarusti, PhD
Consultant
CMC Development

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Key Learning Objectives

- Learn a simple and novel way of increasing the resolution in analytical and preparative reversed phase–high performance liquid chromatography (RP-HPLC).
- Understand how to increase the preparative RP-HPLC output for peptides using SSP/ASP bound to reversed-phase columns.
- See how the purification output of SSP/ASP-Prep-HPLC is more than 10 times the output of classical Prep-RP-HPLC.

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For questions, contact Ethan Castillo
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Employing a Lean Lab Approach to Optimize Lab Processes: Part 2: "Improve Productivity"

ON-DEMAND WEBCAST

Lean manufacturing principles are increasingly being adopted in the laboratory environment. If Lean Lab is properly implemented, the results can be impressive, delivering simpler workflows and processes, reduced lead times, and increased laboratory efficiency. Operational changes—such as optimization of workflows and workplaces or standardization of equipment and software—can be initiated one step at a time. Often, it is the simplest or smallest changes that can bring about the most significant improvements.

Part 1 of this webinar introduced the basic concepts of Lean Lab and the 10 fields of improvement that should be considered when analyzing the current status of your lab. In Part 2 of this webinar, experts will give advice on how to identify the actions that have the biggest potential impact on improving lab productivity, and determine the next step toward a lean lab. Value stream mapping will be examined in more detail, with examples of how to identify unnecessary steps in an analytical workflow and how to visualize where issues exist.

Key Learning Objectives

- Identify the next step to improve the efficiency of your lab
- Understand how to eliminate unnecessary steps and optimize workflows
- Discover ways to measure the performance of your lab

Presenters

Erwin Studer
Managing Partner
Profact AG

Daniel W. Fuchs
Head of Product Marketing and Training, Laboratory Weighing
Mettler-Toledo GmbH

Moderator

Adeline Siew
Editor
Pharmaceutical Technology Europe

Who Should Attend

- Laboratory managers, laboratory supervisors, and production managers from analytical, research and development, quality assurance and quality control (QA/QC) laboratories
- Contract research organizations (CROs)
- Contract manufacturing organizations (CMO)
- Laboratory planners and facility managers
- OPEX, Lean or Six Sigma managers, champions or belts
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For questions, contact Kristen Moore at kmoore@advanstar.com

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F. Total Distribution (Sum of 15c and e)	26,987	27,169
G. Copies not Distributed	418	98
H. Total (Sum of 15f and g)	27,405	27,267
I. Percent Paid and/or Requested Circulation	62.74%	67.39%

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MANUFACTURING/PROCESSING EQUIPMENT

Mixing/Blending/Drying

ASK THE EXPERT— *contin. from page 94*

The concepts set forth in the FDA guideline are also set forth in the European regulations (2).

High-risk areas to assess

One of the most critical areas for establishing your risk assessment is the subject of proper gowning technique. If the operator can't follow the proper gowning requirements, the product will be at risk the moment the operator enters into the critical manufacturing area. It is interesting to note that in a recent draft guidance issued for compounding facilities, the failure to properly gown is considered to be an insanitary condition (3).

Another discipline that should be considered as high risk in the risk assessment is cleaning. The cleaning of the line after manufacturing is personnel dependent and, if done incorrectly, can put the next product manufactured on the line at risk of microbial and/or cross contamination. There are many different disinfectant procedures, and it is important that they be executed effectively. Again, proper training and oversight should help maintain the employee's skills, therefore avoiding potential product contamination.

Bottom-line, when establishing your risk-assessment program, some of the highest risk areas/activities will be those where there is a high level of human involvement. Assessing those areas first as contributing factors to your environmental problem will help you effectively manage your resources. But be advised that whatever the risk-ranking you give to each area/activity involved in your aseptic manufacturing each area must be thoroughly evaluated and vetted because any of the areas could be the potential source of your microbial problem.

References

1. FDA, *Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice* (CDER, CBER, ORA, September 2004).
2. European Commission, *EudraLex*, Volume 4, Annex 1 (November 2008).
3. FDA, *Draft Guidance for Industry, Insanitary Conditions at Compounding Facilities* (CDER Office of Compliance, August 2016). PT

Ad Index

Biocompatibility Testing of Combination Devices

New Regulatory Guidance

LIVE WEBCAST:

Thursday, Nov. 3, 2016 at 8 am PDT | 11 am EDT | 3 pm GMT | 4 pm CET

Register free at
http://pages.pharm.lancasterlabs.com/CombinationProducts-Registration.html

EVENT OVERVIEW:

Navigating the technical and regulatory pathways for combination products is challenging enough when considering the complex requirements dictated by both the pharmaceutical and medical device components. The challenge increases when facing the subtle nuances imposed by regulators when filing in multiple international markets. FDA's guidance document on ISO 10993-1, issued in June 2016, provides additional considerations for biocompatibility testing that pharmaceutical companies should be mindful of as they develop their combination products.

Join this informative webinar to learn how to implement an efficient testing program for assessing the biocompatibility of a combination product's device component, which incorporates the relevant requirements of ISO 10993-1, to satisfy both US and international regulatory agencies.

This presentation will include real-world case studies and best practices for

- Chemical characterization, including extractables and leachables testing
- Toxicological risk assessments
- Biocompatibility testing
- Pitfalls to avoid while developing testing plans
- Future trends for combination products
- Implications of new FDA guidance on the use of ISO 10993-1

Who Should Attend

Bio/pharmaceutical scientists, managers, and directors who are responsible for the development, biocompatibility assessment, and US and International regulatory submissions of combination products.

Presenters

Albrecht Poth, PhD
Scientific Director,
Eurofins Medical Device Testing

Jennifer Roark, BS
Manager,
Chemistry & Container Testing
Eurofins Medical Device Testing

Odete Mendes, DVM, PhD, DACVP, DABT
Director of Toxicology and Pathology
Product Safety Labs (PSL)

Moderator:

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

Defining Risk Assessment of Aseptic Processes

Susan Schniepp, distinguished fellow at Regulatory Compliance Associates,
discusses the assessment of risk in the processing of intravenous injectable drugs.

Q: I work in the quality group for a manufacturer who makes intravenous (IV) injectable drugs using aseptic processing techniques. Recently, the facility has experienced an increase in the number of viable organisms in our environmental monitoring program. Management has asked me to do a risk-based assessment so we can use our resources effectively. Can you offer some advice on how I should proceed in putting together this assessment?

A: Aseptic processing of IV injectable drugs is certainly one of the riskiest manufacturing operations. Your management is correct to be concerned when there is a reported increase in the number of viable organisms in the environment. It is often difficult to determine where a potential microbial ingress is coming from. This is why so much attention is given to monitoring personnel, equipment, air quality, etc., for microbial organisms and identifying and trending what those organisms are and where they are coming from. A risk-based approach to determine the source of the microbial increase is a good start. It is important to remember aseptic does not mean sterile and the objective in aseptic processing is to keep the product, components, and environment as close to sterile as possible. This is accomplished through proper building, equipment materials, and design; established and validated cleaning procedures; proper training for personnel; and continuous monitoring of the personnel and environment to make sure the sterile core area and the areas supporting it are properly maintained at all times to avoid product contamination that would impact patient safety.

Developing a risk-based approach

The first step in developing a risk-based approach for your facility is to break down your operations into the various steps and determine the highest risk posed to those areas. The highest risk areas tend to be those where personnel are intimately involved. Of these areas, one of the most risky is personnel gowning. Proper gowning is crucial to the aseptic operation because, in some cases, such as compounding pharmacies or manual fills for small clinical trial batches, it may be the only barrier between the product and the human. Because we can't sterilize the human being, we must take care to make sure they understand the proper gowning technique and fastidiously adhere to it so the patient can be assured the product is safe.

Proper aseptic technique is critical to maintaining the sterile environment where the aseptic product will be filled. In September 2004, FDA finalized their guidance for industry titled *Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice* (1).

When establishing your risk-assessment program, some of the highest risk areas/activities will be those where there is a high level of human involvement.

This document placed considerable emphasis on the training and behavior of the personnel involved in the aseptic fill operation. It is important for the company to continually focus on personnel behavior to avoid complacency and potential product risk. As stated in the guideline, "As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. To ensure maintenance of product sterility, it is critical for operators involved in aseptic activities to use aseptic technique at all times." To establish an operator's skills, the company should have basic training topics covering personal hygiene, proper aseptic technique during operations and gowning activities, proper plating techniques for microbial monitoring, among others. In addition, the company should establish an ongoing training program as a way to maintain and continually improve the operators' performance. This training should be documented by the quality department through training records, evaluation of the ability of the operator to follow standard operating procedures (SOPs), and monitoring deviations for breaches in aseptic technique during production.

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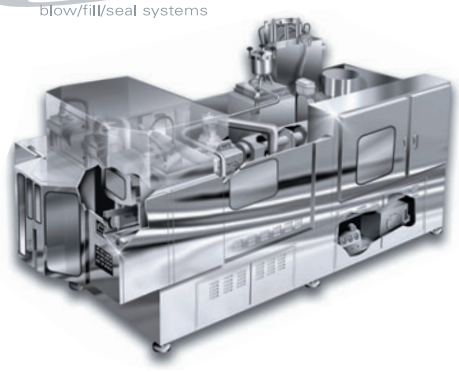

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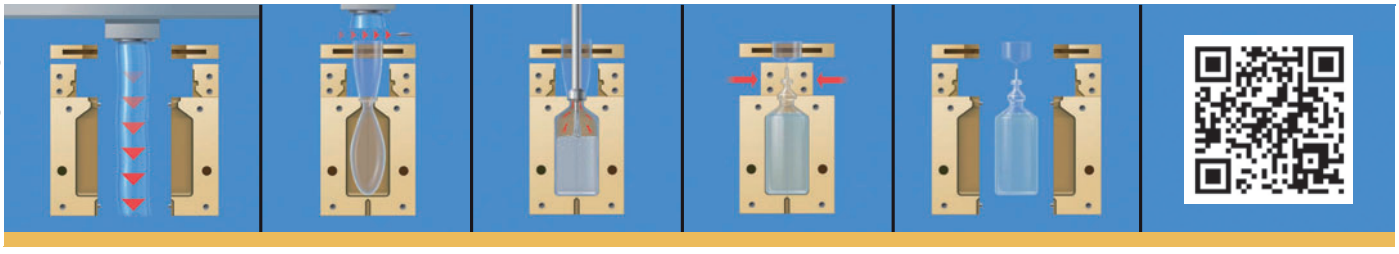

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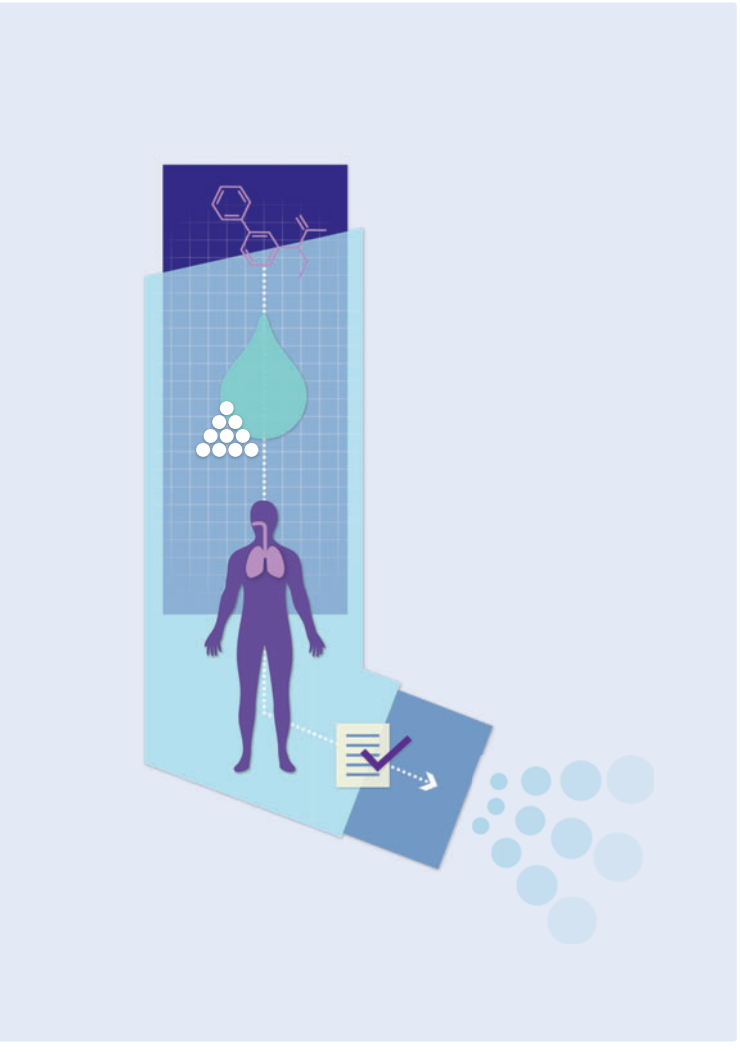

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