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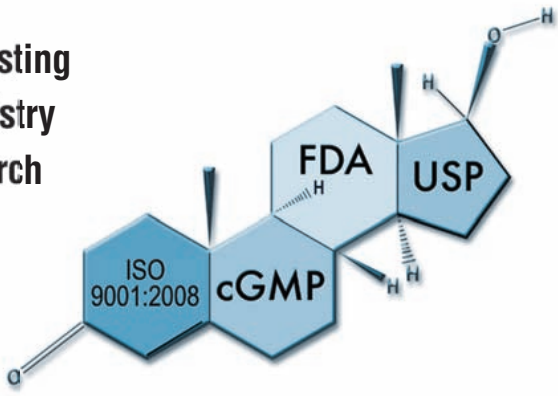

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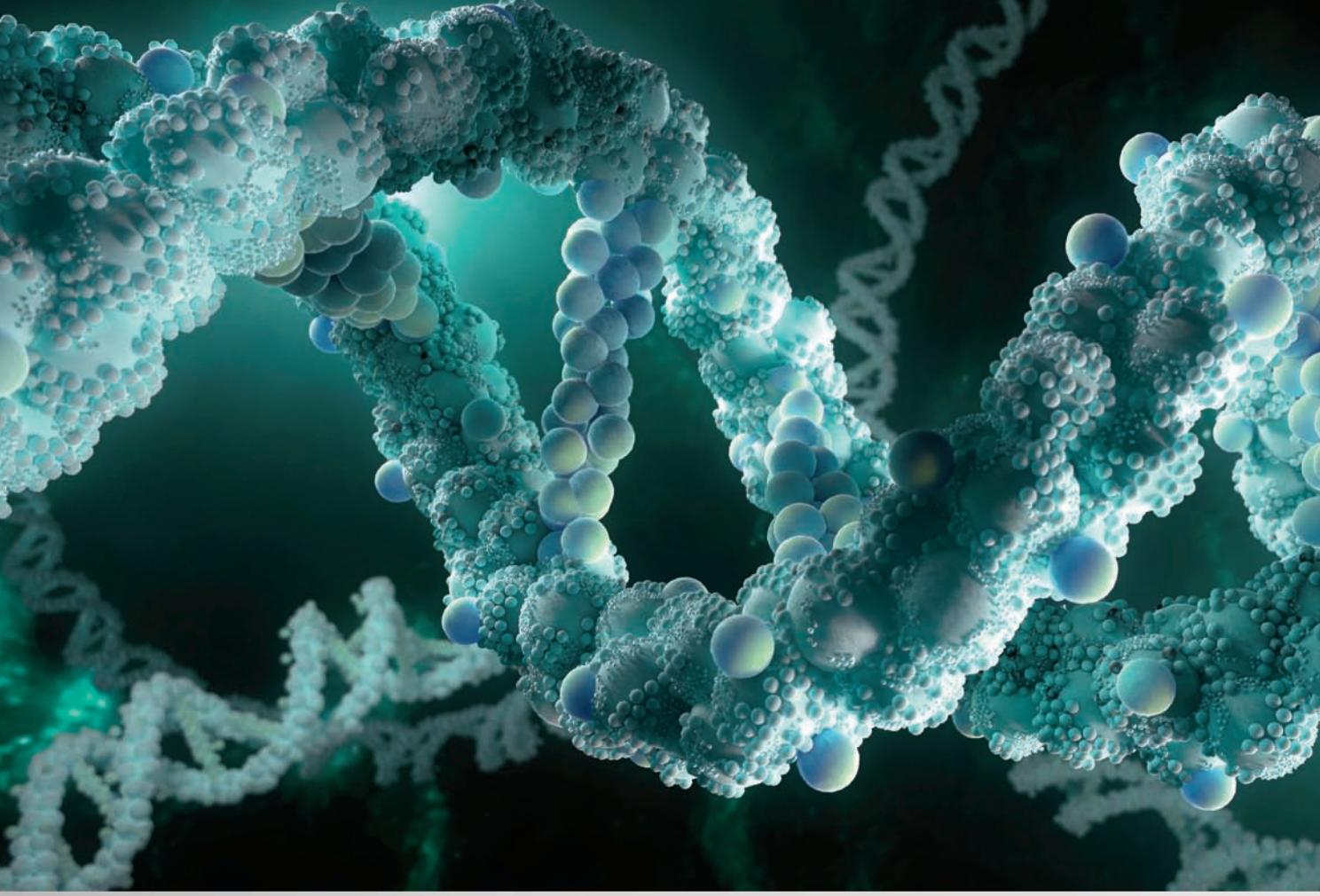

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Illustration by Dan Ward
Images: Wladimir Bulgar/Science Photo Library/Getty Images

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Correction:

On p. s22 of the August 2015 Outsourcing Resources supplement to *Pharmaceutical Technology,* a sidebar in the article "Handling HPAPIs: Do Your CMOs have the Right Stuff?" inadvertently left off Pfanstiehl, Inc. from the list of Safebridge-certified API suppliers. Pfanstiehl was one of the first companies to be certified by Safebridge and has maintained certification since then.

Pharmaceutical Technology is selectively abstracted or indexed in:

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

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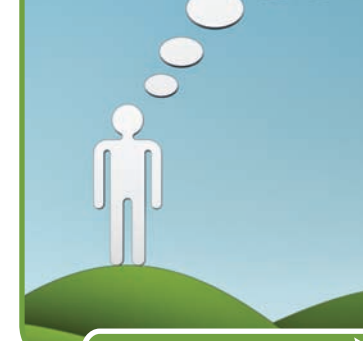

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Evolving to Meet Industry Changes

Alice Till

In the development of biopharmaceuticals and pharmaceuticals, the line is blurring.

Like any other discipline, the pharmaceutical science industry is not immune to change. In recent years, it has seen company consolidations, expansions, and mergers; limited/declining research funding; and a decreasing pool of workforce talent. The nature of our industry has shifted, and the growing interest in biotechnology has led to a metamorphosis. Pharmaceutical companies continue to diversify into biologics through acquisitions of biotechnology companies, in-licensing of products, academic-industry partnerships, and R&D alliances.

A decade ago, a clear distinction was made between biopharmaceuticals and pharmaceuticals based on their origin and method of manufacture. Since then, however, various industry business reports, including those supported by the Pharmaceutical Research and Manufacturers Association (PhRMA), have asserted that with the metamorphosis of the industry noted above, driven in part by the adoption of significant technological advances, "pharmaceutical" and "biopharmaceutical" are essentially synonymous, signaling that the lines between large and small molecules, chemical entities and biologically derived therapeutic drug products, and also between large and small companies are rapidly disappearing, which is—in fact—reflected in and across the PhRMA and the Biotechnology Industry Organization memberships.

AAPS is working to merge its National Biotechnology Conference and its Annual Meeting beginning in 2018.

As of 2011, consistent with these industry trends, nearly 50% of American Association of Pharmaceutical Scientists (AAPS) members are now affiliated with small biopharmaceutical/pharmaceutical companies, contract research organizations, or consultancies, with many of these pharmaceutical scientists having, or expected to have in the future, overlapping responsibilities for the discovery, development, and manufacturing of both small and large chemical and biologically derived molecules, as do those members affiliated with large biopharmaceutical/pharmaceutical companies, regulatory agencies, and universities. With the acceptance of biosimilars, pharmaceutical scientists affiliated with both brand and generic-drug companies, large and small, are likely to have overlapping responsibilities for large and small molecules. Though details may differ, the overarching principles, processes, and challenges of academic pharmaceutical research, industrial drug development and manufacturing, and regulatory review, approval, and oversight of new therapeutic products are not significantly different for large and small molecules.

AAPS is working to merge its National Biotechnology Conference and its Annual Meeting beginning in 2018 to provide a forum for all pharmaceutical scientists to work together to advance the field and facilitate the discovery, development, and approval of new medicines. The programming for this single meeting will be designed to leverage the diverse expertise of its members to provide opportunities for sharing of cutting-edge science, building on the commonalities between large and small molecules, as well as for furthering the understanding of unique differences.

As the pharmaceutical industry changes, the association must change as well if it is to remain relevant. The new combined meeting is a response to one key aspect of the evolving industry and consequently the professional needs of our members; other changing needs have been and will continue to be identified and addressed through the dynamic strategic planning and management processes initiated this past year. AAPS is playing an important part in advancing the capacity of pharmaceutical scientists to develop products and therapies that improve global health. **PT**

Alice Till, PhD, is the 2015 president of the American Association of Pharmaceutical Scientists.

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FDA Faces Controversy Over Quality Metrics and Biosimilars

Manufacturers challenge details in new policies designed to promote access to important therapies.

FDA officials have been busy addressing some difficult drug regulatory issues important to biopharma manufacturing, marketing, and R&D. In July 2015, the regulators rolled out a much-discussed proposal for how companies should collect and submit data to measure the quality and reliability of manufacturing systems, only to meet strong objections from industry (1, 2). FDA followed the metrics program with a highly controversial plan for naming biosimilars and innovator biotech therapies, which continues to divide innovator and generic-drug firms (3, 4).

A stated goal of these and related FDA policies is to facilitate patient access to needed medicines, a process that involves preventing and reducing critical drug shortages. The FDA Safety & Innovation Act (FDASIA) of 2012 addressed shortages—in addition to providing FDA authority to collect additional manufacturing data for its metrics program—by enabling the agency to require early manufacturer notification of expected supply disruptions for life-saving medicines. FDA issued a final rule in July 2015 that addresses shortages by requiring a broad range of companies to provide advance (six months) notification of an event likely to cause a "meaningful disruption" in the supply of critical medicines (5). Biotech manufacturers had protested extending the initiative to vaccines and other biologics, and generic-drug makers complained that even a five-day notification requirement may be a burden, but those concerns did not stop FDA from implementing what it considers a practical early notification policy.

Slightly different biosimilar names

Much more contentious is FDA's proposal for addressing the hot-button issue of how to identify biosimilars related to innovator products. Biosimilar makers and payers want their new products to carry the same proprietary names as reference drugs to encourage prescribing and reimbursement; brand companies argue that different names are necessary to prevent inadvertent substitution and confusion regarding adverse events.

FDA appears to lean towards the "ensure safety" camp by establishing a new biosimilar naming policy that adds a unique, four-digit suffix to a "core" name for all biotech therapies (3).

This approach aims to prevent erroneous prescribing and dispensing of biosimilar and reference products and to facilitate tracking of postmarketing safety issues, a process that FDA says can't rely on national drug code numbers (NDC) because many biologics are administered in hospitals and clinics. Biosimilar advocates fear that even slightly different names will discourage product uptake, but analysts note that the similar core names will permit brands and biosimilars to be grouped together on health system databases, which will encourage their use.

While innovators may support FDA's approach for differentiating biosimilar names, they are up in arms about the agency's unexpected related proposal for adding suffixes to all biotech therapies, including those already on the market. To start what is sure to be a lengthy process of revising product names retroactively, FDA issued a proposed rule that specifically applies the new naming policy to six licensed biologics facing near-term competition from biosimilars (6). Requiring new names for old products has never occurred before, says Gillian Woollett of Avalere Health, noting that significant database and software changes may be needed to accommodate the new system.

Still unclear is how FDA will apply the new naming policy to biosimilars that achieve "interchangeable" status, which applies to a drug that can be substituted by the pharmacist without prescriber permission; while this may be the case for most conventional generics, biosimilars may be approved as similar. One option is to permit the same suffixes for these products, and FDA seeks comments on this issue, as well as its broader naming policy.

Go slow with metrics

Both brand and generic-drug firms are troubled by FDA's plan for collecting data on a range of measures for the reliability and quality of drug-production operations and resulting products. After three years of workshops and white papers on developing quality metrics, FDA finally spelled out its program in a draft *Request for Quality Metrics* guidance document (1). Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), opened an Aug. 24, 2015 public meeting to discuss the plan by suggesting that the proposed metrics are what "any manufacturer would want to know" and that FDA had worked hard to keep the new data collection initiative manageable and useful. The guidance outlines a number of data points that CDER and the Center for Biologics Evaluation and Research (CBER) believe will help field inspectors assess the ability of an operation to reliably produce high-quality medicines; firms with good reports may merit less frequent plant inspections and reduced reporting of post-approval manufacturing changes.

Somewhat surprising after such extensive FDA-industry collaboration were the many objections raised by manufacturers about the metrics proposal being too broad, unclear, and moving towards mandatory implementation too quickly. Industry reps stated at the August 2015 meeting that gathering and reporting the data will be costly and time-consuming and voiced fears about the program generating "report-card" listings and superficial comparisons open to misinterpretation by patients and payers.

Genentech Vice-President Diane Hagerty, representing the International Society for Pharmaceutical Engineering (ISPE), advised FDA to phase in the initiative, starting with higher risk facilities and products, and to drop for now a measure

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for on-time completion of annual product reviews. Camille Jackson, director for science & regulatory advocacy at the Pharmaceutical Research and Manufacturers of America (PhRMA), questioned FDA's use of guidance, as opposed to more formal notice-and-comment rulemaking, to provide sufficient authority for the agency to require metrics reporting in advance of inspections. Similarly, David Gaugh, senior vice-president of the Generic Pharmaceutical Association (GPhA), speculated whether FDA can require metrics reporting by foreign companies, a limitation that he said could encourage US firms to shift drug production overseas.

Excipient makers objected to the idea of collecting metrics on "high risk" excipients, while API producers raised a host of questions about providing quality measures on products made for many drug companies. Non-prescription drug firms want to limit initial metrics to high-risk medicines, as opposed to hand creams. And Gil Roth, president of the Pharma & Biopharma Outsourcing Association, voiced uncertainties about how contract manufacturers can submit data on a facility making drugs for multiple clients. Richard Johnson, president of the Parenteral Drug Association (PDA), optimistically described the FDA proposal as "a good place to start," but cited challenges in assessing the "quality culture" at companies—potentially the next phase for the program, but now apparently on the back burner.

All these objections clearly disappointed FDA officials, who said they sought an objective list of measures that companies already collect internally and that could be assessed easily by field inspectors. FDA believes the program will assist in inspection scheduling and in efforts to avoid supply disruptions. But staffers acknowledged the need to clarify terms, how data will be used, and reporting relationships for contractors and suppliers. Issuing final guidance "is a high priority," said Russell Wesdyk, acting director of the Office of Surveillance in CDER's Office of Pharmaceutical Quality, but FDA extended its comment period through November 2015, and no one expects any revisions until 2016, at the earliest.

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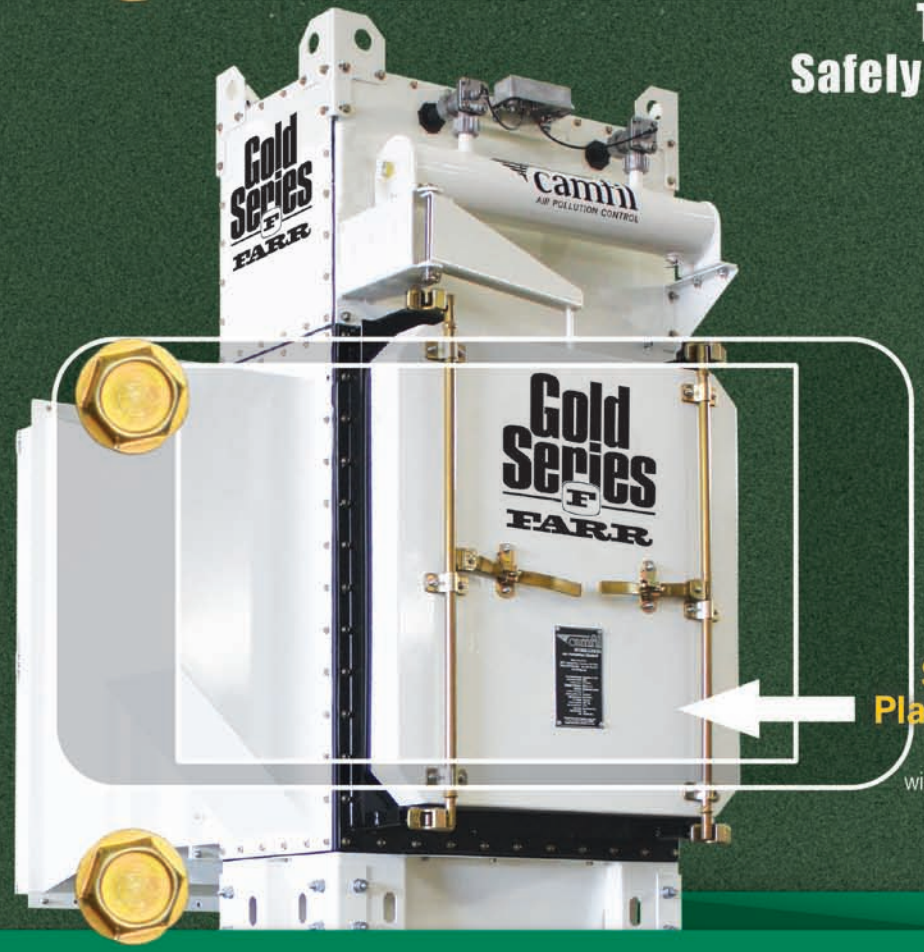


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Serialization Shake Out

The complexity of new packaging regulations laid out in the European Falsified Medicines Directive could threaten the existence of smaller pharma and packaging companies.

The European pharmaceutical sector and its packaging suppliers could be destined for a shake-out because of the inability of small companies to comply with new rules on packaging safety features aimed at combating counterfeiting. The European Commission, the European Union's executive, published its last draft (1) of the rules in August 2015, and they are likely to become European Union law by the end of 2015 or in early 2016. Pharmaceutical producers and their packaging contractors will then have three years to comply with the new regulation or be forced to take their products off the EU market.

Packaging experts believe that three years may not give many companies enough time to complete the process of re-engineering their packaging lines to meet the new obligations required by the EU's Falsified Medicines Directive (FMD) (2). At the core of the rules is a requirement for the serialization or unique identification of each medicine pack, which will necessitate major changes to most packaging lines.

"Companies, especially the smaller packaging companies specializing in pharmaceuticals, could disappear or be bought up by larger companies," says Bart Vansteenkiste, EU life sciences sector manager, at Domino Printing Sciences plc, Cambridge, England, in an interview with *Pharmaceutical Technology*. "A lot of companies have left compliance with the new regulations very late. Already suppliers of packaging hardware and software are reporting full order books and longer lead times."

3C Integrity Consulting, a UK-based specialist in FMD packaging requirements, has compared the threat to the industry to the extinction of the dinosaurs. A big difference will be that the big creatures, namely the large multinational pharmaceutical players, will survive because they have prepared themselves well in advance for the impending changes. Instead, it will be the smaller and usually more versatile ones that will become extinct.

Upgrading packaging lines

"For any remaining pharma companies that have doubts about whether or not they should progress their FMD readiness program, any suggestion that they should further delay [the preparation] would certainly be considered a courageous decision," the consultancy said in a bulletin issued after the publication of the final draft of the rules in what is called a *Delegated Act (3). 3C Integrity advises companies yet to start preparing for the new regulations to find out immediately what needs to be done to ensure compliance, both in-house and along their supply chain. "Simply—get started," 3C Integrity said in the bulletin. " If you are not in that position, then things may be getting uncomfortable soon."

In a survey (4) by Domino in June 2015 of small to large research-based pharmaceutical manufacturers, medicine-device makers, generic-drug producers, and packaging contractors, 65% had started a program of upgrading their packaging lines. "Most of these companies have installed a pilot line to determine what changes they need to make to their existing packaging lines," explains Vansteenkiste. "The remaining 35% have either just started looking into what they need to do or are doing nothing."

What has been stopping companies even budgeting for a re-engineering of their packaging lines has been a lack of detail about certain aspects of the FMD serialization system, even though the main features of it have been clear since the approval of the directive in 2011. Knowledge of the basic requirements has enabled the pharmaceutical majors to press ahead with their own re-engineering schemes so that many of their packaging lines have been producing packaging with unique identification of individual packs for several years. "[There is] nothing in this [final] draft Delegated Act that we have not had visibility of before," says 3C Integrity. "The key features have indeed been set in stone since the publication of the directive itself in 2011."

The cost of compliance

However, among SMEs in particular, there are concerns about the expense of FMD compliance. "The Delegated Act is really only about how and precisely when [the directive should be implemented]," says Warwick Smith, director general of the British Generic Manufacturers Association (BGMA). "None of our members has raised concerns about the necessary changes, though everyone has noted that it will be a very costly exercise."

The European Generic and Biosimilar Medicines Association (EGA) informed *Pharmaceutical Technology* that it has estimated that upgrading packaging lines for FMD compliance could cost generic-drug manufacturers a total of approximately €1 billion ($1.1 billion). The EGA is alerting generic-drug companies to the dangers of delaying preparations for the compliance deadline but also warning that the squeeze on margins due to the extra cost could lead to products being taken off the market.

*The concept of the Delegated Act (DA) was introduced by the EU's 2007 Lisbon Treaty to enable the European Commission to draw up regulations on non-essential, mainly technical, matters relating to new legislation. The European Parliament and the Council of Ministers—the EU's two legislative arms—would lay down the objectives, scope, and duration of the DA. Once the DA has been finalized by the Commission, usually after lengthy consultations, it becomes law as long as the Parliament and Council raise no objections to its content.

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"We are encouraging members to start with the implementation since the number of suppliers of this type of equipment for the packaging lines is limited," says Maarten Van Baelen, EGA's market access director. "We are very concerned about the number of medicinal products that will be withdrawn from the market because they will no longer be profitable."

Domino calculates that the average upgrading cost per packaging line is approximately €125,000. But with the addition of aggregation or the essential matching of serialization codes with data on batch-carrying pallets and shipped cases, this cost increases to €250,000, according to Vansteenkiste. With the compliance deadline getting nearer, companies are, nonetheless, faced with a Catch-22 dilemma of equipment and software prices going up as delayed purchasing decision leads to demand outstripping supply.

The Delegated Act lays down rules on the harmonized structure and content of the unique identifier.

Unique identifier

The Delegated Act lays down rules on the harmonized structure and content of the unique identifier. It also requires each pack to have an anti-tampering device, but its specification is left to the manufacturer. It stipulates details of an "end-to-end" system for the verification of the authenticity of each pack's safety features. This system will operate through a centralized data base or repositories network, into which the unique identifier data of each medicine pack will be fed from the packaging unit and then verified by the pharmacist at the dispensing point. The network is to be managed by industry stakeholders under the supervision of the relevant authorities of each of the EU's 28 member states.

The unique identifier will consist of a product code, serial number, national reimbursement number (if necessary), batch number, and expiry date. It must be encoded in a GS1 Data Matrix ECC200 2D barcode. In addition to being machine readable, all the data, except the batch number and expiry date, must also be human readable.

The serial number must comprise "a numeric or alphanumeric sequence of a maximum of 20 characters, generated by a deterministic or a non-deterministic randomization algorithm." The randomization requirement is outside GS1 specifications for barcodes used in the supply chains of multiple sectors.

An important stipulation in the Delegated Act is that the only 2D barcode allowed on the packs is the one "carrying the unique identifier for the purpose of their identification and verification of their authenticity." This limitation may necessitate that companies redesign their packaging to remove other barcodes, such as those related to inventory and price.

The Delegated Act also lists medicines exempted from the serialization requirement. These medicines include homeopathic products, advanced therapy medicines containing tissues or cells, intravenous solution additives, allergic diseases tests, and allergen extracts.

Coding, printing, and verification

For compliance, pharmaceutical companies will need higher-performing code-printing equipment. With inkjet printing, which currently accounts for approximately 70% of printed codes on medicine packs, more durable and light-resistant ink will have to be used to meet a requirement of machine readability for up to five years, according to Vansteenkiste.

Another challenge is aligning the printing process with an adjacent machine-vision system with technologies for optical character recognition (OCR) to check the content of the text and for optical character verification (OCV) to assess quality. As indicated in the Delegated Act, these should ensure that the barcodes meet the joint standards on printed security information of the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC).

The Domino survey (4) found that with nearly half of respondents, the biggest worry was the task of integrating the serialization hardware into current systems. "There are unlikely to be any shortages of coding and vision equipment because it is not difficult to increase their manufacture," says Vansteenkiste. "But integrating all the new hardware and software into each packaging line could pose big problems. With software, the main issue is manpower. As the deadline approaches, there could be shortages of the right expertise."

Companies are also looking beyond FMD to compliance with other possible legislative initiatives in the future both inside and outside Europe. They are willing to pay extra for a packaging operation that is able to respond positively to future developments in serialization and the management of all the data that comes from it. They can, at least, expect that as serialization become more widespread across the world, the cost of the hardware and software needed for its up-to-date application will be much less expensive than it is today.

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Stretching Product Value through Reformulation Strategies

Adeline Siew, PhD

New formulations that enhance bioavailability, optimize drug-delivery profiles, reduce dosing frequency, or improve patient experience have the potential to deliver quicker returns on investments than developing a completely new drug.

Reformulation of existing drug products is often seen as the cornerstone of lifecycle management strategies in an increasingly cost-constrained environment. While pharma's R&D productivity appears to be showing signs of recovery (1), developing a new, innovative molecule is not only a lengthy and expensive process, but the risk of failure is also high. On the other hand, new formulations exploiting advanced drug-delivery technologies—whether aimed at reducing dosing frequency, improving patient experience, or using alternative routes of administration—have the potential to deliver quicker returns on investments.

"Pharmaceutical companies are increasingly reformulating existing compounds, often using the FDA's NDA [new drug application] 505(b)(2) pathway (2), which is generally faster and more cost effective than bringing new compounds to market," says James Coward, global head of market development, Capsugel Dosage Form Solutions. "The pathway can provide patent extension for existing compounds that secures continued market exclusivities for several additional years. 505(b)2 product development often targets enhanced bioavailability and/or optimized drug delivery profiles—which can result in reduced pill burden—as well as new indications or specialized formulations for pediatrics."

There are many different approaches to reformulation, depending on the strategic imperative, observes Jon Sutch, PhD, manager of formulation development at Patheon's Milton Park facility in the United Kingdom. "If the strategy is marketing-driven, a line extension such as a new presentation, for example, changing a capsule to a tablet or reformulating as a softgel, may be used to differentiate it from the original product," says Sutch. "There may also be a clinical requirement to improve compliance, in which case, an enteric-release or other controlled-release formulation may be developed, or a fixed-dose combination (FDC) may be used to improve therapy in a particular area. Additionally, extensions to the original indication or patient group might lead to reformulation such as solutions, suspensions, or mini-tablets for pediatric or geriatric use as well."

According to Sutch, a new presentation must be based on a combination of the target product profile (TPP) and the characteristics of the API. "The

TPP, which is driven by the marketing and clinical considerations for the new presentation, must direct the pharmaceutics team in terms of the specifications required—whether it is the dissolution rate for a controlled-release formulation or the dosage levels for FDCs, for example," he explains. "For more marketing-led line extensions, presentation aspects may also be included to meet the needs of the target population, while the characteristics of the API are important in defining what is practical."

Sutch cites ibuprofen as a classic example of how reformulation has been used to extend product lines. "Ibuprofen is a non-steroidal anti-inflammatory drug and, therefore, has applications in many areas of medicine. From the original ibuprofen tablet came a controlled-release version for chronic pain and gastric side-effects prevention. Today, however, ibuprofen can be found in many presentations used in different markets or disease areas," says Sutch. "For example, the softgel presentation of ibuprofen claims to have a faster onset because its active ingredient is dissolved in the softgel matrix—presenting a potential advantage for acute pain. Other ibuprofen presentations include pediatric suspensions, fast-melt tablets, topical gels, and combination products with analgesics or decongestants. Formulations or presentations and packaging that target specific disease areas (such as menstrual pain or headaches) are also available for this drug, each having a marketable advantage for its particular market or disease area."

Reducing dosing frequency with extended-release formulations

Extended-release drug products, whether they are oral dosage forms or injectable depots, are often developed as part of a pharmaceutical company's reformulation strategy to differentiate its brand from generic competition and thereby extend market exclusivity. Although more challenging to formulate, extended-release drug products provide added value and well-recognized advantages such as improved pharmacokinetic profiles, prolonged duration of therapeutic effect, lower incidence of adverse reactions (due to the maintenance of drug concentration within a desired range without exposing the patient to potentially toxic drug levels), and better patient compliance as a result of reduced dosing frequency, especially in cases of chronic diseases where complex drug regimens are involved (3).

FDCs can be used either to combine different actives into one, single-dosage form, or to achieve a precise release profile of a specific active (e.g., combining an immediate-release with an extended-release formulation).

Pfizer, for example, has reformulated its twice-daily, immediate-release 5-mg tablet (tofacitinib citrate, Xeljanz) for rheumatoid arthritis into a once-daily, modified-release formulation. It was announced in July 2015 that FDA has accepted for review Pfizer's NDA for Xeljanz 11-mg once-daily, modified-release tablet (4). The NDA was based on data from a clinical pharmacology program that demonstrated pharmacokinetic equivalence in key parameters with Xeljanz 5 mg twice daily.

The bisphosphonate ibandronate, marketed as Boniva, was initially approved as a once-daily tablet for the treatment and prevention of osteoporosis in postmenopausal women (5). Roche, in collaboration with GlaxoSmithKline, further reformulated the oral bisphosphonate into a once-monthly formulation. FDA's approval of the improved formulation made Boniva the first-ever oral treatment to be administered on a monthly basis for any chronic disease (6).

Oral bisphosphonates, however, have to be taken according to a strict treatment regime, which involves remaining in the upright position and not eating, drinking (except water), or taking other medications for a period of time before and after administration of the drug. As such, oral bisphosphonates may not be suitable for some women, either due to other medical conditions or because the patient is unable to stay upright for the required length of time. To meet this need, Roche and GlaxoSmithKline developed a quarterly intravenous injection of ibandronate (7). Boniva injection comes in a prefilled syringe, which is administered as a 15- to 30-second injection by a healthcare professional once every three months.

Reducing the pill burden with fixed-dose combinations

Reformulating and combining drugs that have been proven to be safe and effective into FDCs is another popular lifecycle-management strategy for pharmaceutical companies seeking to maximize the value of their products. FDCs can be used either to combine different actives into one, single-dosage form, or to achieve a precise release profile of a specific active (e.g., combining an immediate-release with an extended-release formulation).

One of the advantages of FDCs is the enhanced efficacy through the synergistic effect of potentially lower doses (8, 9). "In addition to delivering increased therapeutic benefit, FDCs reduce the pill burden and can thereby increase overall patient compliance," says Coward.

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Examples of successful FDCs include:

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- antiretroviral combinations for the treatment of HIV/AIDS—Prezcobix (darunavir + cobicistat); Atripla (efavirenz + emtricitabine + tenofovir disoproxil fumarate)
- antitubercular combinations—Voractiv (rifampicin + isoniazid + pyrazinamide + ethambutol)
- antimalarial combinations—Coartem (artemether and lumefantrine)
- topical combination therapy for acne—Onexton gel (clindamycin + benzoyl peroxide).

Improving patient experience with user-friendly dosage forms

The increasing focus on patient-centricity is driving the shift towards the development of more user-friendly dosage forms. Martin Koeberle, PhD, senior manager of Analytical Development at Hermes Pharma, defines such formulations as dosage forms that provide a more positive experience compared to traditional tablets and capsules. "User-friendly dosage forms also overcome the widespread problems associated with swallowing traditional solid oral dosage forms," he highlights.

Findings from a 2014 survey revealed that more than 55% of people from all age groups and genders experience swallowing difficulties when taking their pills (10). Various reasons were cited by survey respondents, but the most frequent ones were related to the tablets or capsules being too large, getting stuck in the throat, or having an unpleasant taste or odor.

Swallowing difficulties are known to have a negative impact on patient compliance. "By offering an active ingredient solely as a tablet or capsule, pharmaceutical and life-sciences companies ignore the needs of more than 50% of their target audience," said Thomas Hein, PhD, senior vice-president, Commercial and Regulatory Affairs, Hermes Pharma, in a press release (10). "Given the weaknesses exhibited by conventional tablets and capsules, there is a significant opportunity to capture market share by formulating user-friendly dosage forms."

The increasing focus on patient-centricity is driving the shift towards the development of more user-friendly dosage forms.

Reformulating large tablets, such as paracetamol into effervescent tablets or aspirin into orally disintegrating granules (ODGs), avoids swallowing difficulties and provides a faster onset of action due to the dissolved API, according to Koeberle. "There is also the option to include additional APIs (e.g., caffeine or phenylephrine) due to the removal of tablet-size restrictions," he adds.

Lately, there has been a lot of interest in orally disintegrating tablets (ODTs) and ODGs as a solution to the widespread problem of swallowing difficulties. With ODGs, patients pour the granules into their mouths, where they dissolve without the need for water, says Koeberle.

"ODTs are primarily defined by their performance characteristic of rapid oral disintegration in saliva with no need for chewing or drinking water," explains Robert Smith, Zydis global R&D director at Catalent. Catalent's Zydis ODT fast-dissolve formulation is a freeze-dried product that disperses almost instantly in the mouth, usually in about three seconds, according to Smith, and no water is required. Another key feature of the Zydis technology is the ability to formulate peptides, allergens, and vaccines into fast-dissolve ODTs. "Benefits include low-temperature processing, which minimizes manufacturing losses of labile drugs; solution or suspension dosing, which achieves good content uniformity for low-dose actives; the solid dosage form and low water activity, which aid long-term stability; liquid processing, which facilitates containment of potent drugs in production; and the potential for sublingual or buccal absorption," Smith adds.

Capsugel has designed its Coni-Snap Sprinkle capsules to address swallowing difficulties, particularly prevalent in pediatric and geriatric patients. "Our sprinkle capsules feature an innovative closure that makes it easier and safer for patients and/or their caregivers to open the capsule and administer the medication by sprinkling the contents—typically powders, pellets, or granules—onto soft food for oral consumption," explains Coward.

"We tested sprinkle capsules with older consumers and caregivers of young children to gauge usability, ease of opening, and user accuracy when sprinkling capsule contents," he says. "Eighty-one percent of participants described the new design as 'easy' or 'very easy' to open. The convenience of sprinkle capsules may encourage those with swallowing difficulties to more easily comply with taking their medicine as prescribed. It's also an easier alternative to using reconstitutable powders administered via sachet/stick-packs or bottles."

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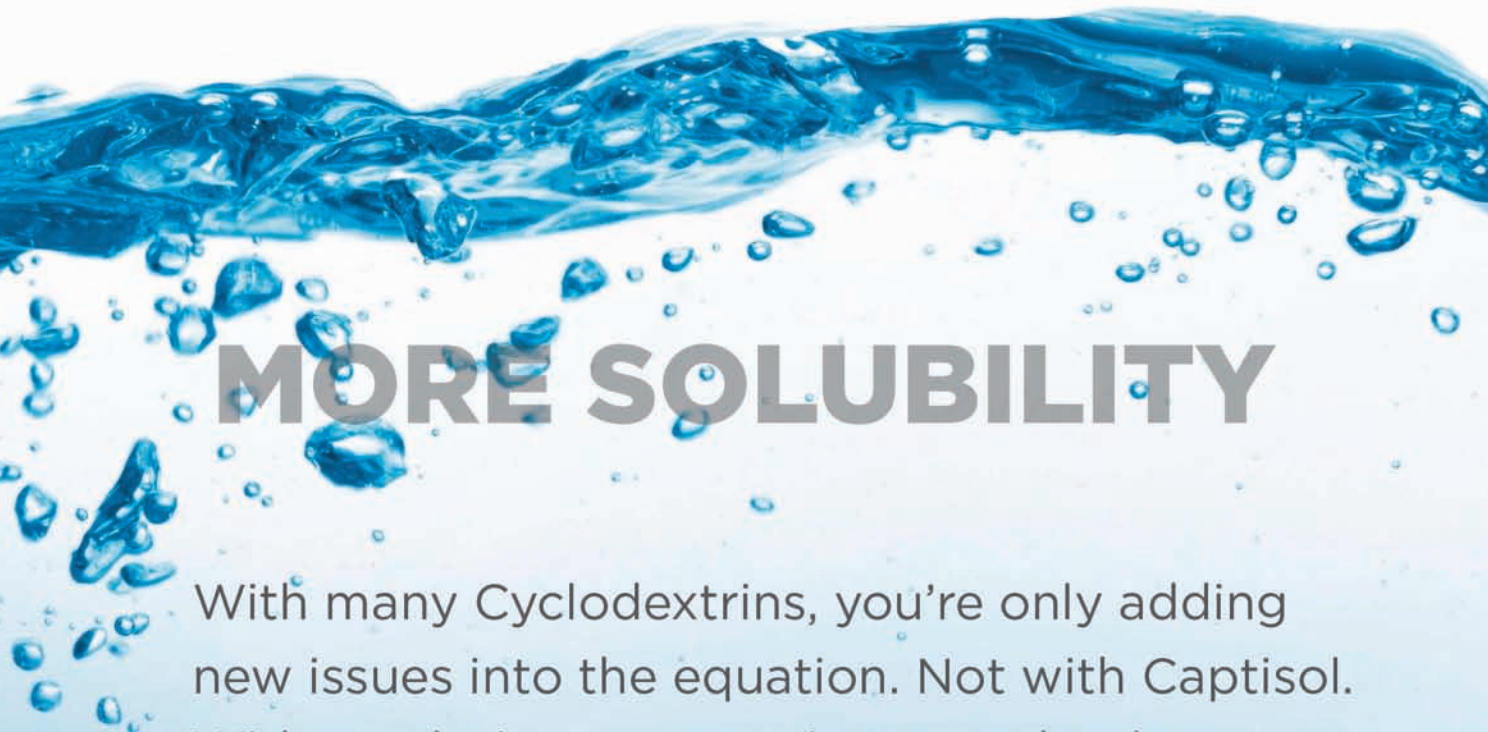

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Using alternative routes of administration

Reformulation strategies can also include using alternative routes of administration. AstraZeneca's nasal spray formulation of zolmitriptan (Zomig) for the acute treatment of migraine is one example. It was developed in addition to zolmitriptan tablets and ODTs as a lifecycle management strategy to expand AstraZeneca's Zomig product line. The nasal spray provides rapid onset of action for migraine sufferers and is a convenient, alternative, non-oral formulation for patients who experience nausea or vomiting in conjunction with their migraine attacks (11).

Reformulation strategies can also include using alternative routes of administration.

Another alternative to the oral route is transdermal drug delivery, which offers a number of advantages such as the avoidance of first metabolism and gastrointestinal toxicity. It allows the administration of drugs with narrow therapeutic windows, can prolong the activity of drugs with short half-lives, and eliminates the need for hypodermic injections (12).

"Patient preference is becoming increasingly important," Simmon Schaefer, director of business development, 3M Drug Delivery Systems, told *Pharmaceutical Technology*, "and transdermal patches are a great alternative for those who struggle with swallowing pills and want a more comfortable alternative to injections." Another advantage is that, in the event of adverse reactions or other problems, patients can terminate the therapy rapidly at any point, simply by removing the patch (12).

The pharmaceutical landscape is becoming more competitive, driving the demand for new drug delivery devices, observes Mark Tomai, head of TLR and MTS Business Development, 3M Drug Delivery Systems. "In general, patient-friendly delivery systems, such as microneedles or passive transdermal patches, are attractive options when considering reformulation as a lifecycle management strategy," he says. "For instance, reformulating an oral drug into a transdermal patch may be ideally suited for caregiver-intensive conditions. Elderly patients often have difficulty swallowing (dysphagia) or remembering to take their medications. That's where reformulation into a transdermal system may help, providing a potential to increase compliance, and ultimately treatment outcome."

According to Tomai, the 3M Hollow Microstructured Transdermal System offers a number of unique benefits that could be advantageous for lifecycle management strategy, including reproducible intradermal delivery, a proven ability to deliver formulations up to 2 mL with various viscosities, and API-dependent pharmacokinetic profile benefits. "Its patient-friendly features and the ability for patients to self-administer opens new opportunities to move treatments out of the clinic and into the patient's own home," he adds.

The process of developing a transdermal patch is not straightforward, "which is why companies turn to experts in drug delivery for help with selecting the right technology for their drug product, and then developing and manufacturing the final product," says Tomai. "Product lifecycle management, technological performance, and opportunity to capture additional market share are just a few of the many factors that should be considered when considering a reformulation strategy, such as converting from an oral dosage form to a transdermal patch or from injectable into microneedle administration. It is essential to involve your contract manufacturing organization early on, so they can help avoid unnecessary pitfalls, such as delays in project timelines and/or additional steps during formulation processing."

Summary

Reformulation strategies include both technical and commercial objectives, according to Coward. "The first step involves defining the goals of reformulation, whether it is to improve ease-of-swallowing, enhance taste, or offer convenience. The approach can also address specific marketing objectives, helping to strengthen a brand or identifying new target groups and effectively meeting their expectations," says Koeberle. "Then comes the evaluation of the current product and its requirements: the characteristics and strength of the API, the particular dosage form, and the kind of packaging (e.g., child resistant versus senior-friendly packaging). These are important factors that give users a more positive experience when taking their medication, and will benefit companies and patients alike by improving compliance."

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Characterization and Formulation Screening of mAb and ADCs by High-Throughput DLS

Aileen La, Ananda Seneviratne, Gaya Ratnaswamy, and Jihea Park

High-throughput dynamic light scattering effectively screens for optimal ADC formulations by investigating the effects of buffer conditions and temperature on aggregation.

Antibody-drug conjugates (ADCs) are promising biotherapeutic candidates that combine highly potent cytotoxic drugs with monoclonal antibodies (mAbs) for targeted drug delivery in the treatment of cancer or neurodegenerative disorders. However, while the underlying mAb may be a relatively stable molecule, the addition of the drug and linker often destabilizes the protein or adds undesirable intermolecular interactions. As a result, ADC biotherapeutics are heavily prone to aggregation. Uncontrolled aggregation can lead to a loss in clinical efficacy *in vivo* or, in extreme cases, invoke a serious immunogenic response in patients. Monitoring and controlling the behavior of the ADC complex during formulation is, therefore, essential to ensure that ADC compounds meet commercial, performance, and safety targets.

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This article illustrates the optimal formulation of ADCs by means of high-throughput dynamic light scattering (HT–DLS) using an automated HT–DLS plate reader to investigate the effects of buffer conditions and temperature on aggregation.

The ADC challenge

ADCs, also known as immunoconjugates, are a novel class of biotherapeutics that combine IgG_1 and IgG_2 mAb with small-molecule cytotoxic drugs, such as maytansines, auristatins, duocarmycin, or calicheamicin. As of early 2015, two ADC-based drugs are currently available for targeted cancer treatment, with many more undergoing clinical trials. ADC product development presents a complex formulation challenge in comparison to standard mAb drugs. As more small-molecule drugs are attached to the mAb base, the conjugate becomes increasingly hydrophobic, which may compromise critical performance attributes, such as solubility and physical stability.

Dynamic light scattering (DLS) is one of the most effective techniques for submicron size analysis of proteins, their aggregates, and other nanoparticles. DLS provides rapid measurements of hydrodynamic radius (R_h), degree of polydispersity, temperature of aggregation onset, and colloidal stability. Formulation screening with DLS helps developers rationalize variables such as temperature, pH, or concentration in terms of their impact on stability, solubility, or propensity to aggregate. Identifying the formulation conditions that are most likely to deliver ideal behavior during early phase screening accelerates the development process and greatly reduces the risk of downstream failure.

Traditional DLS measurements are performed in single-sample cuvettes, making multiple formulation sample analysis a time- and labor-intensive process. Advances in DLS technology have helped to increase the productivity of formulation screening while maintaining the high performance and

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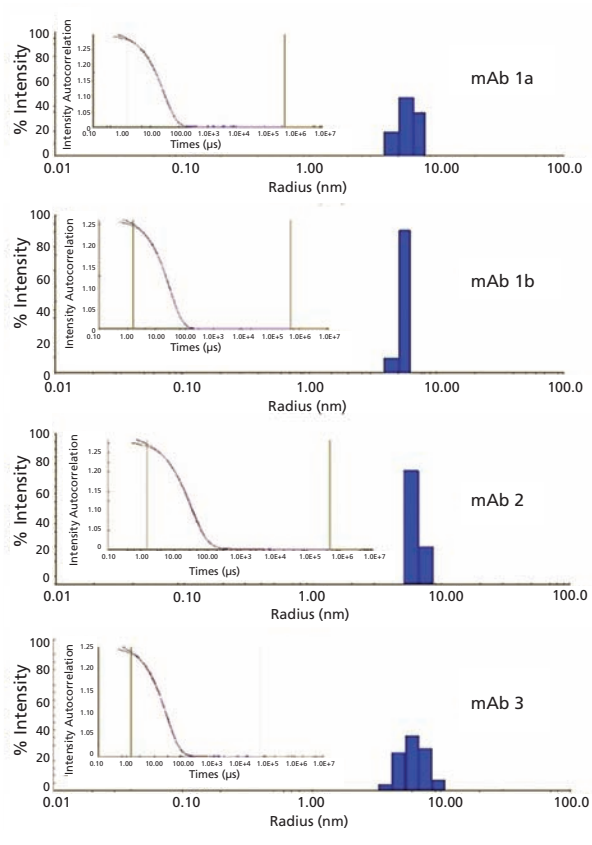
Table I: The hydrodynamic radii and polydispersities (%Pd) of IgG_1 vs. IgG_2, calculated by two different methods. mAb is monoclonal antibody.

		mAb 1a IgG_1	mAb 1b IgG_1	mAb 2 IgG_2	mAb 3 IgG_2
Cumulants	Average radius (nm)	5.3	5.3	5.6	5.0
	%Pd	15.3	13.4	25.7	21.5
Regularization	Main peak radius (nm)	6.1	6.0	6.7	6.2
	Main peak mass, %	100.0	100.0	99.6	100.0
	Main %Pd	21.6	18.0	31.6	27.3

Table II: The dynamic light scattering data of antibody-drug conjugates (ADCs): IgG_1 (mAb1a-ADC and mAb1b-ADC) vs IgG_2 (mAb2-ADC and mAb3-ADC). mAb is monoclonal antibody.

	Type	mAb1a-ADC (ADC1a)	mAb1b-ADC (ADC1b)	mAb2-ADC (ADC2)	mAb3-ADC (ADC3)
Cumulants	Average radius (nm)	5.6	7.2	5.2	6.5
	%Pd	15.7	30.8	23.5	34.5
Regularization	Main peak radius (nm)	6.5	7.4	6.9	8.0
	Main peak mass, %	99.4	99.6	100.0	100.0
	Main %Pd	21.6	18.0	32.3	33.9

Figure 1: The autocorrelation functions and regularization histograms of monoclonal antibody (mAb) 1a, mAb1b (IgG_1) vs. mAb 2 and mAb 3 (IgG_2).



accuracy demanded by industry, by performing automated, HT–DLS analysis *in situ* in standard 96-, 384-, or 1536-well microtitre plates. In this study, the hydrodynamic radii and physical stability of samples of IgG_1, IgG_2, and ADCs based on those molecules were measured using a HT–DLS system (DynaPro Plate Reader II, Wyatt Technology Corporation) under a variety of formulation conditions.

mAbs (IgG_1 and IgG_2, expressed in two different cell lines) and ADCs (IgG_1-Drug 1 and IgG_2-Drug 1) were characterized using DLS. The R_h, polydispersity (*%Pd*), and presence of any high molecular-weight species in solution were measured. Regularization analysis was performed to determine R_h, *%Pd* and the relative mass of the fitted peaks.

A 20–70 µL sample volume was used at a concentration of 1.0 mg/mL. Prior to sample analysis, the microtitre plate was centrifuged at 3000 rpm for 1 minute to remove air bubbles. Each sample was measured in triplicate, in which a single measurement consists of 10 acquisitions for 10 seconds at 25 °C. The raw data (auto-correlation functions) were analyzed by cumulants analysis and/or regularization analysis. The distribution plots were obtained from regularization analysis. The data were acquired at 25 °C using the temperature controlled DynaPro Plate Reader II and DYNAMICS v7.1.9 software (Wyatt Technology Corporation). A 384-well plate was used to enable automated, high-throughput sample analysis.

Figure 1 shows the dispersion plots and histograms for mAb 1a and mAb 1b (IgG_1) and mAb 2 and mAb 3 (IgG_2). The results in **Table I** show that IgG_1 and IgG_2 have almost the same R_h while IgG_2 has a greater degree of polydispersity

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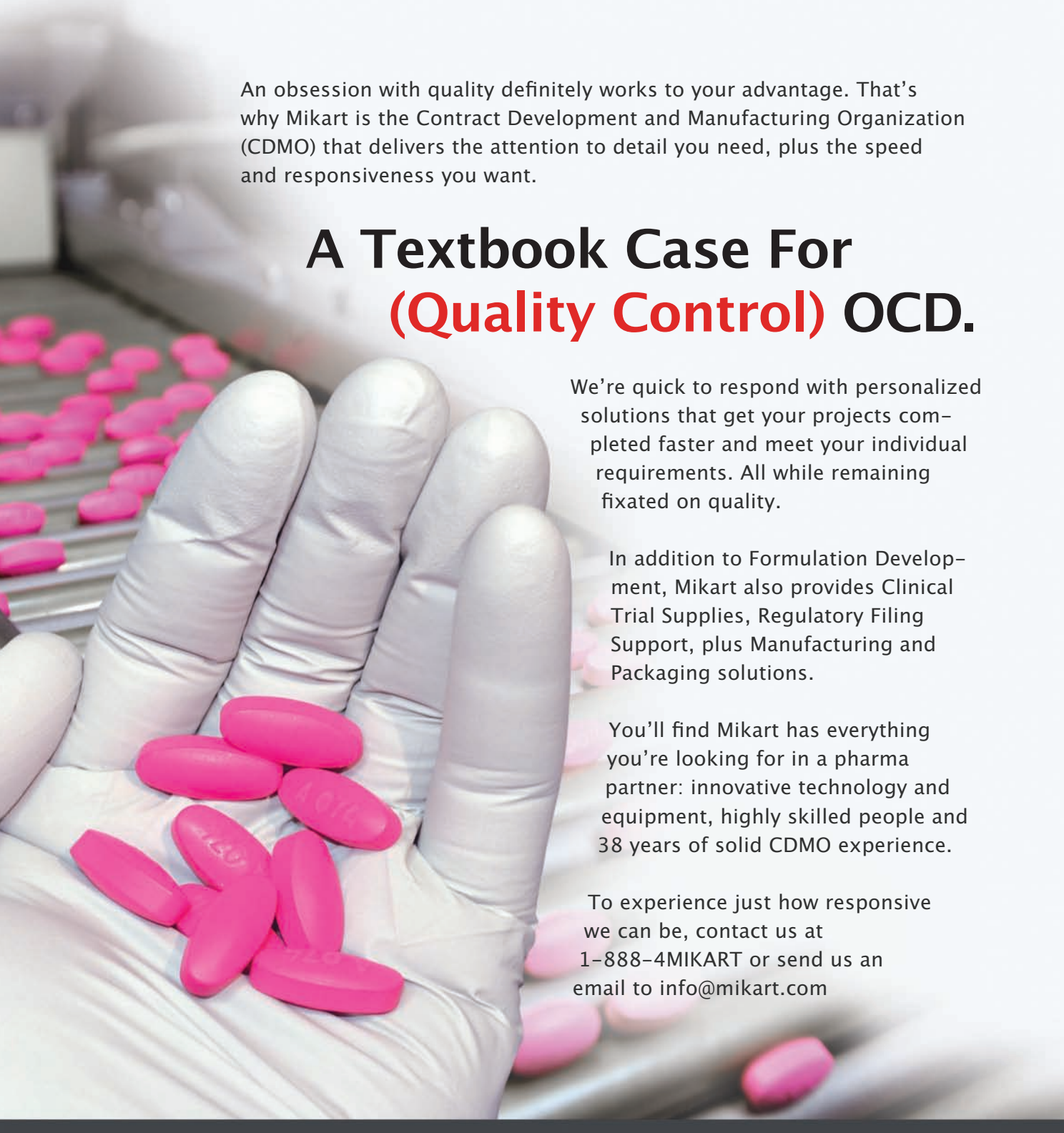

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Building Safe and Effective Antibody Drug Conjugates, by Adeline Siew, PhD

Antibody-drug conjugates (ADCs) have revolutionized the field of cancer treatment but despite the rapidly growing clinical pipeline, developing an ADC is no easy task. The challenge of optimal ADC design lies in the overall complexity of these molecules and the increasingly clear requirement to optimize each aspect relative to any given antibody–toxin pair and its target, according to Jennifer L. Mitcham, PhD, SMARTag Business Development, Catalent Biologics. There are a number of parameters that must be taken into account when designing an ADC, observes Albert Garofalo, PhD, group leader, Chemistry, Catalent Biologics. "The antibody is set based on the target antigen, and the payload might be set based on intellectual property considerations or the desired mechanism of action. This leaves the linker as the one area of the ADC that can be chemically manipulated to affect physicochemical properties such as solubility, protein aggregation, therapeutic index, and efficacy," he remarks.

Target antigen and antibody selection. The choice of target for the antibody is a key consideration, notes Cynthia Wooge, PhD, Global Strategic Marketing at SAFC. "The chosen cell-surface antigen should be over-expressed in the tumor cell and relatively non-expressed in normal tissue," she highlights. This is because the tolerability of an ADC is affected by the specificity of antigen expression in cancerous tissue versus normal tissue, Dave Simpson, PhD, CEO of biotech company Glythera, adds. "Non-specific expression results in toxicity and reduced efficacy due to a reduction in the dose of conjugate available to the tumor," he explains. "Therefore, the ideal tumor antigen must be specifically localized to the tumor cell surface to allow ADC binding and, preferably, display differential expression between tumor and normal tissue, with increased expression in cancer cells."

Ian Evetts, PhD, commercial director of Glythera, points out that antigen choice is also dictated by its ability to internalize upon ADC binding. "Internalization of an ADC occurs through receptor-mediated endocytosis, followed by ADC degradation in the lysosome, which leads to free drug release for effective cell killing," he says. "However, endocytosis is not guaranteed for all cell-surface antigens, and the rate of internalization can vary considerably. Optimal drug release into the cell requires minimal recycling of the ADC to the cell surface as well as enhanced delivery of an internalized antigen/ADC to the lysosome. The ideal tumor antigen then should be cell-surface expressed, highly upregulated in cancer tissue, internalized upon ADC binding, and able to release the cytotoxic agent inside the cell."

Once the target antigen has been identified, it is important to select a suitable antibody. "Among the key attributes, high specificity for the tumor antigen is essential," Evetts says. "And ideally, antibodies should possess optimal pharmacokinetic properties including relatively long half-lives and slower clearance in the plasma."

Drug selection. The drugs being used to construct ADCs generally fall into two categories: the microtubule inhibitors and the DNA-damaging agents, although Simpson notes that other drugs such as polymerase II inhibitors are also being investigated. A key consideration is that the drug selected for ADC construction must contain a suitable functional group for conjugation and be stable under physiological condition. "It is important that therapeutically appropriate amounts of the cytotoxic are linked to the monoclonal antibody (mAb) to optimize the potential effectiveness of the ADC once it reaches the target cancer cell," Simpson stresses. "The cytotoxic should also be chemically tractable and stable while bound to the mAb."

The crucial role of linkers. A crucial part in ADC development is choosing the right linker and method of attachment. The linker connects the small-molecule API to the large-molecule antibody that is engineered to bind to the target antigens on specific cell types. To be effective, the ADC must remain stable in the bloodstream until it reaches the target cell, whereupon following internalization, the cytotoxic payload is delivered. Any premature drug release will be detrimental to normal cells.

Ultimately, the main role of linkers is to ensure specific release of free drug in the cancer cells, Simpson says. The linker can influence the distribution and pharmacokinetics of an ADC, and hence, its safety and efficacy, Wooge adds. Depending on the preferred site of attachment on the antibody, linkers utilizing different functional groups or chemistries can be employed.

The selection of suitable linkers, however, remains a key challenge in ADC design and manufacture, according to Garofalo. "The long circulating half-life of an ADC demands linkers that have high plasma stability in order to minimize off-target effects," Mitcham says. "Yet, balancing the need for plasma stability with the need for selective intracellular drug release can be quite challenging."

There are two types of linkers used in ADC development—cleavable and non-cleavable. "As the cytotoxic payload is delivered into the cell, it can either be freed by digestion of the whole antibody, or it can be released by selective cleavage of the linker," notes Vivek Sharma, CEO, Pharma Solutions, Piramal Enterprises.

The majority of ADCs in the clinic use cleavable linkers, observes Evetts, in particular, the protease-cleavable valine-citrulline dipeptide linker, originally designed to balance high plasma stability with intracellular protease cleavage.

Cleavable linkers release the free drug in a state that is more likely to permeate from the cell and kill surrounding cells—the by-stander killing effect, observes Mark Wright, site lead at Piramal Healthcare UK. "Should a conjugate be required to kill not only the highest expressing cells in the tumor, but also the surrounding ones, a cleavable linker is preferred."

Non-cleavable linkers are more stable in the blood than cleavable linkers, according to Simpson, but they are wholly dependent on internalization, lysosomal delivery, and ADC degradation to release drug payload. They cannot kill neighbouring tumor cells through the by-stander effect, he says.

Attachment chemistry. While linkers are generally selected based on the preferred method of drug release from the antibody, the attachment chemistry used to link both drug and antibody will determine the overall stability and clinical performance of the ADC. According to Simpson, most approaches use maleimide chemistry, whereby maleimide selectively attaches to exposed or engineered cysteines via a covalent Michael addition. "However, maleimide is inherently associated with (i) deconjugation in physiological conditions via the reverse-Michael reaction, resulting in free drug in circulation and (ii) hydrolysis of the succinimide ring," he explains, stressing that these factors hamper conjugate stability, ADC stability, and consequently, the therapeutic activity. Simpson believes that non-maleimide approaches may offer a better option for delivering stable conjugation of drug to antibody.

There is also a growing body of evidence that a structure–activity relationship approach is required for optimal ADC design. This approach involves testing each design component of the ADC, such as toxin placement, drug-to-antibody ratio, conjugation chemistry, and novel linker technologies as applied to any given mAb–toxin pair.

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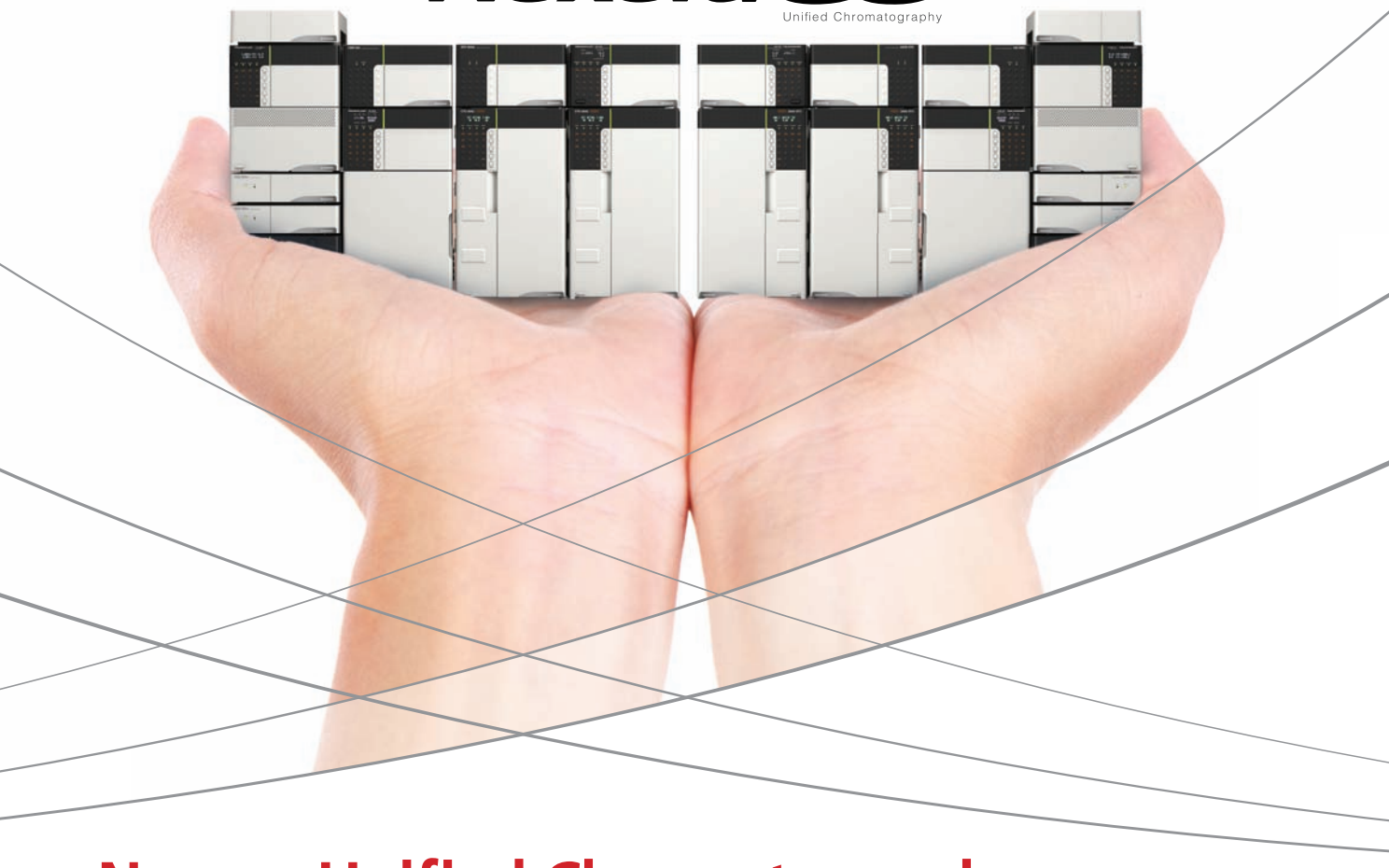

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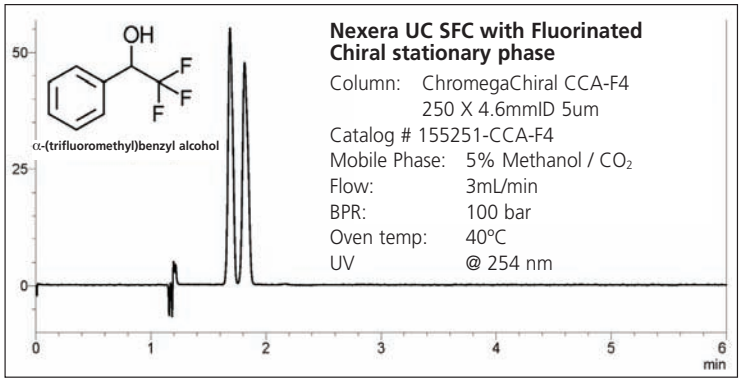

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Figure 2: The autocorrelation functions and regularization histograms of antibody-drug conjugate (ADC) ADC1a, ADC1b (IgG_1) vs. ADC3 and ADC4 (IgG_2).

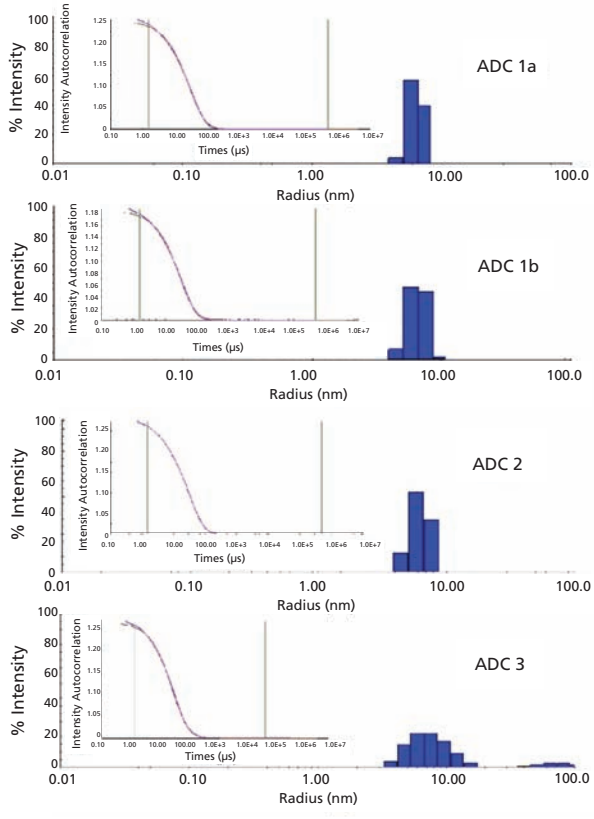


Figure 3: Formulation screening: % polydispersity (Pd) of histidine formulations (a) vs. citrate formulations (b) and the histogram of the F5 formulation (c).

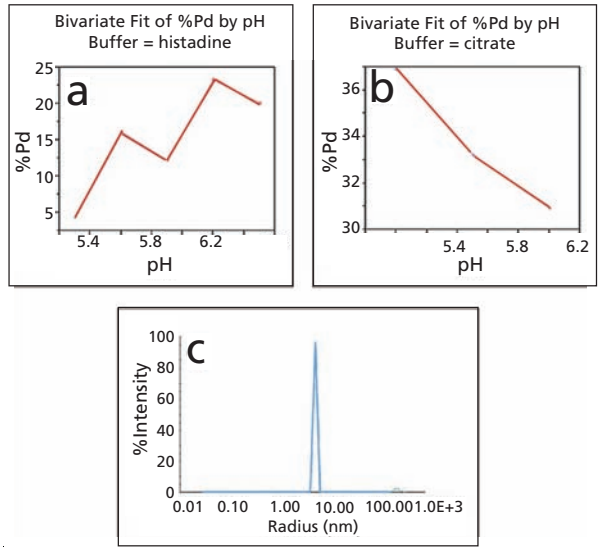


Table III: Dynamic light scattering data of eight ADC formulations in histidine (F1–F5) and citrate buffers (F6–F8). These data suggest that proteins in formulation F5 are the most stable. *Pd* is polydispersity, R_h is hydrodynamic radius.

Formulation (ID)	pH	R_h	*%Pd*	%Mass
H6.5T (F1)	6.5	5.985	20.0	99.8
H6.2T (F2)	6.2	6.056	23.3	99.8
H5.9T (F3)	5.9	5.526	12.1	99.9
H5.3T (F4)	5.6	5.448	16.0	99.7
H5.6T (F5)	5.3	5.931	4.2	99.6
C5.0T (F6)	5.0	8.338	36.9	99.8
C5.5T (F7)	5.5	8.084	33.2	99.8
C6.0T (F8)	6.0	7.818	30.9	99.5

than IgG_1. This may be attributed to the two additional disulphide bonds present in IgG_2, which often lead to greater heterogeneity.

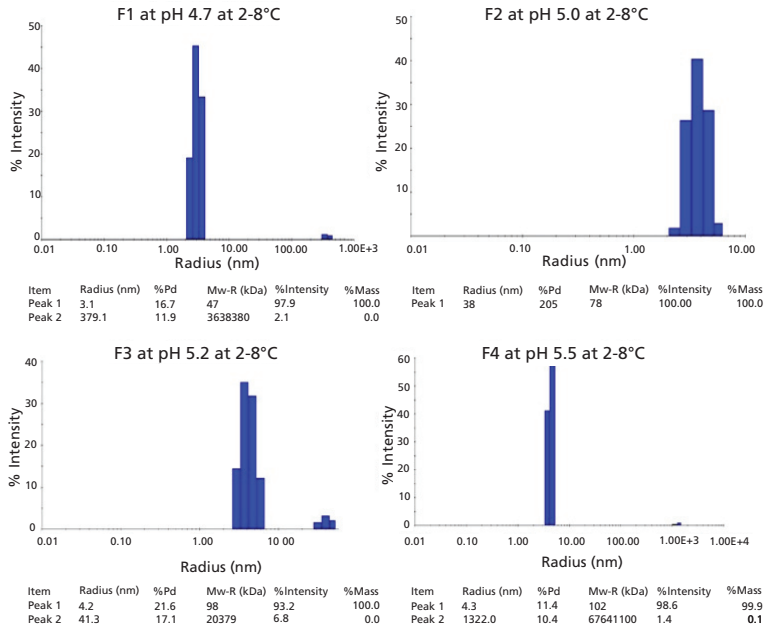
Figure 2 and **Table II** provide a comparison of corresponding IgG_1 vs. IgG_2 ADCs in the recommended lead formulations. A sample exhibiting *%Pd* < 20% is generally considered to be monodisperse. Therefore, a measured level of polydispersity beyond 20% indicates heterogeneity within the sample. The data suggest that although attachment of the small molecule drug to the mAb does not change R_h, the ADC samples become more polydisperse than the mAb samples. Hydrophobicity also increases slightly, indicating the presence of some high molecular-weight species.

Formulation screening

Four mAb formulations that were stored at 2–8 °C were screened using automated DLS to determine their behavior under different conditions. **Figures 3** and **4** show how *%Pd* and R_h of the proteins vary as pH is incrementally increased while temperature remains within the range of 2–8 °C. At pH 5.5, *%Pd* falls to 11.4 indicating that the sample is mostly monodisperse with less protein present in the higher molecular-weight region. **Figure 4** also shows that R_h increases with pH. The shift can be attributed to increased electrostatic repulsion at higher pH. Additionally, a temperature trend study shows that at pH 5.5, the antibodies are relatively stable with a slight increase in R_h around 40 °C (data not shown).

Finally, eight ADC formulations were analyzed in different histidine (F1–F5) and citrate (F6–F8) buffer solutions (see **Table III**). **Figure 3** shows that proteins in three citrate formulations (F6–F8) are more polydispersed, with higher R_h than the histidine formulations. Overall, these data suggest that F5 at pH 5.3 with R_h of 6 nm and *%Pd* of 4.2% is the most stable formulation.

Figure 4: Dynamic light scattering histograms of R_h for four monoclonal antibody (mAb) formulations at different pH values.



Item	Radius (nm)	%Pd	Mw-R (kDa)	%Intensity	%Mass
Peak 1	3.1	16.7	47	97.9	100.0
Peak 2	379.1	11.9	3638380	2.1	0.0

Item	Radius (nm)	%Pd	Mw-R (kDa)	%Intensity	%Mass
Peak 1	38	205	78	100.00	100.0

Item	Radius (nm)	%Pd	Mw-R (kDa)	%Intensity	%Mass
Peak 1	4.2	21.6	98	93.2	100.0
Peak 2	41.3	17.1	20379	6.8	0.0

Item	Radius (nm)	%Pd	Mw-R (kDa)	%Intensity	%Mass
Peak 1	4.3	11.4	102	98.6	99.9
Peak 2	1322.0	10.4	67641100	1.4	0.1

Rapid and reliable ADC characterization with HT–DLS

Routine optimization of formulations by DLS is made feasible by the speed and automation of *in situ*, plate-based DLS measurements using low-cost microtitre plates. HT–DLS is a rapid and useful biophysical method for characterizing and screening biotherapeutic formulations via extensive trend studies into pH, temperature, buffer, and excipient variations.

The analysis of hydrodynamic radius and polydispersity over a series of conditions enables drug product developers to closely monitor and control the stability of their formulation throughout every stage of the development process. The specific results in this study show that the attachment of small-molecule drugs to the mAb does not appreciably change the molecule's average hydrodynamic size. Polydispersity, however, increases slightly, indicating the presence of some high-molecular-weight species in the form of small oligomers. **PT**

Regulatory Considerations for Alcohol-Induced Dose Dumping of Oral Modified-Release Formulations

Thomas P. Friebe, Firouz Asgarzadeh, Ann Gray, Kevin Hughes, Johann-Philipp Hebestreit, Yvonne Rosiaux, Mahmud Yunis, and Amina Faham

This article looks at the current status of alcohol-induced dose dumping of modified-release formulations and the need for regulatory harmonization in handling this challenge.

Over the past decades, modified-release (MR) systems have revolutionized the delivery of APIs. Patient compliance is improved and side effects are reduced through more consistent plasma levels, leading to more effective therapies. The vast majority of patients benefit from the pharmacological advantages and administration convenience of MR formulations. However, there is a subgroup of patients who are vulnerable to accidental overdose through concomitant consumption of alcoholic beverages with these medications. As drug release in MR systems is either controlled by a polymer matrix or by a polymer film coating, dose dumping may occur if the release control is compromised through dissolution of the controlling agent in hydro-alcoholic liquids. "Dose dumping" refers to the rapid release of the entire dose or a significant fraction thereof in a short period of time (1). Depending upon the therapeutic index, the pharmacokinetics, and the therapeutic indication of the API, critical side effects or even fatality can result. Dose dumping resulting from consumption of alcoholic beverages in timely connection with the administration of a medication is referred to as "alcohol-induced dose dumping" (ADD).

Thomas P. Friebe is senior regulatory affairs manager at Evonik Nutrition & Care GmbH; **Firouz Asgarzadeh** is director, Technical Services at Evonik Cyro LLC; **Ann Gray** is global product manager, Oral Excipient at Evonik Nutrition & Care GmbH; **Kevin Hughes** is regulatory affairs manager at Colorcon Limited; **Johann-Philipp Hebestreit** is manager, Technical Service Pharma Ingredients & Services Europe at BASF SE; **Yvonne Rosiaux** is manager, Solid Oral Dosage Forms at Gattefossé SAS; **Mahmud Yunis** is technical director at BIOGRUND GmbH; and **Amina Faham** is global pharmaceutical technical support and development leader at DOW.

Thomas P. Friebe, Kevin Hughes, Johann-Philipp Hebestreit, Yvonne Rosiaux, Mahmud Yunis, and Amina Faham are members of the IPEC Europe ADD Working Group.

Modified release—a benefit, but also a risk

Alcoholic beverage consumption is widespread throughout the world. Certain patient populations, such as people with chronic pain or those suffering from depression, may have the tendency to turn to alcohol as a way to cope with their conditions, because the physiological effects of alcohol are similar to those of anesthetics (2). Accidental ADD may occur when patients combine the consumption of alcoholic beverages with prescribed medication despite product warnings to the contrary. Although concomitant use is often the case, ADD could also be due to residual alcohol that is still present after earlier ingestion. Intentional ADD occurs when a person knowingly uses highly potent alcoholic beverages as a medium to extract high doses of API (usually opioid analgesics) from sustained-release formulations in order to "get high." This article will not address intentional ADD (including formulations that are commonly referred to as abuse-deterrent formulations or tamper-resistant formulations), but will instead focus on MR dosage forms that require an appropriate, robust formulation to assure patient safety, for example, if the drug has a small therapeutic window.

The "Palladone case" in 2005 raised awareness of ADD among regulatory au-

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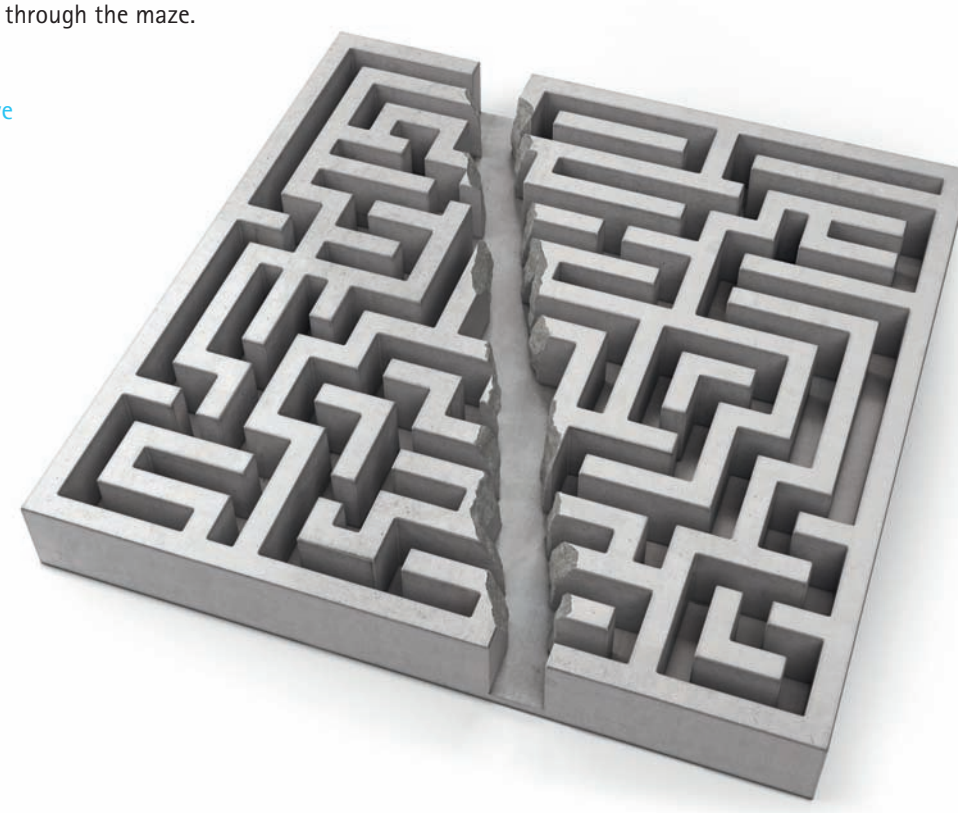

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Figure 1: Alcohol-induced dose dumping (ADD) risk evaluation based on the EMA guidance (8, 9).

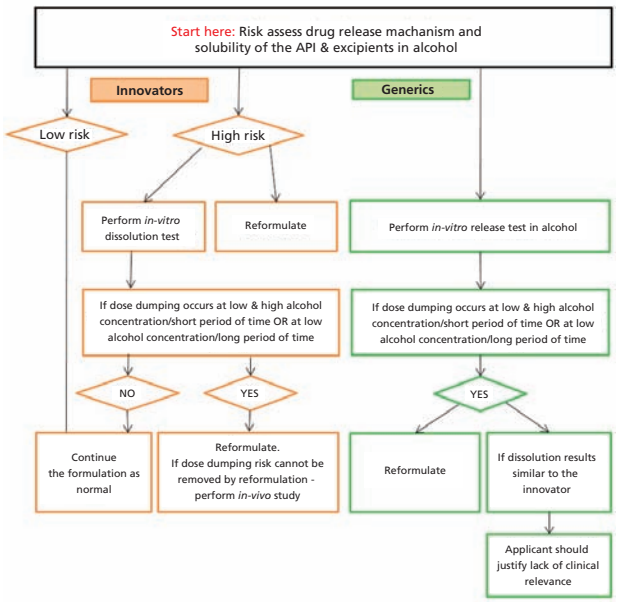
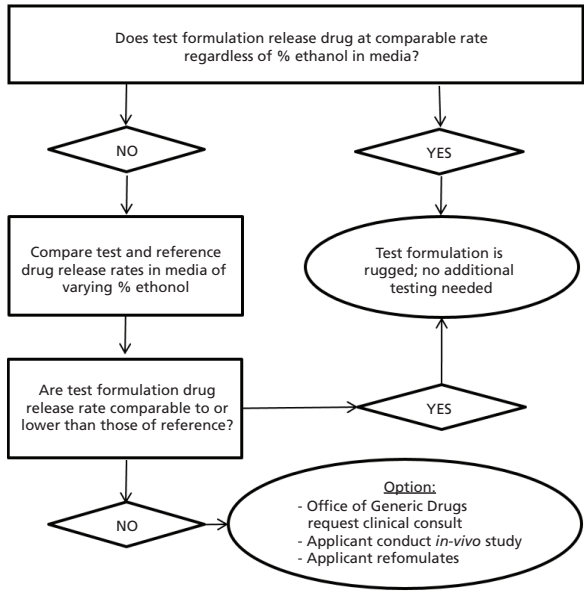


Figure 2: Possible scheme for the handling of alcohol-induced dose dumping (ADD)-critical generic formulations (13).



thorities (3, 4). Palladone was a hydrocodone multiparticulate capsule that used ammonio methacrylate copolymer type B and ethylcellulose (5) as release-controlling polymers, both of which are soluble in ethanol. A pharmacokinetic study in healthy subjects showed that co-ingestion of a 12-mg Palladone capsule with 240 mL (8 ounces) of a 40% (80 proof) alcoholic beverage resulted in an average peak hydromorphone plasma concentration approximately six times higher than when taken with water. These elevated levels could potentially be lethal (6). Palladone was, therefore, subsequently withdrawn from the US market. This case initiated a movement toward new guidance, and consequently, it became a requirement for the industry to take ADD into consideration during formulation development.

Regulatory considerations

Guidance for ADD has been provided by regulatory agencies in various documents in the European Union (7–9), the United States (1, 10), and other countries (11); the International Conference on Harmonization does not provide any guidance. To date, no major regulatory agency has all the pertinent information summarized in one single document.

European Union. *In-vitro* testing in the presence of alcohol is based on one adopted guideline (8) and a Q&A section on the EMA website in the Quality Working Party area (9). The applicant is required to evaluate all types of MR formulations for the risk of unexpected API release. If ADD is observed or suspected, the product should be reformulated. **Figure 1** shows the flowchart for the decision pathway.

In 2011, an EMA assessment (12) requested marketing authorization holders (MAH) to present data on their opioid products and their sensitivity to alcohol. Eight applicants submitted data of 14 products. Each applicant, however, used a different set of alcohol concentrations in the evaluation. The method variability in this case was not only inefficient but also made it more difficult for the assessors to judge and compare the data. The recently published EMA Q&A (9) provides better guidance concerning the required alcohol concentrations to be used, for example.

United States. In 2011, FDA's Office of Generic Drugs (OGD) provided a simple scheme (13, 14) for supporting the handling of ADD-critical formulations, mainly for generics (see **Figure 2**).

A Guidance for Industry (15) from 2014 lists inadequate dissolution data as reasons to refuse to receive an abbreviated new drug application (ANDA). In addition, FDA provides detailed bioequivalence dissolution recommendations for an extensive list of APIs (16), including non-opioids such as metoprolol succinate (17), clonidine (18), memantine (19), metformin

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Table I: Comparison of FDA and EMA requirements with regard to *in-vitro* testing of formulations at risk for ADD.

Topic	FDA	EMA
Methodological requirements	Dissolution medium: 0.1N HCl Alcohol concentrations: 0%, 5%, 20%, and 40% Time: every 15 minutes until 2hrs	Dissolution medium: same as that proposed for routine testing Alcohol concentrations: 5%, 10%, and 20% Time: not defined
Products to be tested	At least all (generic) versions for modified-release opioid drug products; more preferably for (all) modified-release drug products with risk of alcohol-induced dose dumping	All oral modified-release applications
Acceptance criterion	Generic drug formulation should show rugged performance in alcohol (20). If a generic drug formulation releases more rapidly in alcohol, the rate should be comparable to that of reference product.	If *in-vitro* alcohol incompatibility of the drug product is demonstrated, product should be reformulated. If alcohol effect cannot be avoided and is present also in the reference product, applicant should justify or demonstrate that it lacks clinical relevance.

and sitagliptin phosphate (21), or trospium chloride (22), which are widely prescribed treatments for chronic conditions. Generally, for these APIs, alcohol testing concentrations up to 40% are required.

The ADD requirements of EMA and FDA are not fully harmonized and sometimes even conflicting. **Table I** shows some differences between them for three major topics. Of particular interest is the FDA requirement for testing in dissolution medium containing 40% ethanol, which differs from the 20% required by the EMA. It should be noted that reaching a 40% alcohol concentration in the stomach would require the intake of 240 mL of an alcoholic beverage with 56% alcohol content (based on 100 mL gastric liquid present in the stomach) (4, 23) into an empty stomach. This drastic intake seems to be achievable only in extreme cases of so-called "binge drinking." In addition, alcohol is quickly resorbed and eliminated from the stomach and the intestine, usually within 30 minutes (24). Hence, the requirement for robustness *in-vitro* at an ethanol concentration of 40% seems likely to be more relevant to abuse-deterrence, while a concentration of 20% is likely a more realistic approximation for accidental ADD. These differences between EMA and FDA requirements might create confusion for formulators regarding which guideline to follow. Because many pharmaceutical companies operate globally and would prefer not to sell different formulations in different regions if at all possible, formulators may be forced to achieve resistance to 40% ethanol, whether this is physiologically relevant or not. This represents a significant technical hurdle for formulation development, and may even hinder the launch of valuable medications.

Assessing alcohol sensitivity

Sensitivity to alcohol of the API and/or the excipients does not necessarily mean that a formulation will dose dump. A formulator needs to assess the degree of sensitivity; and to do so, the formulator needs to rely on a practical and commonly accepted tool or guidance. N. Jedinger et al. (25) discussed some interesting approaches on how to handle this issue, including physicochemical factors influencing ADD and appropriate matrix systems and technological strategies to minimize the risk of ADD.

Dissolution profiles may be considered similar by virtue of overall profile similarity including similarity at every dissolution-sample time point. Different approaches are available to compare profiles, but the one discussed most often in FDA documentation (26–28) for NDA and ANDA is as follows:

A simple model independent approach uses a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles (29). The difference factor (f1) calculates the percent difference between the two curves at each time. The similarity factor (f2) is a measurement of the similarity in the percent dissolution between the two curves. For curves to be considered similar, f1 values should be close to 0, and f2 values should be close to 100. Generally, f1 values up to 15 (0–15) and f2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves.

Complicating factors

The regulatory guidance described in the previous sections of this article is related to *in-vitro* testing. This requirement is necessary, given that clinical trials performed to determine the risk of ADD *in-vivo* would expose volunteers to unnecessary risk and would, therefore, be regarded as unethical. Even then, simplification of a complex event can lead formulators to overemphasize some factors (such as solubility of pure polymer in ethanol) and overlook others (such as formulation design). Successful development of a robust formulation includes considerations involving the drug and excipient properties and the formulation design. In fact, *in-vitro* results in 40% hydro-alcoholic media as required by regulatory authorities do not necessarily predict *in-vivo* behavior. This lack of correlation is due to the complexity of the *in-vivo* environment and is well-illustrated by two selected examples:

- Sustained-release matrix tablets are often considered to be robust against ADD. Opana ER, an oxymorphone sustained-release matrix tablet was formulated with hydrophilic polymers (TIMERx drug-delivery technology). The MR polymers used—xanthan (30) and locust bean gums (31)—are both

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alcohol-insoluble hydrocolloids. Opana ER passed ADD dissolution tests *in-vitro* but failed *in-vivo* (32).

- Although the transit time of multiparticulate dosage forms through the stomach is much shorter than for monolithic tablets, coated MR multiparticulates are usually considered to be more vulnerable to ADD because of the higher effective contact surface for the ingression of acidic hydro-alcoholic medium. Carvedilol was formulated as a multiparticulate system (Micropump), using methacrylic copolymers in the MR coatings. Methacrylic copolymers are generally soluble in ethanol, and the formulation did indeed fail ADD requirements under *in-vitro* dissolution test conditions. The *in-vivo* performance, however, was not affected in the presence of alcohol (33).

These two examples provide evidence that ADD *in-vivo* is a multifactorial event. Therefore, the currently applied standard methods for *in-vitro* characterization are not necessarily predictive for the *in-vivo* behavior. There is obviously a need for specifically designed test methods. The selection of suitable formulation approaches and processing technologies must always be considered individually, keeping all factors in mind: both API and excipient properties, the formulation design, the therapeutic indication, and the risk in case of dose-dumping.

Summary

ADD of MR dosage forms poses a possible risk to a subsegment of the patient population. Regulatory agencies have, therefore, introduced guidance for formulators to mitigate the risk of a potentially concerned formulation with regard to ADD. However, the necessity of testing in simplified *in-vitro* systems that may not represent probable physiological conditions may create technological hurdles to developing efficacious dosage forms at reasonable costs to patients. The current lack of alignment of requirements between regions increases complexity, and hence, increases cost of medicines for globally active companies.

Given the increasing globalization of the pharmaceutical industry, the FDA and EMA guidelines should be harmonized concerning ADD *in-vitro* testing conditions, reflecting physiologically relevant alcohol concentrations and exposure times.

IPEC Europe ADD Working Group

The IPEC Europe ADD Working Group plans to publish a position paper that will address pertinent aspects of the ADD issue and suggest modifications of the currently available guidelines as well as provide several recommendations for formulators.

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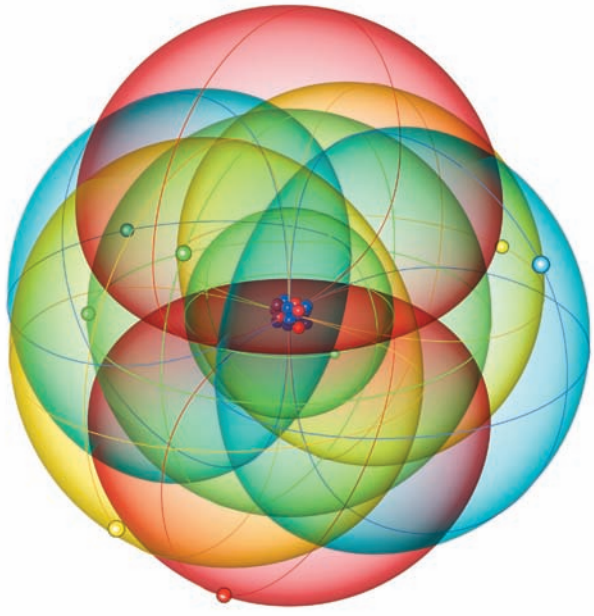

Advances in Fluorination Chemistry for API Synthesis

Cynthia A. Challener

Safer solid reagents and new coupling chemistry are important developments.

Fluorine atoms have a unique combination of electronic and physical properties. As such, when incorporated into APIs, fluorine atoms often influence their protein binding affinity and lipophilicity. Fluorination can thus significantly impact the bioavailability of drug substances. "Fluorination is a key reaction in organic synthesis, as evidenced by the fact that between 15% to 20% of all medicines and agrochemicals on the market contain at least one fluorine atom in their structure, where fluorine is used to modify properties of the drugs like lipophilicity and bioavailability or metabolic stability," states Rafael Antunes, director of API portfolio development with Hovione.

Traditional and cost-effective fluorinating reagents are corrosive and often toxic and, therefore, require special handling and equipment. In addition, they cannot be used with intermediates containing other sensitive functionality. Thus, the synthesis of organic fluoro-compounds is not trivial at industrial scale—it requires special equipment, materials of construction, reaction conditions (sometimes cryogenic), and controls to tackle the difficulty in safely handling and disposing of fluorinating reagents, according to Antunes. "Reaction control is a fundamental aspect. The low selectivity (chemo-, regio-, and/or stereo-) of the reactions, the low stability of some fluorine-containing species, together with hazardous sampling and sample handling impose a heavy burden for the synthesis of fluorochemicals," he adds.

The search for safer, easy-to-handle, inexpensive, and selective fluorinating reagents has been underway for decades and continues today. Most recently, solid reagents are showing promise, at least for use by medicinal chemists. Even more promising are coupling reactions that allow the incorporation of fluorinated synthons through carbon–carbon rather than carbon–fluorine bond formation.

New reagents show promise

Several solid fluorinating reagents have been introduced to the market. One example that has recently been attracting more interest is XtalFluor-E from Manchester Organics (developed in partnership with OmegaChem). (Diethylamino)difluorosulfonium tetrafluoroborate is an easily handled crystalline solid with enhanced thermal stability when compared to other reagents in this class, including a higher decomposition temperature with lower exothermic heat and higher onset temperature for self-accelerated decomposition (1), according to Dave Tovell, director of Manchester Organics. In addition, it does not generate free hydrogen fluoride (HF) and thus is usually compatible with glass equipment. The partnership has also demonstrated that this fluorinating reagent typically produces fewer elimination side products, and thus greater selectivity, than more traditional nucleophilic fluorinating reagents.

With their attractive physical, reactivity, and health and safety profiles, these newer reagents are finding growing use at the discovery and early process phases of drug development. They do, however, carry a relatively higher cost than traditional fluorinating reagents (HF, potassium fluoride [KF] and fluorine gas [F_2]) and thus are generally less economical for use on the commercial-scale.

Organometallic coupling reactions are most exciting

Newer difluormethylation and trifluoromethylation chemistry, which involves the formation of carbon-carbon bonds rather than direct fluorination, is one of the most exciting developments in organofluorine chemistry in recent years, according to Tovell. "These reactions occur under mild conditions and often tolerate many different functional groups," he notes.

Hartwig's trifluoromethyl(1,10-phenanthroline)copper ((Phen)Cu-

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

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CF_3) reagent is an easily handled, thermally stable, single-component reagent for the trifluoromethylation of both electron-rich and electron-deficient aryl and vinyl iodides, including sterically-hindered iodoarenes, in high yields under mild conditions (2). Notably, aldehyde, nitroarene, ketone, and ester functionalities are tolerated. The reagent is sold under the trade name Trifluoromethylator by Catylix and is commercially available through Aldrich Chemical.

Shibata developed a method for the electrophilic α-trifluoromethylation of β-ketoesters using the fluorinated Johnson reagent [(oxido)phenyl(trifluoromethyl)-λ^4-sulfanylidene]dimethylammonium tetrafluoroborate (3). Meanwhile, hypervalent iodine(III)–CF_3 reagents developed by Togni are widely used for the trifluoromethylation of thiols, alcohols, phosphines, and heteroarenes (4–8). The radical trifluoromethylation of heteroarenes using the Langlois reagent (sodium trifluoromethanesulfinate) or zinc(II) bis(trifluoromethanesulfinate) ($Zn(SO_2CF_3)_2$) with tert-butyl hydroperoxide have also been achieved by Baran (9–11).

Zinc difluoromethanesulfinate (DFMS), also developed by the Baran group (11), allows for the simple difluoromethylation of a wide range of heteroaromatic substrates in air. Nucleophilic difluoromethylation of carbonyls and imines can be achieved using (difluoromethyl)trimethylsilane (12), a reagent developed by Hu and coworkers.

There are numerous other research groups developing selective and high-yielding nucleophilic and electrophilic difluoromethylation and trifluoromethylation strategies for substrates ranging from carbonyl compounds to alkenes. "These new techniques for the selective incorporation of fluorine atoms into complex organic molecules under mild conditions are very exciting advances for API synthesis. The pharmaceutical industry is under increasing pressure to reduce costs, and any new technologies that can improve route efficiencies and yields and do so cost effectively will attract significant attention," asserts Tovell. He adds that it is still early days with respect to the development of these types of chemistry and he expects further improvements in the coming years.

Organometal-catalyzed direct fluorination also of interest

Organometallic catalysts have also been applied to the direct fluorination of a variety of substrates. Two examples include Buchwald's method for the nucleophilic fluorination of aryl triflates with cesium or potassium fluoride (13) and Ritter's silver-catalyzed fluorination reaction in which aryl stannanes are converted to fluorides using silver triflate as the catalyst and F-TEDA-PF_6, which is an anion-exchange product of Selectfluor (chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); F-TEDA-BF_4) as the fluoride source (14).

Antunes adds that the development of Selectfluor by Eric Banks (marketed by Air Products) is the most important 'recent' development. This reagent has transformed the production of fluorinated pharmaceuticals, with 134 patents published that cite Selectfluor, and approximately 80% of all fluorinated steroids produced using the agent. "This reagent bypasses hazardous fluorine processing steps and makes the production of drugs containing fluorine much cheaper and safer. Every year, around 25 tonnes (worth $7.5 million) of Selectfluor are used in the industry, making it the most commonly used electrophilic fluorinating agent in pharmaceutical manufacturing," he notes.

Exploring the potential of flow chemistry

The benefits of flow chemistry include reduced operating costs, a lower footprint, decreased capital expenditures combined with improved process efficiencies, control, and product quality, and the ability to perform chemical reactions that are not feasible or present significant hazards in batch operations. As a result, there is great interest in this technology for the synthesis of pharmaceutical intermediates and APIs.

Not surprisingly, flow chemistry is a natural fit with fluorination reactions, particularly those involving conventional toxic and corrosive reagents. "Minimizing the quantity of reagents that are needed at any one time not only reduces the hazards associated with these reactions, but also allows for optimization of yields and selectivities," Tovell explains. There are generally high expectations for flow chemistry to overcome many of the challenges of traditional fluorination reactions (the need for special equipment, to handle hazardous chemistries, and run strictly controlled reactions) due to more efficient mass and energy transfers, short residence times, and moisture free-operating conditions, agrees Antunes.

These benefits shouldn't be limited just to traditional fluorination chemistry, however. "Combination of flow chemistry with the newer difluoromethylation and trifluoromethylation

New process improves the bioavailability of active ingredients

A new process that makes amorphous nanoparticles with increased solubility can improve the uptake of drugs in the human body, BASF reports. The process can be applied to both organic and inorganic substances. Researchers from BASF, Harvard, Yale, and the Swiss Federal Institute of Technology developed a microfluidic nebulizer to create small nanoparticles from drugs that are first dissolved in a solvent and then exposed to a stream of air with at 600 meters per second. The increased solubility can result in higher uptake of active ingredients.

"The high-speed air flow enables fast evaporation of the solvent, which leaves no time for the molecules to arrange themselves in the form of a crystal. Molecules, therefore, arrange themselves randomly in an amorphous structure and are ten times easier to dissolve," explained Christian Holtze, research manager at BASF.

techniques has the potential to provide low-cost, highly effective routes to complex fluorinated molecules," says Tovell.

Manchester Organics will be investigating the application of a continuous-flow approach to various fluorination strategies over the next few years. One of the challenges involves optimizing the conditions for reactions that require the use of solid reagents. There are numerous parameters to consider, such as the dilution factor, solvent choice, and reaction temperature. "There is a lot of work to be done, but we believe that this approach will enable the development of effective solutions for many of our customers that are looking for improved methods for the production of their fluorinated compounds," Tovell observes.

More diversity to come

Since the first introduction of reagents with improved handling and toxicity profiles, such as (2-methoxyethyl) aminosulfur trifluoride (Deoxo-Fluor), Selectfluor, and diethylaminosulfur trifluoride (DAST), there has been an explosion in the development of new fluorination methods.

Access to solid reagents such as XtalFluor-E and FLUOLEAD from UBE Industries has led to even further advances in fluorination chemistry, with the number of literature reports on new techniques growing exponentially, according to Tovell. Studies of the reactivities of these various reagents combined with new data obtained using state-of-the-art analytical and modeling technologies are enabling researchers to gain a better understanding of the interactions of fluorine with other atoms in different molecular settings. Tovell believes that this new knowledge will lead to the development of even more effective fluorinating reagents that are highly selective (chemo-, regio-, and stereo), safer to use, can tolerate a wider range of functional groups, are environmentally acceptable, and can be produced at a cost level that will facilitate their use in commercial drug manufacturing.

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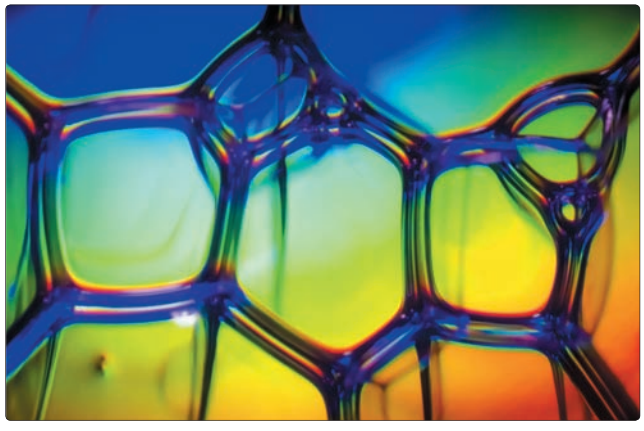
Rethinking Limits in Cleaning Validation

An integrated approach can improve the efficiency of cleaning validation studies.

Richard Forsyth



Cleaning validation programs must have cleaning limits, worst-case residues to validate, and recovery factors to accurately determine how clean the equipment must be. If a program is to be robust, it must also address the question of which products should be validated, and how to test residue levels accurately, to assure compliance with the defined clean validation limits. This article presents an integrated approach that can establish the necessary information in an efficient, compliant manner.

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Submitted: February 26, 2015. Accepted: April 10, 2015.

An effective cleaning validation program requires substantial up-front work to withstand regulatory scrutiny. Acceptable residue limits (ARLs) must be defined prior to any cleaning validation and development work (1,2). The ARL is the level to which product residues must be removed to assure patient safety and that the subsequent product manufactured on the cleaned equipment will not be contaminated.

A number of factors go into the determination of the ARL, including product dosage levels, batch sizes, and equipment product contact surface areas (3). The dosage and batch size parameters are typically well defined for a product before it gets to commercial production. The equipment product contact surface areas, however, require more planning and more steps to execute. Many vendors do not supply product contact surface areas or even dimensions of the product contact surfaces. Measurements and calculations of each piece of equipment's product contact surfaces must be completed, documented, and reviewed to determine the ARL of the product. Although it can be time-consuming to calculate the product contact surface area for a piece of equipment, the resulting figure only changes when the equipment is altered, which would only occur under a documented change control.

In addition to establishing a calculated ARL, the first criterion of a cleaning procedure is that the equipment be visibly clean after the cleaning process. The visible residue limit (VRL) is the level below which a residue is not visible, under defined viewing conditions. It can be a valuable tool when applied to a cleaning validation program. Viewing distance, viewing angle, and viewing light level must be defined for the facility and applied to the determination of a VRL.

VRLs have been used for a number of cleaning validation applications (4,5). Once established, VRLs can be implemented for multiple aspects of a cleaning validation program (6), including routine confirmation that the equipment is cleaned to appropriate levels before changeover to a new product. One approach to cleaning validation is to validate every product manufactured at a site. This approach, however, is impractical at multi-product facilities.

To streamline validation efforts, products can be grouped together by therapeutic family or based on the hardest-to-clean

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products manufactured on the equipment. Defining the worst-case product can itself be a challenge. Solubility of the API is sometimes used as the criteria for determining "hardest to clean," but this approach ignores the product excipients, which can often be more difficult to remove from equipment than the API.

Cleanability of the product residue more closely approximates the actual cleaning procedure necessary to result in acceptably clean equipment. Cleanability study conditions can range from simple immersion to vigorous cleaning actions (7–10). As long as the cleanability parameters are consistent, they can define a relative cleanability ranking of the site product residues.

Even with an executed cleanability study, before validation studies can be executed, cleaning development studies must define and confirm the cleaning conditions necessary to clean product residue effectively, down to an acceptable level. Cleaning development studies define the critical cleaning parameters and their ranges, which will assure the consistent capabilities of the cleaning process. The critical cleaning parameters can include detergent definition and concentration, water temperature, cleaning action (e.g., impingement, cascade, or manual scrubbing), contact time, and rinse times. The conditions established during cleaning development should be confirmed under an executed protocol prior to validation activities.

Finally, recovery factors must be established to demonstrate that swab or rinse samples taken after cleaning are representative of the cleanliness of the equipment (1, 2, and 11). To accomplish this, a known amount of the residue of interest is first spiked onto a coupon of the material of construction representing the manufacturing equipment. The spiked residue is recovered, either by using a swab wet with a solvent to dissolve the residue, or with a known volume of purified water to represent the final rinse of the cleaning procedure. The recovered samples are then tested to determine the amount of recovered residue. The recovery factor is the amount of residue recovered compared to the amount of residue spiked onto the coupon.

Although the data are typically generated for these cleaning validation parameters in separate efforts, a coordinated study can determine all of the factors using available data and an efficient set of experiments. This approach will save time and resources, and result in a more aligned set of cleaning limits, soils to be validated, and recovery factors for the cleaning validation studies.

Acceptable residue limit determinations

The ARL must be determined prior to cleaning development, analytical method validation, visual limits and recovery factors. The subsequent data and recovery factors are all based relative to the ARL of the residue of interest. The primary goal of a health-based ARL is patient safety, and the recommended method to define a health-based calculation incorporates the acceptable daily exposure (ADE) (12), which is the amount of material one can ingest on a continued daily basis without harmful pharmacologic effect. Although the ADE approach is preferred as being more scientifically sound, the ADE can be compared to a currently used 1/1000th minimum-daily-dose (3) approach during the transition period to the use of ADEs to determine if additional validation work is necessary.

The factors that go into an ARL calculation include the dose and the batch size of the next product, which determine the degree to which any carryover is spread among subsequent product dosages. The product contact surface area of the manufacturing equipment assumes an even distribution of any worst-case carry over residue. This assumption of even residue distribution is addressed by swabbing worst-case, hardest-to-clean and critical equipment locations; that is, those locations where residue is most likely to build up, or where residue could be transferred to a small number of subsequent doses.

The swab area and the recovery factor enable one to relate the result for a single sample to a total residue amount in the manufacturing equipment. The health-based calculation employing the ADE is shown in **Equation 1:**

$$\frac{(\text{ADE (mg/day)})/(\text{MDD (doses/day)}) \times (\text{BS (doses)})/(\text{SA (cm}^2\text{)}) \times \text{M (cm}^2\text{/swab)} \times \text{RF} = \text{ARL (mg/swab)}}{\text{(Eq. 1)}}$$

Where:

ADE is ADE of Product A being cleaned (in mg/day)

MDD is maximum daily dose of subsequent Product B (in doses/day)

BS is batch size of product B (in number of doses)

SA is product contact surface area of the equipment train (in cm^2)

M is swab area = $25 cm^2$

RF is recovery factor (e.g., 0.90 for a 90% Recovery Factor)

ARL is acceptable residue limit.

The intent is to consider the health-based ARL and the VRL to satisfy regulatory requirements for cleaning so that the patient is safe and the equipment is visually clean. Although the VRL for residues should be related to the health-based cleaning limit, as well as the analytical detection limit (LOD), the VRLs can be determined prior to defining the final ARL because the VRL is more an experimentally determined physical characteristic of the API or product established under defined condition rather than a relative characteristic based on other factors.

Visible residue limit studies

VRLs must be determined using well-defined viewing parameters to better transfer the implementation of the VRLs to the production equipment and to limit subjectivity. The viewing variables associated with studying visible residue must be defined, and then experimental parameters for the study can be established. The parameters considered are:

- Equipment material of construction
- Light intensity
- Viewing distance
- Viewing angle
- Observer subjectivity
- Solvent effects.

Stainless steel is an obvious choice for surface material, because more than 95% of manufacturing equipment surfaces at a typical pharmaceutical manufacturing site are made from this material. Representative stainless-steel coupons are used for spotting purposes in the laboratory setting.

In addition to stainless steel, other widely used materials of construction (MOC) include:

- Polytetrafluoroethylene (PTFE), including Teflon
- High-density polyethylene (HDPE)
- Low-density polyethylene (LDPE)
- Polycarbonates, including Lexan
- Glass, which can be addressed as part of the cleanability determinations.

Although the VRLs for Lexan and glass are comparable to that of stainless steel (13), VRLs for the remaining MOCs would be higher than the VRL for stainless steel. Cleanability provides a much simpler answer to the question of VRLs for different MOCs.

Lighting conditions in the manufacturing plant typically differ, from room to room. The light intensity is measured in each room of the plant and the wash area to determine a range. For consistency, the light measurement is taken in the same location in each room, for example in the center of each room, approximately four feet from the ground. The light level in a typical pharmaceutical manufacturing plant generally ranges from 200–1000 lux.

The viewing distance and viewing angle are based on the manufacturing equipment that is used at the site. Larger pieces of equipment can often be viewed at a distance of no greater than 10 feet, and, if the equipment is disassembled for cleaning, the viewing angles are marginally limited for visual inspections.

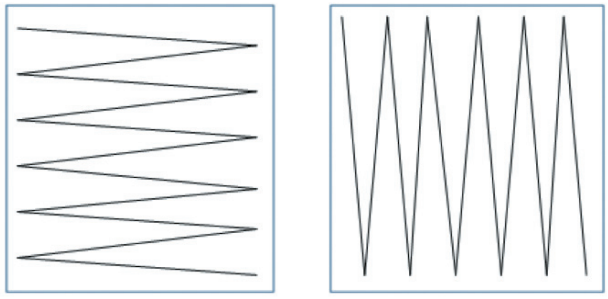
Suspensions of the products are prepared in methanol at concentrations of the API and spiked onto stainless-steel coupons. For products compressed from common formulation blends, the highest potency product is used for the VRL determination. For the remaining products, the single strength manufactured at the site is used for VRL determination.

The spiked coupons are allowed to air dry, and the distance, angle and light level viewing parameters are set. Site personnel view the spiked coupons from multiple distances and angles. The VRLs are determined at a distance of two feet. Increasing viewing distance and viewing angle observations of the spiked coupons establish the viewing parameter limitations on the ability to see the VRL levels. If the observers are not able to see the VRLs at the distance of the larger equipment, this limits the use of VRLs to those pieces of equipment that can be viewed from established VRL viewing limitations. Literature references (6) have shown that most VRLs can be detected from 10 feet. Any seeming inconsistency is likely a result of very low VRLs that were determined experimentally. Some VRLs can be detected at levels as low as 0.1µg/cm^2, compared to the literature average of 1.1µg/cm^2. The viewing

Table I: Spiking preparation and target concentrations.

Spiking solution prep (example dilutions)	Spiking solution concentration	Volume spiked	Residue spiked	Target concentration on coupon (20 cm^2)
Solution A–800 µg/mL	800 µg/mL	100 µL	80 µg	4 µg/cm^2
Solution B–5 mL of A into 10 mL	400 µg/mL	100 µL	40 µg	2 µg/cm^2
Solution C–5 mL of B into 10 mL	200 µg/mL	100 µL	20 µg	1 µg/cm^2
Solution D–5 mL of C into 10 mL	100 µg/mL	100 µL	10 µg	0.5 µg/cm^2
Solution E –5 mL of D into 10 mL	50 µg/mL	100 µL	5 µg	0.25 µg/cm^2
Solution F – 2 mL of E into 10 mL	10 µg/mL	100 µL	1 µg	0.05 µg/cm^2
Solvent	0 µg/mL	100 µL	0 µg	0 µg/cm^2

Figure 1: Swab sampling technique.



angle should be greater than 30° and the light level should be greater than 200 lux (6).

The ARL and VRL will indicate how clean the equipment needs to be. **Table I** shows results spiking preparation and target concentrations for one test. The next step is to determine which product(s) or residue(s) to validate.

Cleanability/cleaning development studies

For efficiency and economy, the initial cleaning development work can be conducted at laboratory scale in three phases. These laboratory-scale process and cleaner studies (PACE evaluation) were executed in the technical laboratory at STERIS Corporation, St. Louis, Missouri. The Phase 1 studies challenge a worst-case set of conditions. Baked-on residues are cleaned using different cleaning agents, cleaning mechanisms, times and temperatures. Once the optimal cleaning agent and conditions have been identified, the cleaning parameters are challenged in Phase 2 studies, to determine the minimum times and concentrations necessary to achieve clean equipment. In the Phase 3 study, the minimum cleaning parameters identified in Phase 2 studies are used to clean the worst-case soil identified in Phase 1 studies, from the MOCs that make up most of the product contact surfaces of the equipment at the facility.

In Phase 1 of the study, to create worst-case conditions, cleanability studies are performed on the products and blends manufactured at the facility, to determine which cleaning agent will adequately remove product residue. The study results will provide cleaning conditions, including the concentration of detergent to be used, critical cleaning parameters, time for rinse, etc.

In the Phase I cleanability study, dry, clean stainless-steel coupons are weighed on an analytical balance (±0.1 mg) to obtain their pre-coating weight; then they are coated with 3–5 mL of 10% w/v slurry or 3–5 grams of sample. They are then baked at 57 °C for 4 hours then air dried overnight, and weighed on an analytical balance. The coated surface area is measured, the dry coating weight calculated, and the "loading" of the sample, in milligrams per square centimeter of dried residue, is determined. The spiked coupons can be cleaned by agitated immersion, spray wash (11 psi), cascading flow, or scrubbed manually using a nylon-bristled brush; in addition to the cleaning technique, the type and concentration of detergent, the cleaning temperature, and the cleaning time are recorded.

After cleaning, the coupons are removed and visually observed for cleanliness; then, each side of the coupon is rinsed, first, with tap water for 10 seconds at a flow rate of 0.5 gal/min and then with de-ionized water. It is then examined for a water break-free (WBF) surface, after which it is dried and weighed on an analytical balance to determine the post-cleaning weight.

A coupon is considered to be clean if it is visually clean, water break-free, and if its pre-coating weight and post-cleaning weight are equal (0.0 mg residue). WBF is a qualitative test that indicates the cleanliness of a metal surface. On a clean surface, free from organic residue, water sheets evenly without breaks in the water film as it runs from the surface of the metal panel. The results of a Phase 1 case study are shown in **Table II**, with the worst-case soils designated. Two soils are designated as worst-case Product A is manufactured in dedicated equipment. Product B is manufactured in multi-use equipment with the remainder of the site product portfolio.

ALL FIGURES ARE COURTESY OF THE AUTHOR.

Table II: Phase 1 PACE study results (CIP is clean in place).

Products	Washing action/cleaning agent concentration			
	Agitated immersion	Spray wash	Cascading flow (0.5 gal/min)	Manual scrub
	1% v/v CIP 100 plus 1% v/v ProKlenz Booster	1% v/v CIP 100 plus 1% v/v ProKlenz Booster	1% v/v CIP 100 plus 1% v/v ProKlenz Booster	3% v/v CIP 100
Product A	**45 °C/30 min.**	**60 °C/30 min.**	**60 °C/30 min.**	**45 °C/60 sec.**
Product B tablets	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/60 sec.
Product C tablets	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/60 sec.
Product D tablets	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/30 sec.
Product E tablets	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/45 sec.
Product F tablets	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/45 sec.
Product B blend	**45 °C/30 min.**	**60 °C/30 min.**	**60 °C/30 min.**	**45 °C/45 sec.**
Product C blend	45 °C/30 min.	60 °C/15 min.	60 °C/15 min.	45 °C/60 sec.
Product D blend	45 °C/30 min.	60 °C/30 min.	60 °C/30 min.	45 °C/30 sec.
Product E blend	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/45 sec.
Product F blend	45 °C/15 min.	60 °C/15 min.	60 °C/15 min.	45 °C/30 sec.

Phase 2 study

Phase 2 studies further evaluate the effectiveness of the cleaning agents that demonstrated positive results in Phase 1. These tests are run under conditions that more realistically reflect what would be experienced in actual use. The major difference in the Phase 2 coupon preparation is that the coupons are air dried only for 24 hours, rather than dried in an oven. Phase 2 cleanability studies are performed to provide a more focused look at critical cleaning process parameters such as time, temperature, concentration of

Table III: Phase 2 PACE study results.

Products	Washing action/cleaning agent concentration			
	Agitated immersion	Spray wash	Cascading flow (0.5 gal/min)	Manual scrub
	1% v/v CIP 100	1% v/v CIP 100	1% v/v CIP 100	1% v/v CIP 100
Product A	60°C/20 min.	60°C/10 min.	60°C/20 min.	45°C/30 sec.
Product B blend	60°C/10 min.	60°C/10 min.	60°C/10 min.	45°C/10 sec.

Table IV: Phase 3 PACE study results–Product B blend. (CIP is clean in place. HDPE is high-density polyethylene and LDPE is low-density polyethylene.)

Material of construction	Detergent	Concentration	Time/temperature	Visual observation
Teflon	CIP 100 detergent	1% v/v	5 min/60°C	Visually clean
HDPE	CIP 100 detergent	1% v/v	5 min/60°C	Visually clean
LDPE	CIP 100 detergent	1% v/v	5 min/60°C	Visually clean
Glass	CIP 100 detergent	1% v/v	5 min/60°C	Visually clean
Lexan	CIP 100 detergent	1% v/v	5 min/60°C	Visually clean

detergent, and cleaning agent, and to demonstrate the ruggedness of the cleaning parameters identified in Phase 1 studies. The two worst cases, one product and one blend, from Phase 1 testing, are tested in Phase 2 to minimize testing resources and the results shown in **Table III**.

Phase 3 study

In Phase 3 studies, the minimum cleaning parameters identified in Phase 2 studies are used to clean the worst-case soil identified in Phase 1 studies from the MOCs that make up most of the product contact surfaces of the equipment at the facility. The worst-case product is applied to different MOC coupons, air dried for 24 hours, and cleaned using agitated immersion at the previously identified cleaning parameters. The results are shown in **Table IV**.

If all of the materials of construction are cleaned for the worst-case soil under the same cleaning conditions, it can be concluded that, if the equipment's stainless-steel surfaces are clean, the other equipment surfaces are cleaned to the same level of cleanliness. An acceptable visual inspection of the stainless-steel surfaces would provide confidence that the other surfaces such as PTFE, HDPE, or LDPE, on which spots would be more difficult to detect, are clean to the same acceptable level.

Swab recovery studies

Swab sampling is the preferred technique to determine equipment cleanliness because it is direct surface sampling and targets hard-to-clean and critical locations such as tablet press tooling.Swab sampling is generally more sensitive than rinse sampling because of the larger volumes associated with final rinses. An accurate swab sample requires that a swab recovery factor be established. The swab recovery factor is established by spiking a known amount of the API or product formulation onto a material of construction coupon, letting it dry, and swabbing the coupon to recover the residue.

To execute a swab recovery study, the parameters of the study must first be defined. These parameters include the coupon MOC, swab area, swab manufacturer and mode, number of swabs, swab solvent, swab technique, the extraction solvent, and the swab extraction parameters. Once these parameters are defined, they can often be applied across the APIs and products that require recovery factors. The last remaining parameter is the level of analyte to recover (i.e., the amount of analyte to spike on the coupons).

The logical level at which to perform a recovery is at the cleaning limit itself, because the cleaning limit is the pass/fail point of the residue test. For relatively safe products, the health-based cleaning limits are often quite high, for example greater than 1 to 10 mg/swab, which most likely would overload the swab and result in low recoveries. These levels also would be easily visible, which would fail the cleaning before the swabs are even taken. An efficient level for recoveries would be around the VRL level, because samples were already made for the VRL determination. For example, samples can be prepared at 5.0, 7.5, 10, and 12.5 µg of API/swab,slightly higher than the reported average VRL of 1.1 µg/cm.[2] These levels are also close to the levels that one would expect to see after cleaning. The risk is that these levels are also close to the limit of quantitation (LOQ) of the analytical test method and could result in low recoveries with high % relative standard deviations (RSDs).

The swab recovery samples are prepared using the suspensions prepared for the VRL study. The 5.0-, 7.5-, 10-, and 12.5-µg samples are spiked onto stainless-steel coupons using 50, 75, 100, and 125 µL, respectively, of the 100-µg/mL suspensions. The spiked coupons are allowed to dry. For swabbing, each sample container is labeled, recording the API/product, amount (µL), volume (mL), name, and date.

The swab is wetted with methanol, water, or other appropriate solvent, which will dissolve the API. Any excess solvent is removed by pressing the swab against the side of the sample

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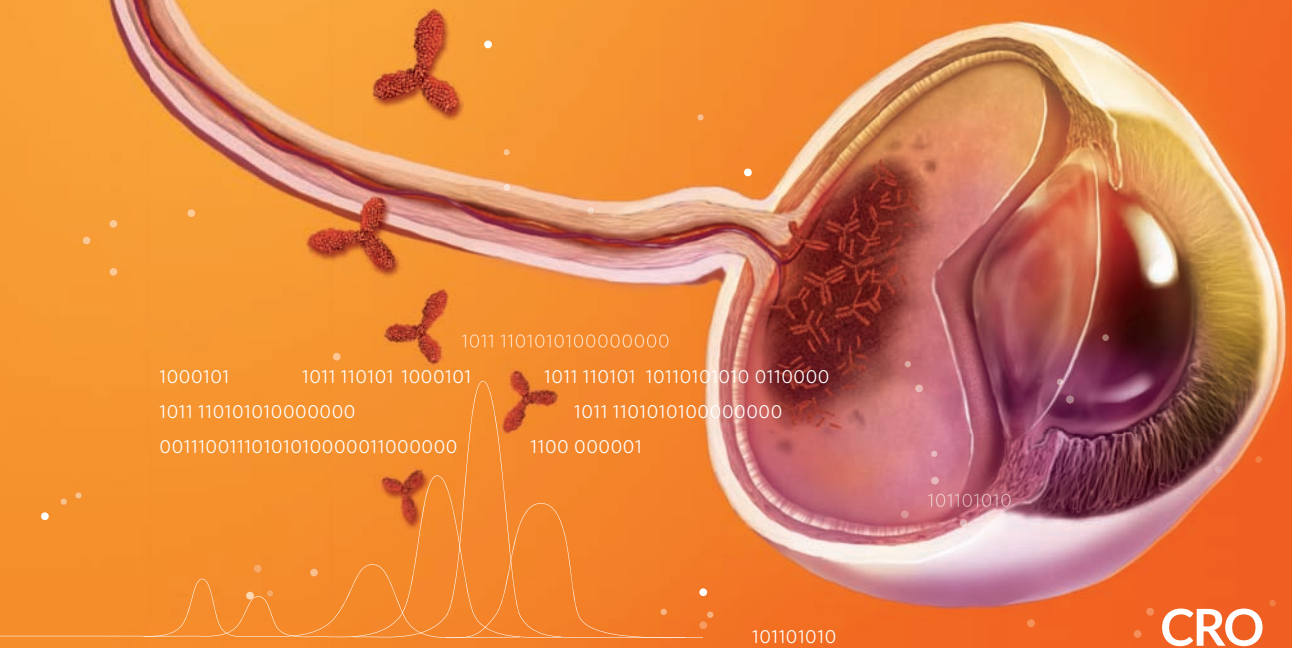

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container to wring out excess solvent from the tip. The swab area is at least 25 cm^2, and pains must be taken to ensure that all the area covered by the dried residue is swabbed.

The swabbing technique is shown in **Figure 1**. Using the flat side of the swab, slight pressure is applied to the swab stick, and full contact is made with the coupon. The coupon should be swabbed, using a back-and-forth motion, for approximately 10 seconds. Then, one should flip the swab over and swab the coupon in a perpendicular direction, using a back-and-forth motion, for approximately 10 seconds. Finally, one should snap the swab head into the sample container and close the container. The swabbing is repeated for each coupon and the samples submitted for analysis. The validated high-performance liquid chromatography (HPLC) test methods used for analysis should be specific for each analyte.

The swab recovery results should be greater than 70% for stainless steel based on historic data (14). The variability (%RSD) should be less than 10%. However, performing recoveries at levels close to the analytical method LOQ can result in lower-than-expected recoveries, with higher %RSDs. The results will be affected by a number of factors:

- Low spike levels near the LOQ of the analytical methods
- Experience level of the staff performing the recoveries
- Robustness of the extraction parameters
- Size of the swab head.

A larger swab head would be expected to retain slightly more residue than a smaller swab head of the same material. Ideally, the swab recovery spike levels are around the VRL, but these levels are likely to be too low for quantitation by the HPLC methods after swab recovery and extraction. That is why the swab spike levels are targeted slightly above the method LOQs. The proximity of the spike levels and the method LOQs could contribute to both low recoveries and high variability if small, variable amounts of analyte adhere to the swab. Also, the lower HPLC area counts near the LOQ could contribute to the higher %RSD compared to comparably spread data with greater HPLC area counts.

Typical validated HPLC methods have LOQs of approximately 1 µg/mL. If the methods can be optimized with real samples prior to validation, a lower LOQ can often be established, and better recovery conditions identified. The effort required for optimization, however, may not be worth marginal improvements to the recovery data, especially when compared to the calculated ADE-based cleaning limit. Although the personnel involved in the recoveries are a factor, their contribution to low and variable results is considered minor compared to analytical issues (14).

Rinse-recovery studies

Rinse-recovery studies are conducted using the materials and previously prepared solutions or suspensions to offer the flexibility to use rinse sampling. Although rinse sampling is considered indirect surface sampling, it covers all of the product contact surface area and more easily samples those areas that are inaccessible to swab sampling. In addition, rinse samples are easier to take and more efficient to test. Rinse sampling, however, is generally less sensitive than swab sampling because of the larger volumes associated with final rinses. The rinse-recovery factor is established by spiking a known amount of the API or product onto a material of construction coupon, letting it dry, and rinsing the coupon to recover the residue.

To execute a rinse-recovery study, the parameters of the study must first be defined. These parameters include the level of analyte to recover, the coupon MOC, the rinse area, the rinse solvent, and the rinse volume. Once these parameters have been defined, they can often be applied across the APIs and products that require recovery factors.

To be consistent with the swab recoveries, the spike level for the rinse recoveries can be set at 10 µg of API or product onto a 25-cm^2 area of stainless-steel coupon. Final rinses are all done with purified water, and a volume of 10–25 mL is used, making sure to keep the final solution at or above the method LOQ.

The rinse recovery results should be more than 70% for stainless steel. The variability (%RSD) should be less than 10%. However, performing rinse recoveries at levels close to the analytical method LOQ can result in lower than expected recoveries and with high %RSDs. The results will be affected by a number of factors: the low recovery levels near the LOQ of the analytical methods and the volume of the rinse water. Too small a volume will not remove the residue and too large a volume will be undetectable. For the residues with high %RSD as well as those for which no quantitative values, an investigation should be conducted to determine a root cause.

Discussion

Although the described studies serve to establish the necessary background data for the cleaning validation effort, there were several issues that could be addressed differently. The VRLs are established under laboratory conditions, and recent VRL levels obtained averaged 0.1 µg/cm^2. This raises the concern that data might not translate to full-size equipment in the manufacturing plant. Future work would answer that question, by taking spiked coupons and placing them inside actual equipment, or equivalent conditions, to confirm the laboratory generated data.

Very low VRLs also raise the question of how the VRLs are defined. Past work had defined the VRL concentration by dividing the amount of material spiked by the entire surface area of the circle formed, even though most of the material forms a ring, leaving the middle of the circle empty. This is not a concern as long as the VRL determinations have been defined consistently. With the VRL defined using this approach, however, the VRL of residues could approach or even be lower than the LOQ of the analytical method. Defining the VRL as the area of only the ring and not the entire circle might be a better, more realistic approach, and could relate more closely to the recovery factors and the analytical test method LOQ.

The LOQ of the HPLC analytical test methods should be optimized for cleaning validation samples. A lower LOQ would alleviate some of the concern with the VRL levels and probably would improve the variability of the swab and rinse recovery studies. The added value must be deemed significant enough, however, to expend the additional resources

for this work. Coordination with the testing laboratories is essential during cleaning development work.

The rinse-recovery study levels of 10 µg are based on swab recovery levels. Because the rinse volumes are higher than the swab extraction volumes, the resulting rinse-recovery concentrations are lower. To ensure accurate data, the rinse recovery samples should be spiked based on the final concentration of solution (µg/mL) of the rinse recoveries.

Conclusion

Background data for a cleaning validation program can be generated in an efficient, coordinated effort for a pharmaceutical manufacturing facility. Using this approach, the ARL calculations and the cleanability data are combined to define the worst-case product for cleaning. The VRL, swab recoveries, and rinse recoveries are established using a single set of product suspensions, which illustrate the relationship among the three factors. These studies clearly demonstrate that a cleaning validation program can be established or revalidated using an efficient, coordinated effort to establish the necessary background information.

Acknowledgement

The author gratefully acknowledges Amanda Deal, Steve Robbins and Paul Lopolito of STERIS Corporation for their support, and for conducting the PACE studies as part of this development project case study.

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Leveraging Change for Continuous Process Improvement

Parveen Bhandola

Managing change and overcoming employee resistance and fear requires a proactive approach.

As the ancient Greek philosopher, Heraclitus, wrote back in 500 BC, "The only thing constant is change." This is especially true for pharmaceutical development and manufacturing, where change can result from modification of facilities, utilities, equipment, computer systems, formulations, analytical methods, specifications, manufacturing and cleaning processes, vendors and components, and documentation.

Depending upon the criticality of the change, some changes may even affect the safety, identity, strength, quality, or purity of the product. Others may trigger the need for new regulatory filings. Managing all this change is perhaps the most important part of any life-sciences quality program.

Change management plays a crucial role in ensuring that processes are, and remain, in control throughout a product's lifecycle. It is, therefore, essential to develop and implement a compliant, effective, and efficient change-management system in accordance with cGMPs and FDA guidelines, notably the revised process validation guidance of 2011 (1).

The whole concept of managing change has been evolving over the past few years, moving from "change control," a term that implied the need to restrict change. Now, the term "change management" is used to describe the oversight of the change process. This oversight must be in place during visualization, initiation, evaluation, and pre-implementation approval, as well as implementation and post-implementation approval of the change, to help ensure that the outcome of any change remains as originally intended. In the future, the term may be "change championship," taking into account the dynamic results of corporate mergers and de-mergers and the human element in change management, making the process more holistic and realistic.

This article discusses the regulatory aspects of change management and how it can be used, not only to ensure regulatory compliance, but for continuous quality improvement.

A validated system may go through more than one change at a single time or at different times during a product's lifecycle. Maintaining proper documentation and an audit trail of all changes is imperative to ensure the continued state of control. FDA expects pharmaceutical manufacturers to implement a compliant, effective, and efficient change-management system, and its inspectors look for such a system during most cGMP inspections.

Priority: maintaining control through robust written procedures

FDA's current cGMP regulations 21 *Code of Federal Regulations* 210 and 211 (2) do not explicitly mandate a change-management system, but they do require establishing written procedures that will maintain a state of control. Therefore, it is necessary to have a well-designed change-management system in place to comply with the regulations and applicable guidelines.

The FDA *Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (3) and the FDA's *Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations* (4) suggest implementing the change control program.

Both of these guidance documents use the term "change control" rather than "change management." The transition from "change control" to "change management/change control" can be clearly seen in the FDA *Guidance for Industry, Q9 Quality Risk Management* (5).

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Tracing the evolution of change management

In 2009, the publication of FDA/ICH's Q8(R2) *Pharmaceutical Development* (6) signaled further change when it emphasized the idea of a design space, wherein a change within the design space would not be considered a change from the regulatory post-approval perspective. This guideline expected applicants to develop a data-based design space derived from product and process knowledge gained throughout the product's lifecycle.

The whole concept of managing change has been evolving over the past few years, moving from "change control," a term that implied the need to restrict change, to "change management ..." In the future, the term may be "change championship" ... making the process more holistic and realistic.

In the FDA/ICH *Guidance for Industry, Q10 Pharmaceutical Quality System* (7), there is no mention of the term "change control." The term has been completely replaced by "change management," and listed as one of the four key elements of a pharmaceutical quality system, that are capable of ensuring continual improvement.

The Q10 guidance document demonstrated a complete transition from attempting to control change to managing changes for process improvement. The goals allow pharmaceutical manufacturers, not only to achieve compliance but to gain business advantage.

Documenting change in a unified company-wide system

Pharmaceutical manufacturers are expected to implement well-documented, detailed change-management procedures to ensure that a company-wide change-management system is in place; individual departments should not have their own change-management systems. Depending on the size of the company and the complexity of its processes, the mechanism of implementing the change-management system will vary. Paper-based manual change-management systems may work reasonably well for smaller companies, but software-based electronic systems are generally needed for larger firms.

Any change-management system typically comprises the following essential phases in its development.

Initiation. Once the need for a change is identified, the person who suggested that change should formally draft a proposal for implementing the change. The proposal must define the change clearly and specify the reasons why it should be implemented. This proposal should be reviewed and approved by the head of the initiator's department before it proceeds further.

Evaluation. Cross-functional teams formally review all proposed changes for the impact that they may have on the state of control as well as the regulatory filing status. Most companies have formal change-management boards or committees to evaluate the changes. While quality assurance and regulatory affairs departments are the most important members of such boards/committees, validation, manufacturing, and engineering are also typically involved in evaluating the change proposals.

Involving the business side

Depending upon the nature of the change, even the marketing, legal, and commercial departments may also be required to evaluate certain changes. The change-management board/committee evaluates all changes to determine whether or not to proceed.

After a change is approved for implementation, the committee/board also formulates the change implementation action plan. Taking various actions might be necessary to ensure that the change succeeds in achieving the intended purpose while simultaneously preventing unintended consequences.

Tracking. A manual or electronic documentation system is essential for any change-management system to efficiently track not only the implemented changes, but the data and documentation that must be generated to support them. Appropriate documentation must support regulatory filing status and a continued state of control, and should allow for full traceability. The supporting documentation should also include data generated to verify the effectiveness of any change after it has been implemented, as well as training records associated with the change implementation.

Training. All employees involved with the initiation, evaluation, and implementation of changes must be trained on the change-management procedure.

Records for the training required by the change-management procedure must be appropriately maintained. Furthermore, implementation of some changes may also require some re-validation and revision of such controlled documents as standard operating procedures and batch records, which may necessitate additional training. Effective training and the documentation of that training are essential for the overall success of the change-management system.

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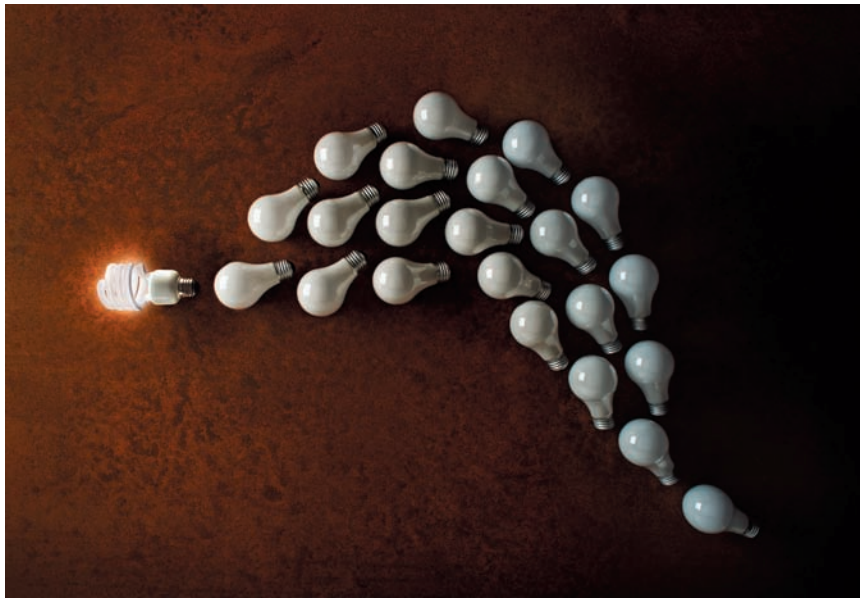

It is ... crucial to ensure that the system reflects any changes that might have been made by materials suppliers and equipment vendors. Vendor audits should verify that an effective change-management system is in place at the vendor's site.

Regulations do not require classifying the changes, and all changes that could affect cGMPs may be treated as equally crucial. It can be helpful, however, to rank changes in categories such as low, medium, and high, based on the risk they pose to the safety, identity, strength, quality, or purity of the product, and their potential impact.

Risk-based classification facilitates the development of a rational and data-driven action plan for implementing the changes. Many companies do not require that "like-for-like" changes go through a formal change-management process. For example, the replacement of equipment parts from the same manufacturer, and of the same model with the same specifications, is generally considered a like-for-like change.

Gaging the potential impact of change isn't always easy

Assigning general categories to the changes based on their potential impact is not always easy. Each change should also be evaluated individually, because even some like-for-like changes may have an impact on the processes. For instance, some equipment replacement parts may come from the same manufacturer, be built to the same specifications, and based on the same model. Nevertheless, they may vary slightly in performance from piece to piece, depending upon the criticality of the process, and the manufacturing controls that have been exercised by the parts manufacturer.

For example, replacing tablet press dies and punches may result in varying tooling tightness. This change in tightness may require that operating parameters be adjusted after the tooling has been replaced. Overlooking actions associated with such changes may result in unexpected process variation.

It is also crucial to ensure that the change-management system reflects any changes that might have been made by materials suppliers and equipment vendors. Vendor audits should verify that an effective change-management system is in place at the vendor's site.

Furthermore, quality agreements should be worded so that suppliers must notify sponsors of any critical changes that they make to the manufacturing process and/or specifications as soon as possible. Any changes that are not communicated by vendors may affect processes, jeopardizing the state of control, and the overall change-management system.

Moving away from "command and control"

Until recently, pharmaceutical manufacturers were constrained by restrictive regulations that did not facilitate the adoption of new technologies. This has caused the life-sciences industry to lag behind other industries in the use of the most modern IT or process-control tools, for example.

This regulatory "command-and-control" approach changed in the last decade, when FDA published "Pharmaceutical cGMPs for the 21st Century—A Risk-based Approach" (8). This report marked a shift from a restrictive to a more liberal risk-and-science-based regulatory approach, throughout a product's lifecycle. This new approach facilitated the adoption of constantly evolving technological advancements and innovations. A well-designed change-management system should enable manufacturers to leverage opportunities to adopt more modern technologies and implement continuous improvement initiatives. Because flexibility and change are the precursors to improvement, any

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change-management system should be conceived so that it provides an opportunity for continuous improvement

Leveraging change management for process improvement can be compared to driving an automobile on four wheels. Each of the wheels must be equally strong and balanced if the ride is to be smooth. For change management, the wheels are:

- Awareness
- A proactive approach
- Interdepartmental communication
- Timeliness.

Utilizing all four wheels can require a change in mindset. Employees, including those in quality assurance and control (QA and QC), can grow so accustomed to performing certain activities in certain ways that they do not like being taken out of their comfort zones.

To minimize resistance to change, managers should make employees aware of the reasons for the change and the benefits that will result from it. This outreach will enable the achievement of process improvement goals.

Employees throughout any organization should be aware of the connections from change management, to process improvement and business benefits. To minimize resistance to change, managers should make employees aware of the reasons for the change and the benefits that will result from it.

Seeing change in a positive light

Taking a proactive approach is also important but represents a break from the past, when changes were only accepted when absolutely necessary, or when forced by circumstances (e.g., when a vendor of a specific type of equipment went out of business).

Life-sciences companies should empower their employees to look, actively, for changes that can bring such benefits as improved quality and yield, easier operation and safer processes, reduced cycle time, and manufacturing cost. Product knowledge and process understanding gained throughout the product lifecycle can lead to the proactive changes that can result in process improvement.

Compliance is just the minimum requirement ... and won't provide any competitive edge unless it is combined with continuous improvement.

Breaking down the silos that can impede progress

Effective change management also requires breaking down the silos that can separate different departments and functions. Change management is a company-wide effort that requires effective communication and coordination among various departments. All departments that would potentially be affected by the change need to be involved in the overall change-management process.

Generally, people want to be associated with positive activities, and communication improves when people work on projects that are seen as progressive and constructive. Emphasizing the potential for process improvement resulting from the change will help improve cross-functional communication and cooperation, and help the change-management process reach its broader business goals.

Any unnecessary delays during the change-management process can have heavy compliance and business costs. It is essential to ensure that all activities and timelines are well thought out and planned in advance to prevent missed opportunities.

As the global business environment continues to become increasingly competitive, life-science companies cannot afford to be content with merely complying with regulations. Such compliance is just the cost of admission, or the minimum requirement, and compliance won't provide any competitive edge unless it is combined with continuous improvement.

Some companies are still struggling to understand the implication of FDA's risk-and-science-based lifecycle approach for adopting technical innovations, and fostering continuous improvement. However, others have started taking advantage of this change in thinking by formally incorporating the "process improvement" and "innovation through sound science" concepts into their change-management systems.

A well-conceived change-management system will take advantage of, and echo, FDA's current thinking about risk-and-science-based regulation. Embracing change, and managing it proactively and well, can help companies go well beyond compliance to continuous improvement.

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Connecting MES to Process Control

Jennifer Markarian

Integrating automated systems can improve efficiency and minimize change management.

As pharmaceutical manufacturers implement automated electronic systems, such as a manufacturing execution system (MES) and electronic batch records (EBRs), there is an increasing need to simplify communication between process systems to improve manufacturing efficiency. The International Society of Automation's (ISA) procedural model for batch automation, ISA-88 (1), is a common framework of standards that can be used to develop batch automation software. ISA-88 can act as a common language to enable people and systems to work collaboratively to implement automated batch systems. *Pharmaceutical Technology* interviewed Jonathan Lustri, life sciences industry consultant for Process Systems & Solutions at Emerson Process Management, about recent advances in using ISA-88 to coordinate MES and distributed control system (DCS) (i.e., the system that controls the processing equipment and the process) platforms.

Design standard

PharmTech: What is an ISA-88 design?

Lustri: ISA-88 is a standard for implementing batch process automation and includes a procedural model and an equipment model. The procedural model defines the hierarchy of objects used to configure batch processing logic. This model includes a master recipe, procedures, unit procedures, operations, and phases that are configured into reusable software components (i.e., class-based objects) for common actions, such as 'heat a tank.' This way, whenever a tank must be heated, regardless of the type of process involved, the code can be used without having to be revalidated.

Coordinating MES and DCS

PharmTech: What are some of the challenges in implementing MES and how do ISA-88 standards help?

Lustri: One of the challenges is the management of the ISA-88 procedural model across two different software systems. MES and DCS systems both use this model. The design, implementation, and operation of two different systems, both designed around the ISA-88 model, can be a challenge to interface and to keep coordinated and synchronized during batch execution. It can also be a challenge to decide in which system manufacturing activities should be implemented: the MES or DCS. In the pharmaceutical industry, the MES system is typically used to implement electronic batch records. The effort to transform the existing paper batch record documents into an ISA-88 procedural model and integrating this with the ISA-88 batch model (executing within the DCS) requires significant analysis. To make things more of a challenge, it can't be assumed that everything currently in the paper batch record document should be implemented within the MES.

The DCS is good at interfacing with instrumentation and values and at performing automatic sequencing and control actions. The DCS is also good at capturing data from process instrumentation. The MES performs operations management. The responsibility of the MES during manufacturing is handling material transactions and managing manual activities that must be done by operators, such as equipment preparation, taking samples, or charging materials into a vessel. These manual activities, which have traditionally been tracked by personnel with paper records, are now often performed electronically using an MES 'workflow.' An operator still physically takes a sample, for example, but the MES makes the request to the operator to take the sample and may provide instructions on where to take the sample from, print the label, and require an electronic signature. The challenge is how to coordinate the automated equipment activities controlled by the DCS and manual activities executed by the MES. For example, an operator shouldn't take a sample until the equipment cool-down phase is completed. Both MES and DCS levels use ISA-88 models for common procedural methods. For a complete system, however, both process control automation and MES workflow activity must be integrated. Another challenge is implementing the systems in a simple way that minimizes change-management requirements.

PharmTech: How can these issues be resolved?

Lustri: Opinions differ on the most rational, cost-effective way to implement both MES and DCS. Over the past few years, I have concluded that the master recipe (procedural model) should be in the DCS, and we are seeing more customers go in this direction. This approach starts with a philosophy to maximize the use of instrumentation and valves to automate the process with the DCS and minimize the manual activities to the extent practical; the MES looks after the remaining manual ac-

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tivities. The master procedural model is designed into the DCS, and the DCS is the 'quarterback', requesting the MES execute the manual transactions when they are required. The MES workflows are designed to be product and equipment independent, and the product- and equipment-specific data are passed to the MES workflow as parameters when the workflow is requested by the DCS. Once the MES workflow is completed, the MES simply waits until the DCS requests another manual workflow to be performed. The value in this strategy is to minimize or eliminate the need to coordinate between the MES workflow and the DCS batch. Defining small, activity-based workflows that only are instantiated when needed reduces or eliminates the need for this coordination.

Future advances

PharmTech: What do you foresee as changes or advances in MES and DCS in the near future?

Lustri: One advancement we see is manufacturing companies investing in improving the efficiency of technical transfer from process development to manufacturing. This transfer requires creation of new master recipes and coordination with other manufacturing information technology (IT) systems, such as lab information systems and enterprise resource planning systems. Today, a process development team typically generates a stack of paper and gives it to IT and automation to implement without regard to the impact on system configuration. In the future, we see manufacturing companies implementing standardized data models across process development and manufacturing departments to speed technical transfer. Once standardized data models are agreed to within a company, it becomes possible to implement product lifecycle management systems with data structures that can facilitate transfer from process development into manufacturing faster, with fewer errors.

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Identifying Powder Properties that Define Process Performance

Jamie Clayton

Dynamic properties provide insight into powder behavior, such as flow rate in feeders.

Improved, knowledge-led powder processing has a vital role to play in transforming manufacturing efficiency in the pharmaceutical industry. The successful commercialization of continuous manufacturing, the realization of real-time release, and the competitive development of generic drugs all rely on understanding how to optimize the handling and processing of powders. It is essential, therefore, to develop strategies and tools to supply insight into powder properties.

Powders consist of three distinct phases: solids (particles), air, and often water. Interactions between these phases give rise to the unique, industrially valuable properties that powders exhibit, but at the same time make it impractical to predict powder behavior from the properties of constituent components. Multi-faceted powder characterization has proven to be a pragmatic alternative. This approach generates a database that can be used to identify the properties that correlate most strongly with process performance.

Powder properties can be used, for example, to predict the volumetric flow rate through a screw feeder. Screw feeders are used routinely within the pharmaceutical industry to control the flow of material from one part of the process to another, typically from a feed hopper into a processing vessel. A poorly specified feeder—one that is unsuited to the powder it is handling—may deliver low or erratic powder feed rates, may block completely, or may even increase the risk of batch-to-batch contamination from powder accumulated on the walls of the feeder. The following case study shows how to identify powder properties that can be used to predict screw-feeder performance with a high degree of certainty.

Characterizing powder properties

The properties of six different powders (calcium hydroxide, maltodextrin, milk protein, cellulose, calcium citrate, and lactose) were measured with an FT4 Powder Rheometer (Freeman Technology) using methods for measuring dynamic, bulk, and shear properties (1). **Table I** summarizes the results. The dynamic properties of basic flowability energy (BFE), specific energy (SE), aeration energy (AE), and flow rate index (FRI) directly quantify how easily the powder flows under different conditions, such as when unconfined, forced to flow, or aerated. Bulk properties such as compressibility, permeability, and bulk density deliver insight into the packing behavior of particles within the powder bed and the ease with which the bed retains and releases air. Shear properties include the parameters flow function and unconfined yield strength, which relate to the cohesivity of a powder stored under consolidation and are widely used to design powder hoppers. These data are an important resource for process optimization.

Quantifying process performance

The second step in developing robust correlations for process optimization is to identify those metrics that define process performance. Factors that influence screw-feeder specification include installation constraints, process requirements, and material properties, but feed capacity is usually the primary design parameter. Being able to predict feed capacity for any given powder is therefore crucial. Design variables that can be manipulated to meet specification criteria include the size of the feeder (i.e., diameter and length) and the geometry, drive, and pitch of the auger. Feed rate may be controlled on the basis of weight (gravimetric) or volume (volumetric).

Samples of all of the powders characterized in the first stage of the study were run through two different screw-feeder models. The first was a compact, full-flight single-screw feeder (DIWE-GLD-87 VR, tube No. 3, Gericke) used for high accuracy, dry solid feeding, pilot-scale studies, and applications requiring frequent material changeover. The second was a flat-bottom, double-screw feeder (DIWE-GZD, 12x13.5mm tube with a conical core, Gericke), a self-cleaning, twin-screw extruder used for low-capacity applications and handling poorly flowing materials.

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Table I: A comprehensive database of powder properties is generated by multi-faceted powder characterization. BFE is basic flowability energy; SE is specific energy; SI is stability index; FRI is feed-rate index; AE is aerated energy; AR is aeration ratio; NAS is normalized aeration sensitivity; CE50tap is consolidated energy (50 taps); BD50tap is bulk density (50 taps); CBD is conditioned bulk density; CPS is compressibility; PD is pressure drop; UYS is unconfined yield strength; MPS is major principal stress; FF is flow function; AIF is angle of internal friction; and WFA is wall friction angle.

	Dynamic Parameters								Bulk Parameters					Shear Parameters					
Material	BFE	SE	SI	FRI	AE40	AR40	NAS	CE50tap	BD50tap	CBD	CPS%	PD@ 1 kPa	PD@ 15 kPa	UYS	MPS	FF	Cohesion	AIF, ϕ	WFA, ϕ
Calcium hydroxide	354	6.92	1.30	2.40	65	4.1	0.417	460	0.538	0.499	25.2	14.87	65.30	5.89	18.21	3.09	1.525	35.2	30.8
Maltodextrin	1282	5.19	1.11	1.16	13	107.3	0.156	1341	0.608	0.557	7.1	0.51	0.54	0.88	16.42	18.57	0.221	36.9	27.4
Milk protein	330	8.49	0.91	1.37	102	3.3	0.182	613	0.311	0.267	24.3	3.07	9.06	3.96	20.71	5.23	1.091	32.3	24.6
Cellulose	630	8.92	0.87	1.34	19	46.0	0.619	4124	0.376	0.327	22.2	2.75	3.97	6.68	22.06	3.30	1.579	39.4	17.5
Calcium citrate	680	12.50	1.07	1.40	225	3.0	0.077	914	0.261	0.234	41.6	1.02	37.82	8.14	22.59	2.78	1.877	40.5	41.0

Table II shows the volumetric flow rate delivered by each feeder, operated at an auger rotation speed equivalent to 80 Hz. Volumetric flow rate (in L/hr) was calculated from measurements of mass flow rate (in kg/hr) and poured density. Performance of the feeder varies significantly as a result of the differing properties of the materials.

Table II: Volumetric flow rates of powders through a single-screw feeder (GLD) and a double-screw feeder (GZD) show that flow rate is dependent on equipment design and the properties of the material being handled.

Material	GLD in L/hr	GZD in L/hr
Calcium hydroxide	185.2	33.02
Maltodextrin	138.9	29.88
Milk protein	128.7	18.67
Cellulose	115.8	34.98
Calcium citrate	50.13	10.39

Producing a robust correlation

Performing a multiple linear regression using both sets of measured data reveals correlations between individual powder properties and the volumetric flow rate from the feeder. In basic terms, this mathematical process quantifies the probability that any specific parameter is making a statistically significant contribution to a developing correlation. The smaller the p value, the more likely it is that an independent x variable (in this case a powder property) is influencing the dependent y parameter (volumetric flow rate through the feeder).

For this study, a p value of 0.1 was taken as the upper limit for relevance, and parameters with p values higher than this were eliminated to derive a robust relationship. Data for five of the powders were included in the linear regression exercise, leaving the lactose data available for testing the predictive powers of the developed model.

For the single-screw feeder, this analysis generated the following relationship, where FRI is flow rate index and SE is specific energy:

$$\text{Feed Rate} = 49.54\ \text{FRI} - 13.81\ \text{SE} + 163.8$$

For the double screw feeder, the observed relationship was as follows, where AE is aerated energy:

$$\text{Feed Rate} = -0.1114\ \text{AE40} + 34.82$$

Both of these models are statistically robust, as indicated by the R^2 values (0.9466 and 0.8383, respectively), which quantify the 'goodness of fit' between the model and the data. Furthermore, both are relatively simple in terms of the number of the powder properties that are found to be of significance. For the single-screw feeder, two dynamic properties (FRI and SE) are needed to robustly predict feeder performance, while for the double screw feeder, only AE is considered to be statistically significant.

The parameter SE reflects the flow characteristics of a powder in an unconfined state, while FRI describes whether a powder's resistance to flow increases or decreases as it is induced to flow at a higher or lower rate. Incidentally, all the powders assessed in this study generated an FRI above 1, indicating that they offer less resistance to flow as the rate of flow increases.

AE is a parameter that directly quantifies how a powder flows when aerated. With a cohesive powder, aeration does little to reduce resistance to flow, but for a free-flowing powder, AE can become very low as the powder fluidizes. The materials tested in this study exhibit a relatively broad range of AE values, but

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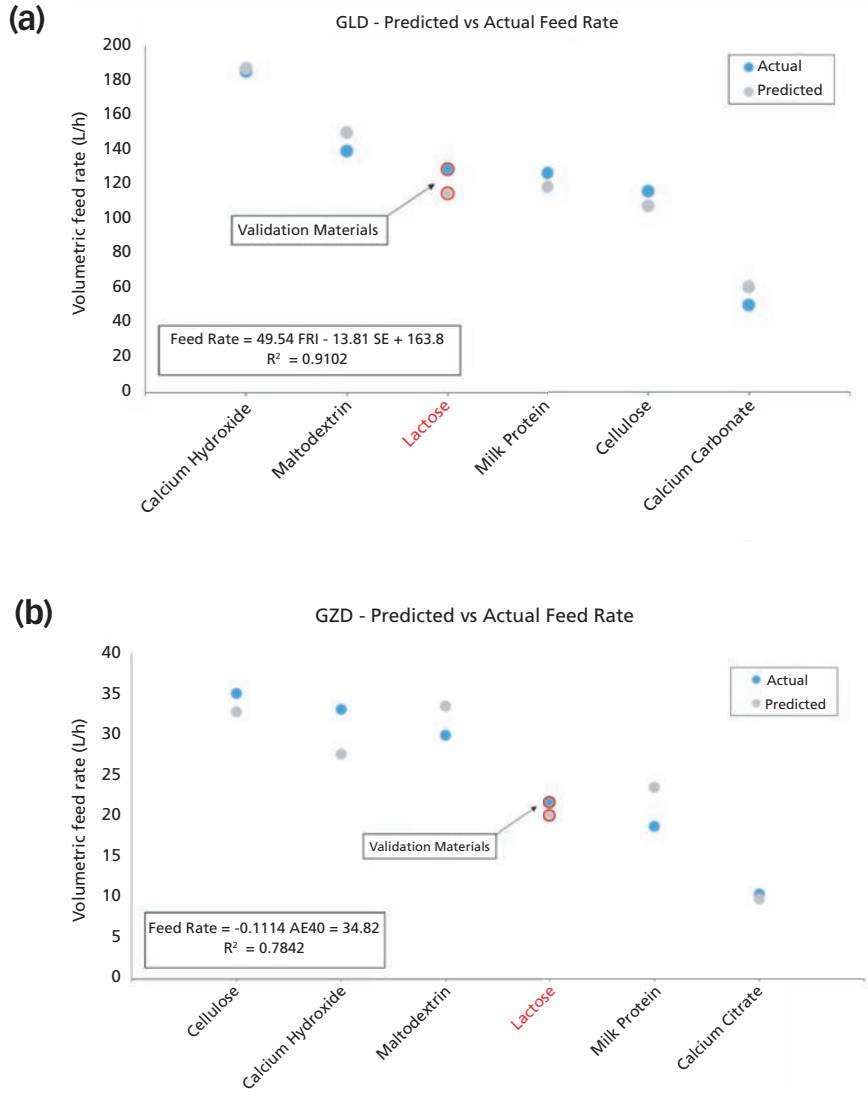
Figure 1: Robust correlations enable the prediction of volumetric feeder flow rate from measurable powder properties for (a) the single-screw feeder (GLD) and (b) double-screw feeder (GZD). FRI is feed-rate index; SE is specific energy; AE is aerated energy; R^2 is a measure of the fit of the data to the model.



a robust relationship between AE and volumetric flow rate for the double-screw feeder holds for all materials.

In addition to the fact that the derived correlations are relatively simple, it is also interesting to note that both contain only dynamic powder properties, which indicates that dynamic powder properties are more relevant to behavior in this particular process than any of the measured shear and bulk properties. An analogous study employing more traditional testing techniques, such as tapped density methods (Carr's Index/Hausner Ratio) or shear cell analysis, would have failed to produce a robust correlation for process optimization studies.

Testing the model

To challenge the reliability of the derived models, the equations were used to predict the performance of lactose from its measured properties. **Figure 1** shows that the models predict feeder performance well, with revised R^2 values showing little deviation from those of the initially developed correlations.

These results demonstrate the value of the outlined strategy for producing robust correlations to support equipment selection, optimization, and troubleshooting. They also illustrate the importance of a multi-faceted approach to powder testing and the need to incorporate dynamic powder testing. In these examples, different powder properties proved most relevant for the prediction of performance in different feeders, but in both cases, dynamic powder properties were of most value.

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Parenteral Packaging Advances

Hallie Forcinio

Manufacturers of parenteral drugs face challenges to increase efficiency, control particulates, and eliminate product/package interactions.

Manufacturers of parenteral drugs face many challenges, particularly in light of the expanding population of more sensitive biopharmaceuticals. With smaller batch sizes and a need to control particulates and extractables and leachables, the industry is seeking more flexible equipment and new material options.

Due to their biological foundation, biopharmaceuticals tend to be fragile and susceptible to product/package interactions. To eliminate negative interactions, materials must be carefully sourced and tested.

With biologics, assumptions made about materials may not be valid. "Things we assume are safe, may not necessarily be safe," says Andy Polywacz, vice-president of quality and regulatory affairs at West Pharmaceutical Services, a supplier of components and systems for injectable drug delivery. He explains, "Every molecule is different. Sterilization has an impact on formula shelf life and extractables. The effect of gamma and steam [sterilization] could be different. The design of the container/closure needs to be assessed. A standard plunger may not be suitable. The historical design may not work in a new delivery system." As a result, there's strong interest in materials and components that deliver a lower extractables and leachables profile.

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Material options

In containers, cyclic olefin copolymer (COC) is receiving a lot of attention due to its inert nature and glass-like transparency. Christopher Cassidy, vice-president of sales and marketing, North America, at Schott, a supplier of glass and polymeric parenteral packaging, says the polymeric packaging is break-resistant, withstands higher-force syringes, doesn't darken when exposed to gamma sterilization, and is easier to form for custom designs and larger syringes with volumes more than 10 mL.

COC is the basis for the Schott TopPac SD prefillable syringe system. Designed to ensure stability of sensitive drugs and compress time to market, careful component selection and processing minimize extractables and leachables. COC barrels release no ions or heavy metals and reduce chances of a chemical interaction with sensitive drugs. Pure elastomer components and steam sterilization of plungers also help minimize extractables and leachables. For the same reason, ethylene oxide sterilization is used rather than gamma for the barrel and tip cap. In addition, cross-linked silicone significantly reduces sub-visible particles while retaining lubrication performance. Fully integrated cleanroom production results in syringes with low particles and low contamination. Other TopPac SD syringe advantages include standard tub and nest offering and integrated luer lock. It's also compatible with needleless intravenous connectors (1).

For enhanced protection of the drug product, Clariant's Masterbatches unit supplies Mevopur ultraviolet (UV) filters and absorbers for COC resin. The material blocks product-degrading UV light and is available in a range of colors. To make the transition to COC easier, Clariant has completed extractables and leachables testing.

To limit interaction with proteins and elastomeric stoppers, Aptar Stelmi applies a thin fluoropolymer coating. The PremiumCoat stopper provides a barrier to extractables and leachables that can be released from the elastomer and contaminate the drug. Produced in 13-mm and 20-mm diameters, the PremiumCoat stopper is available worldwide. Target applications include cytotoxic drugs used in cancer therapies, novel vaccines, blood derivatives, hormones, and compounds used to treat auto-immune diseases, including monoclonal antibodies (2).

Particulate control is important too, because particulate contamination continues to be the reason behind many recalls. A new syringe line installed by Nipro in Germany laser-cuts tubular glass to minimize particulate generation. In addition, Nipro has installed 100% (rather than random) siliconization inspection. Toward the end of the line, an x-ray inspection captures two images of each syringe to confirm the needle is not bent or piercing the shield.

Attention to particulate generation from the beginning of the supply chain is essential. The further back in the supply chain particulate generation occurs, the greater the number of finished products likely to be affected. With needs outpac-

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ing legacy capability, "investments in equipment need to be made," says Jennifer Riter, senior director of global analytical services at West Pharmaceutical Services. West's ready-to-sterilize products come with a particulate guarantee based on particle size, so manufacturers can determine how it will affect their process.

When controlling particulates, parenteral product manufacturers must consider whether they removed or added any particulates during the manufacturing process. In addition, manufacturers must choose automated or manual particle counting. Manual counting has advantages because the eye can identify hard-to-distinguish particles from materials such as polyethylene and elastomer or the product itself. "Automation has to have the right hardware and software," says Riter.

Ready-to-fill lines

Exhibitors at INTERPHEX (April 21–23, 2015 in New York, NY) featured ready-to-fill (or ready-to-use) vials, cartridges, and/or syringes in nests, or machines designed to handle this format. Although ready-to-fill syringes have been available for some time, ready-to-fill vials are just beginning to come on the market. Prefilled syringes answer the need for easier administration, in some cases enabling self-administration. Cost is also a driver in the transition to prefilled syringes, according to Steve Hourmezian, West Coast sales manager at Nipro Glass Americas, a global maker of ampules, vials, syringes, cartridges, and specialty products. "Prefilled syringes offer longer shelf life and less handling at point of administration," he explains.

Handling vials in nests and trays prevents glass-to-glass contact, glass-to-machine contact, scratches, and potential breakage better than traditional bulk packaging or shrink-film bricks. Minimizing contact not only reduces reject rates, but also preserves the cosmetic quality of the containers.

Ready-to-fill containers offer the potential for cost savings due to increased flexibility and reductions in equipment, labor, and turnaround time. Because arriving containers are clean, sterile, and depyrogenated, the end user doesn't need washing equipment, water-for-injection systems, or depyrogenation tunnels along with related labor and floor space. In addition, eliminating these steps saves time and reduces validation and maintenance requirements. Less handling also reduces particle generation and lowers the risk of stops and downtime.

Now available from several sources, ready-to-fill options include ez-fill vials, cartridges, and syringes from Ompi. Vials may be ordered in a variety of diameters, heights, and crimp finishes and can be delivered in nest and tub or tray/light-tray packaging. The 3-mL ez-fill cartridges can be supplied capped or uncapped in a nest and tub (3). The ez-fill syringe range includes a glass option for more sensitive products, a choice of staked needle or luer, as well as a variety of sizes and closure styles. Needle sizes range from 22 to 29 G with lengths from 0.5 to 1 in. Plunger options include ready-to-sterilize, pre-sterilized, or coated plungers (4).

The Dara SFL syringe filling and plugging machine from NJM Packaging handles nested glass or plastic syringes or vials, operates with several filling and barrier options, and can be configured for duplex operation.

IMAGE IS COURTESY OF NJM PACKAGING.

Schott also offers ready-to-fill syringes and vials. Its adaptiQ vials are especially well suited to clinical trials and smaller batch sizes and are being qualified by several customers. A patented nest securely holds up to 100 clean and sterile vials in an industry-standard tub. "Many pharmaceutical manufacturers aren't set up to wash and sterilize smaller volumes," explains Christopher Cassidy, Schott's vice-president Sales and Marketing, North America. Available in 2-, 4-, 6-, 8-, 10-, 15-, 20-, 25-, and 30-mL sizes, the ready-to-fill adaptiQ containers also offer benefits to contract packagers by allowing them to focus on the product rather than setup and validation of washing and sterilizing operations.

Although prefilled syringe lines may be able to handle nests of vials, transitioning to ready-to-fill vials could require new filling and closing equipment. There are several flexible machines available to handle trayed or nested containers. Equipment for ready-to-fill parenteral packaging tends to be modular. For example, the compact 72 x 36 in. (183 x 91 cm) Dara SFL syringe filling and plugging machine from NJM Packaging can be equipped with an isolation barrier or restricted access barrier (RAB). Capable of handling glass or plastic, filling options include a peristaltic pump or valveless rotary piston pump. Fill volumes range from 0.5 to 20 mL for syringes and 0.5 to 50 mL for vials. Operators load and remove nests or trays of syringes or vials at entrance and exit passboxes. Filling and closing occurs at up to 35 units per min. on a 1-mL fill. For higher speed requirements, a duplex unit handles up to 80 units per min. Changeover is recipe-driven, requires no tools, and takes less than 10 minutes. An easy-to-use operator interface simplifies input parameters for handling a different package type and/or size with a different tray configuration. A one-head system can be converted to a two-head system in the field as volume grows. Options include a clean-in-place system, a sterilize-in-place system, and gas flushing (5).

The intermittent-motion Optima H4 filling and closing machine handles nested syringes, vials, and cartridges at a rate of up to 600 per min. The modular system can be equipped with time pressure, rotary piston, or peristaltic pumps and is easily upgraded as needs change. Retrofitting vacuum filling and stopper insertion as well as in-process controls is an option. The system displayed at INTERPHEX featured an open RAB containment system, but a closed RAB system or isolator also could be installed. During operation, when the tub arrives from the debagger, the Tyvek removal robot pulls the lid off and puts it in a bin. The open tub indexes, and the nest is lifted out and placed in frame for filling and stoppering. Ten vials are filled at a time. Fills range from 0.5 mL to 20 mL for syringes and up to 50 mL for vials. Cartridge fills measure 3 mL. After stoppering, the nest is replaced in the tub, and it moves on for plunger insertion, labeling, and other post-filling operations (6).

Handling nests of containers for parenteral products often depends on a robot. In fact, "Robot filling is a major trend," reports Biljana Medic Taddei, sales engineer at Vanrx Pharmasystems. Robots also load and unload the company's lyophilizer interface. The series of workcells transfer nested vials from a Vanrx SA25 aseptic filling workcell to a freeze-dryer. The digitally driven, bridgeless loading system requires no conveyors or gloves and starts up with the push of a button.

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SVETA DEMIDOFF/GETTY IMAGES

Small-Molecule API CMOs are Thriving

Jim Miller

Despite emergence of biologics, small-molecule APIs benefit from industry growth.

It has been the general consensus among bio/pharmaceutical industry participants, investors, and observers that small-molecule drugs are becoming obsolete as the industry focuses on biologics. To paraphrase what Mark Twain allegedly said about his own situation, reports of the death of small-molecule drugs are greatly exaggerated.

Small-molecule pharmaceuticals accounted for 82% of all new drug application (NDA) approvals in 2014 and 60% of all new molecular entities. Further, they represent two-thirds of the drug-development pipeline. While there can be no doubt that the number and share of large-molecule therapeutics is increasing, small-molecule drugs are an important and highly effective component of the bio/pharmaceutical portfolio. Many of the most important drugs introduced in recent years, including kinase inhibitors such as Gleevec and anti-retroviral products such as Sovaldi, are small molecules.

Small molecules have some considerable advantages over large molecules. They can be engineered to deliver a strong therapeutic effect with a small dose, often below 10 mgs and even into micrograms. The smaller amounts of API, combined with the maturity of chemical manufacturing technology, typically translate into a lower cost of goods relative to efficacy versus large-molecule therapeutics. Analytical technology for small molecules is highly refined, ensuring quality, efficacy, and reproducibility.

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Certain segments appear to be especially strong, notably controlled drugs and highly potent APIs.

Further, small molecules can be formulated into orally delivered dose forms, which offer better compliance and a lower cost of administration than injectables, the principal delivery route for large molecules. There is a vast amount of formulation expertise and experience with small-molecule drugs, enabling highly controlled formulations that can be delivered to specific sites and released over specific time periods.

Clinical trials involving small-molecule therapeutics are often simpler and less expensive than those involving large-molecule drugs. Process development and manufacture of clinical-trial materials for small molecules are typically much less expensive for small-molecule candidates. Clinical supplies for small molecules must be handled carefully, but they often don't require the cold chain assurance of large molecules, which makes shipment and storage of clinical supplies costly. Further, procuring comparators for biopharmaceutical candidates (i.e., drugs already on the market) can be extremely expensive.

Outstanding performance

Small-molecule therapeutics have participated fully in the explosion of drug development activity of the past few years, which has been fueled by record amounts of fundraising and spending for research and development. Contract manufacturing revenues of publicly-traded "pure-play" small-molecule contract manufacturing organizations (CMOs) grew 15% in the first half of 2015, with some companies enjoying growth in excess of 20% (see **Figure 1**).

Within the small-molecule API world, certain segments appear to be especially strong, notably controlled drugs and highly potent APIs (i.e., cytotoxics, hormones, and very low-dose compounds). These products require specialized facilities that protect operators from exposure to the chemical and, as with controlled drugs, may have to meet special regulatory requirements.

Demand for capacity to manufacture high-potency products has been so strong that CMOs with the capability have been expanding it while those lacking the capability have been adding it. CMOs that have recently completed or announced expansions include SAFC, Johnson-Matthey, Cambrex, Carbogen-Amcis, and Novasep.

On Sept. 1, 2015, Fareva (Luxembourg) announced that it is acquiring an API manufacturing site in La Vallée, France from Merck and will invest €25 million

Calibration and Qualification of Laboratory Instruments

in Accordance with GMP Requirements

ON-DEMAND WEBCAST

Originally aired Tuesday, October 6, 2015

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EVENT OVERVIEW:

Calibration is relevant to everyone. Even the most precise measurement instrument is of little or no use if you cannot guarantee that the reading is accurate, or you are unaware of the measurement uncertainty. The US GMP rule for pharmaceutical manufacturing, 21 CFR Part 211, article 68(a) provides details on calibration of measuring equipment. Similar statements can be found in other regulatory or guidance documents, such as ISO9001, which emphazises the traceability to international or national measurement standards. The challenge is to determine how to put these regulations into practice—to be confident that you comply with the requirements without an excessive amount of effort—but without compromising product quality.

Key Learning Objectives:

- Learn how to achieve effective calibration, including determination of measurement uncertainty, in accordance with GMP and USP requirements.
- Understand the roles and responsibilities of different parties with regards to qualification processes (EQ/IQ/OQ/PQ).
- Recognize the impact of risk-based routine testing on the quality, efficiency and cost-optimization of laboratory weighing processes.

This 60-minute webinar will educate participants on all aspects of calibration, verification, and routine testing necessary to ensure quality and USP and GLP/GMP compliance, with a focus on laboratory weighing instruments. Instrument qualification responsibilities (EQ/IQ/OQ/PQ—equipment qualification, installation qualification, operational qualification and performance qualification) and their relation to standard operating procedures will also be discussed.

Presenters:

ED SZCZESNY
Senior Quality Specialist
Rhodes Pharmaceuticals

IAN CIESNIEWSKI, PhD.
Technical Director, Laboratory Weighing
Mettler Toledo Inc.

Moderator:

Rita Peters
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Pharmaceutical Technology

Who Should Attend:

- Anyone involved with qualification, testing and calibration of instruments in a GMP regulated laboratory
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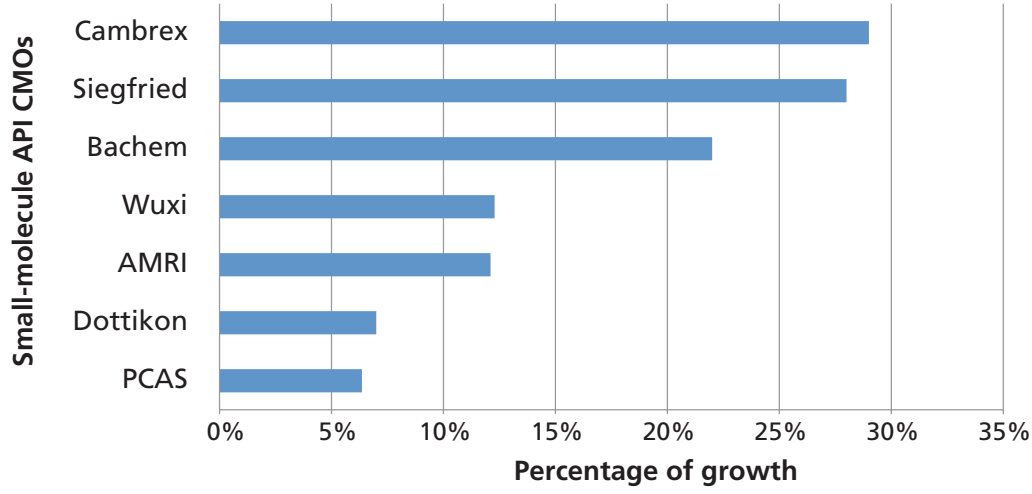
Figure 1: Growth in custom manufacturing revenues of small-molecule API contract manufacturing organizations (CMOs) in the first half of 2015.



($28.3 million) to build two units at the site with occupational exposure band 4 (OEB 4) containment. Fareva already has high-containment API manufacturing capability at its facility in Feucht, Germany, but needs to expand its capacity to meet market demand.

M&A activity

Further speaking to the attractiveness of the small-molecule API space has been acquisition activity. There have been a number of significant deals with prices equating to multiples of two or more times the acquired company's revenues.

In March 2015, Patheon acquired Irix (Florence, SC), a mid-size API manufacturer with development and commercial capabilities. The acquisition added small-molecule capabilities to Patheon's offerings in large-molecule API and dosage forms. In July 2015, AMRI announced it would acquire Gadea Pharmaceutical Group (Valladolid, Spain), a specialist in hormone and steroid APIs. That followed its 2014 acquisition of Cedarburg Laboratories (Grafton, WI), which has controlled and high-potency drug capabilities. Also, Siegfried (Zofingen, Switzerland) announced in May 2015 that it will acquire the API business of BASF, giving it three additional manufacturing sites and considerable greater scale and presence in the industry.

The level of business, acquisition, and capital investment activity in the small-molecule API market shows that the industry is taking full advantage of all of the technologies in its tool box to address the opportunities being revealed by the increased understanding of disease processes. New therapies like antibody drug conjugates are marrying the specific capabilities of large and small molecules to delivery highly effective drugs to specific sites, and the technology is expanding beyond its initial focus on delivering cytotoxic compounds to broader applications.

In times like these, when investment activity reaches frenzied levels, investors and executives can be distracted by fads or the latest technologies no matter how untested they might be. Small-molecule APIs have performed well and cost effectively for patients and pharmaceutical companies for decades and there is every reason to believe that small-molecule API CMOs will participate in the bio/pharmaceutical industry's success for decades to come. **PT**

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The Role of Semisolid Microstructure in Topical Formulation Performance and Functionality

Norman Richardson, Global Technical Development and Marketing Manager, Skin Delivery at BASF

Dr. Bozena Michniak-Kohn, Professor and Director of Center for Dermal Research at Rutgers University

BASF explains how the selection of excipients in topical semisolid formulations can determine the structure of microscopic phases that form during processing.

Semi-solid formulations are in a non-equilibrium state composed of numerous possible microstructures. Microstructure is critical in product performance and may be determined by the choice of excipients. Microstructure semisolid formulations are of great interest to global regulatory authorities because the performance of topical products, particularly bioavailability, is governed not only by the list of ingredients and the respective amounts, but by the resulting microstructure.

Pharmaceutical Technology magazine recently spoke with Dr. Bozena Michniak-Kohn, Professor and Director of Center for Dermal Research at Rutgers University, and Norman Richardson, Global Technical Development and Marketing Manager, Skin Delivery at BASF, about the importance of semisolid microstructure and the impact they have on the final formulation.

Pharm Tech: Can you explain why this topic is important and worthy of consideration by the dermatological industry?

Norman Richardson: Medicated semi-solid formulations like creams, lotions, gels, and ointments are very complex. One can see this just by looking at the list of inactive ingredients on the package; it's not uncommon for a topical cream to have 10, 20 or even more ingredients. The ingredients typically can include oils, waxy solids, emulsifiers, polymers, solvents, and fluid humectants. On the other hand, oral dosage forms like tablets or injectables and parenterals only have around five ingredients.

Pharm Tech: Why do topicals have so many ingredients?

Bozena Michniak-Kohn: The purpose of semisolid formulations is to transfer an active, from the package to the skin surface, and then to spread it in such a way that it would remain at a particular location and deliver its active to the skin. All topical formulations have to be designed to meet certain basic performance criteria. For example, all topical semisolid formulations must have enough rigidity or viscosity so that they can be squeezed or extruded onto the skin from the bottle or tube and then spread easily onto the treatment site.

So the formulator must design for specific rheological properties and these properties can also maintain the homogeneity of the dispersed active in the product, so that every dosing from the package has the same concentration of the active during the entire shelf life of the product.

For efficacy, it's most important that the drug in the formulation is released from the formulation and then gets to a specific location or compartment in the skin where it's going to exert its effect. Many of these criteria are driven and influenced by what is known as the microstructure of the semisolid formulation that results from the interaction of the ingredients.

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Pharm Tech: Please describe the complexities of topical products as a result of excipients.

Norman Richardson: In fact, these products are composed of many different structures that result from the complexation and the self-assembly of the many ingredients. Mixing oils and waxes, emulsifiers, and water can result in a multitude of different micron or nano-scale structures such as micelles, emulsion droplets, lamellar structures, liquid crystalline phases, crystals, gel phases, and others. If you look at a thin film of cream under the microscope, you can see many features that are a result of these microstructures crowded together. These structures can be identified through cross-polarized microscopy or by other analytical methods.

Furthermore, if you compare two different semisolid products under the microscope, you'll see that they do not look the same. Different compositions yield different combinations of colloid microstructures. The choice of ingredients and the amount of each ingredient can influence the microstructure. The mixtures and microstructures are always the same when you have the same combination of water, oil and emulsifier. And formulators and regulators are discovering that it is this combination of microstructures that influences the performance and the efficacy of topical semisolid formulations.

The physical properties of an excipient—melting point, the molecular weight, the alkyl chain length—can impact microstructure.

Pharm Tech: How much does excipient selection influence the property of this microstructure?

Norman Richardson: The physical properties of an excipient—melting point, the molecular weight, the alkyl chain length—can impact microstructure. We assume also that the purity of the excipient can have an impact. For pharmaceutical excipients the compendium monograph sets the limits on purity. However, if the limit is not less than 90% and you are meeting that criteria of 91%, then there is still 9% of whatever that remains. That 9% is not controlled and can vary.

Also excipients can be derived from plant, animal, petroleum, microbial or purely synthetic sources. The origins and processing of the excipient will have an influence on the residuals and could therefore have an impact on microstructure and product performance.

Pharm Tech: Have you made any observations about how microstructure can affect topical drug delivery?

Bozena Michniak-Kohn: To achieve efficacy, there are two things that have to occur: the drug molecule has to come out of the formulation to be available for biological activity, and it must get into and through the skin to the location where it's going to have its effect.

Consider a lipophilic drug in a cream formulation. Cream formulations usually contain waxes and solid lipophiles that can mix with emulsifiers and water to create hydrophobic domains in the water's continuous micro-structural milieu. A lipophilic drug may solubilize into the hydrophobic domains or may perhaps intercalate into the lamellar structures. When applied to the skin, the water will evaporate and the lipophilic drug may remain in the resulting film or lipophilic phases and crystals on the skin's surface. If solubilized, there may be little chemical potential to drive that drug from the product film. In this case, the preferred alternative formulation could be a gelled emulsion, where the drug is solubilized at a high concentration in an oil and then stably dispersed in a gelled aqueous continuous phase.

Microstructure can also influence drug retention in the skin after application. Consider a petrolatum-based topical antibiotic ointment. The microstructure is composed of higher melting point paraffinic hydrocarbon crystals that are suspended in a lower melting point paraffinic oil. Those crystals are tightly packed together, giving the petrolatum stiffness or consistency. The crystals can easily break and move so that the ointment has a soft and lubricious sensory character. Once spread, the ointment has sufficient viscosity or rigidity to stay in place and doesn't flow away, and also has the ability of flowing into and mixing with the lamellar lipids of the stratum corneum. The APIs are held in place to prevent microbial colonization and infection, and the thickened oil film creates a physical barrier. If the patient finds that the greasy after-feel is unpleasant then they may opt to use an antibiotic cream instead. And, the less greasy sensation results from a microstructure based on a water-continuous emulsion that has consistency resulting from extensive swollen lipophilic networks or liquid crystalline phases that form from the mixture of the fatty acids and the emulsifier.

So you can see from just these two examples that the microstructure can influence product performance. And hopefully you also see the value of characterizing and understanding the microstructure of the products that you are designing or replicating.

Impel and 3M Partner to Advance Olfactory Drug Delivery

3M Drug Delivery Systems (3M) and Impel NeuroPharma Inc (Impel) formed a strategic alliance to advance Impel's Precision Olfactory Delivery (POD) technology for the enhanced central nervous system (CNS) delivery of drug products, the companies announced in an Oct. 5, 2015 press release.

The alliance with 3M will enable Impel to expedite the development and commercialization of the POD technology and accelerate Impel's internal pipeline into late-stage clinical trials and subsequent global regulatory submissions. As part of the deal, 3M and Impel will collaborate on programs directed to the continued development and commercialization of POD technology. The alliance will leverage 3M's experience with inhaled and nasal drug-delivery devices.

Impel's POD technology deposits drugs deep into the upper nasal cavity where it can achieve delivery into the brain and central nervous system. POD is a handheld, cost-effective, non-invasive means for delivering CNS therapeutics that can be self-administered by a patient, caregiver, physician, or even family member. POD technology has been shown to be effective across diverse therapeutic areas including Alzheimer's disease, migraine, and pain management, noted the press release.

Merck Millipore Adds Protein Pegylation Services

Merck Millipore, the life-science business of Merck, announced a collaboration with celares GmbH to provide pegylation services to customers developing protein-based therapeutics and biosimilars. The service includes feasibility studies, process and analytical development, and scale-up from milligram to gram quantities for pilot and subsequent commercial scale.

The services will leverage EMD Millipore's functionalized PEG products of different molecular weight and activation chemistry, buffers, solvents and excipients, and unit operations employed during the pegylation process and subsequent purification including tangential and normal flow filtration and chromatography.

BASF Closes Sale of Custom Synthesis Business

BASF announced on Oct. 1, 2015 that the company had completed the sale of its pharma custom synthesis business and parts of its APIs business to Siegfried Holding AG.

Effective Oct. 1, Siegfried Holding AG assumed operational management of the businesses; approximately 850 employees will transfer to Siegfried as part of the transaction.

BASF will provide transitional services until late 2016, including sales and distribution of the divested API portfolio as non-exclusive distributor for Siegfried, BASF reports. The pharma custom synthesis business has been transferred in its entirety to Siegfried.

Vetter Embarks on 300-Million Euro Manufacturing Expansion

Vetter will invest approximately 300 million Euros (US$335 million) to expand and upgrade its manufacturing facilities over an estimated five-year period, the company announced on Sept. 30, 2015. The upgrades are being driven by a changing healthcare market that is affected by issues such as increasingly complex molecules, smaller batch sizes, and more stringent regulatory requirements. Expansion of three sites in Germany will add capacity for logistic services and drug-product manufacturing using an improved system for aseptic processing.

Structural work for the facility enlargement at the Ravensburg Vetter West Center for Visual Inspection and Logistics has been completed. The expansion will more than double this site's current capacity and is on schedule to become fully operational in 2017. Initial construction at the Ravensburg Schuetzenstrasse facility began in 2013, and the Ravensburg Vetter South production site will be expanded.

A central technology element of the planned upgrades will be the implementation of an in-house, improved restricted access barrier system (RABS) concept that will contribute to increased operational excellence in aseptic manufacturing. For decades, Vetter has relied on RABS and isolators as two distinct technologies available today for its aseptic filling processes. RABS achieve the sterility assurance level required by regulatory authorities and allows rapid product changeover coupled with high safety. To better meet future industry trends in quality, safety, and flexibility, a corporate project team has evolved an improved RABS concept by combining the advantages of isolator and RABS technology. The core of the approach is a uniquely fast (by today's standards) three-hour cycle and fa function which allows full automated decontamination of the cleanroom using hydrogen peroxide. Following a successful pilot project in a selected cleanroom, the company will implement this decontamination concept in all of its cleanrooms within the next few years.

Hovione Expands Drug Substance Manufacturing

Hovione is expanding its facility in New Jersey as part of the company's strategy to increase its global development and commercial capacity, the company announced on Sept. 29, 2015. The expansion will add an additional 30,600 ft^2 (2843 m^2) to the 24,000 ft^2 (2211m^2) facility. It will introduce a new commercial spray dryer unit to complement an existing pilot unit, and this installation will be specifically designed to handle potent drug substances (APIs). With this new equipment, Hovione will offer commercial-scale spray drying in Portugal, Ireland, and the US. In addition, the expansion will more than double the drug substance capacity at the site to support the needs of the current and future customer base.

The official ground breaking should occur in the first quarter of 2016 and the doubling of capacity is expected to be fully operational in early 2017. The expansion is expected to add approximately 60 new jobs to the current workforce.

Establishing a Risk Management Plan for Compliance and Pharmacovigilance

ON-DEMAND WEBCAST Originally aired September 23, 2015

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

EVENT OVERVIEW:

Risk Management Plans have become a cornerstone in the pharmacovigilance of new drugs. It was introduced to support a proactive approach in gaining knowledge on safety concerns through early planning of pharmacovigilance activities. In this webinar, EtQ and HighPoint Solutions will cover the regulations around the European Medicines Agency's (EMA) Risk Management Plan and also the Food and Drug Association's (FDA) Risk Evaluation and Mitigation Strategy (REMS). We will also look into the industry and company challenges related to these processes. Finally, we will discuss the current and future states of risk management to show how companies can consolidate their risk management plan, safety concerns and regulatory actions into a single place.

Key Learning Objectives:

- Understanding the regulatory view on Risk Management Plans in EU and US.
- Review the concepts of Risk Management and Pharmacovigilance.
- Provide insight into how to consolidate risk management plans into a single, holistic solution.
- Examine the technology and solutions available to build and update RMPs to ultimately improve quality and consistency.

For questions contact Sara Barschdorf at sbarschdorf@advanstar.com

Presenters:

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Life Science Product Manager,
EtQ

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Vice-President,
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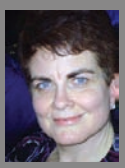
High Point Solutions



Moderator:

AGNES SHANLEY
Senior Editor
Pharmaceutical Technology

Who Should Attend:

- Pharmaceutical and Biotech professionals involved in creating Risk Management Plans for their company.

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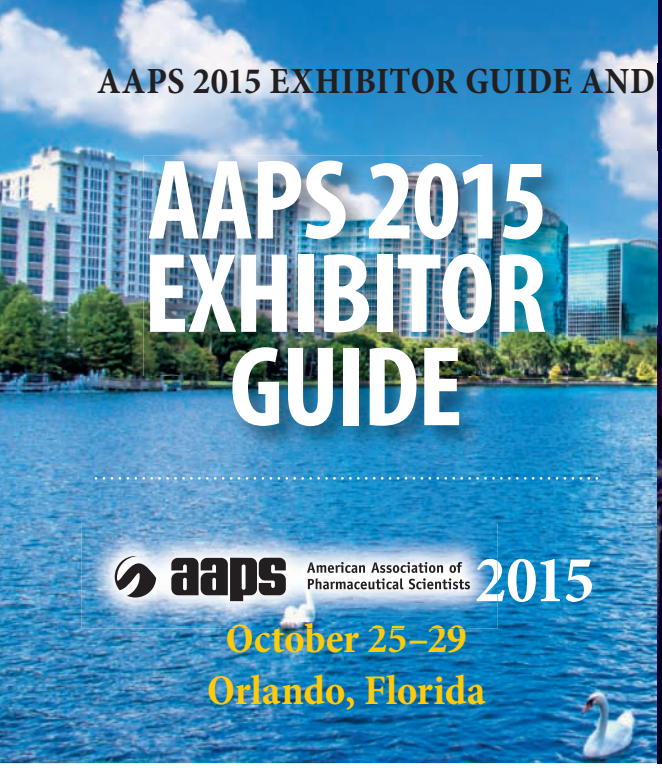

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Twin Screw Wet Granulation for Solubility Enhancement of Poorly Water-Soluble Drugs

ON-DEMAND WEBCAST Originally aired September 9, 2015

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

EVENT OVERVIEW:

Poorly-soluble APIs present formulation and development challenges. Excipient selection and manufacturing process development are crucial. Continuous twin-screw granulation is gaining acceptance as a manufacturing technology to address issues presented by these APIs and offers high production capacity in a small footprint.

This reviews a study of the use of Soluplus as binder and matrix to generate granules. Poorly soluble drugs were investigated for solubility enhancement and good performance was found; the produced granules show approximately 80% of the dissolution performance under non-sink conditions versus amorphous solid dispersions of same drug-polymer ratio. The produced granules show a better benefit-risk ratio than amorphous solid dispersions and can to be a very attractive alternative to melt-extruded solid dispersions.

PRESENTERS

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BASF

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions contact Sara Barschdorf at sbarschdorf@advanstar.com

Key Learning Objectives

- Learn how to improve the solubility of poorly water-soluble active ingredient using twin-screw wet granulation and proper excipients.
- Achieve the right solubility improvement using simple, continuous processing technology.

Who Should Attend

- This webcast targets all formulators tasked to improve the solubility and consequently bioavailability of active ingredients, especially if a simple processing and continuous processing is preferred.

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1. **Publication Title:** Pharmaceutical Technology
2. **Publication Number:** 1543-2521
3. **Filing Date:** 9/30/15
4. **Issue Frequency:** Monthly, except two issues in June
5. **Number of Issues Published Annually:** 13
6. **Annual Subscription Price (if any):** $76.00
7. **Complete Mailing Address of Known Office of Publication:** 131 West First Street, Duluth, St. Louis County, Minnesota 55802-2065
   Contact Person: Rochelle Ballou
   Telephone: 218-740-7005
8. **Complete Mailing Address of Headquarters or General Business Office of Publisher:**
   2450 Colorado Avenue, Suite 300, Santa Monica, CA 90404
9. **Full Names and Complete Mailing Addresses of**
   Publisher: Mike Tracey, 485F US Hwy 1S, Suite 210, Iselin, NJ 08830
   Editorial Director: Rita Peters, 485F US Hwy 1S, Suite 210, Iselin, NJ 08830
   Managing Editor: Susan Haigney, 485F US Hwy 1S, Suite 210, Iselin, NJ 08830
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11. **Known Bondholders, Mortgages, and Other Security Holders Owning or Holding 1 Percent or More of Total Amounts of Bonds, Mortgages, or Other Securities. If none, check box.** → ☑ None
12. **Does Not Apply**
13. **Publication Title:** Pharmaceutical Technology
14. **Issue Date for Circulation Data Below:** August 2015
15. **Extent and Nature of Circulation**

	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
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F. Total Distribution (Sum of 15c and e)	27,137	26,887
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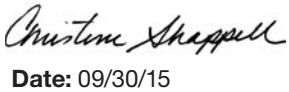

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Investigating Biologics


Susan Schniepp, distinguished fellow, and Andrew Harrison, chief regulatory affairs officer and general counsel, both of Regulatory Compliance Associates, discuss performing investigations of biological products.

Q. I work for a contract manufacturing organization that manufactures traditional and biotech pharmaceutical products, and I am responsible for performing investigations and reporting the results to our clients. It would help me perform my job better if you could tell me the difference between performing investigations for a biological product vs. a traditional pharmaceutical product?

A. The short answer is there is no process difference when performing deviation investigations for traditional pharmaceutical products vs. biotech products. The differences lie in the complexity of the manufacturing processes and thus the variables that need to be considered regarding what could have impact on the deviation. Chemical process, although sometimes quite complex, often have fewer variables even though many of the categories are the same. For instance, when investigating an unknown impurity in a biological process from a simple oligopeptide fermentation process, the considerations may include fermentation conditions (e.g., time, temperature, oxygen uptake, byproduct production), potential contamination of reactants including master cell banks and fermentation reagents, equipment integrity, and performance. Further considerations for the downstream purification process variables and the effect of a final configuration (e.g., folding) also need to be considered.

The purpose of performing an investigation into a deviation is to determine why the deviation happened and what its impact was on the product quality. To determine the impact of the deviation on the product quality, it is important to determine the 'root cause' of the deviation. The process used in the industry to determine root cause is, of course, the investigation procedure. This procedure, regardless of whether the product you are investigating is biotech or traditional, should require the investigator to review various systems and determine whether they were the cause of the deviation being investigated.

It is important to remember when performing an investigation to keep in mind a few general rules. Remember, one size does not fit all. Simple errors require simple corrections while serious deviations require broader investigations. The complexity of the investigation is related not only to the seriousness of the investigation but also to the complexity of the factors that could influence the outcome.

The best tool to have during any investigation is inquisitiveness. Continuing to ask questions and avoid assumptions will lead to a better outcome. Using other tools, such and fishbone diagrams and determination of most probable number (MPN), are to be encouraged but they do not take the place of asking questions. In performing an investigation, it is important for the investigator to widen their perspective and look for ways to relate similar issues. The best way to ensure events are not related is to try and relate them, not the other way around. Keep in mind that human error is rarely a true root cause. There is usually something in the process that causes that human error.

And finally, always verify the facts of the investigation. It is also important to include a historical review. This review should determine if the deviation occurred with this or other products, with the specific manufacturing line or other manufacturing lines and/or with the operators. The historical review can help you prioritize the resources and your detailed system review. In addition, some companies make use of tools (fishbone diagram, MPN) to help prioritize resources. These tools, if used correctly, can be helpful in determining root cause, but remember, they are just tools and do not take the place of thinking.

The detailed investigation should include a review of various systems. The systems most often reviewed are equipment and machinery, the manufacturing process, the raw materials used in manufacturing, the specifications, the environment, and finally, the operators. This is not to imply that these systems are the only areas you should look at during the investigation but that these are the most probable areas where you will uncover the root cause of the deviation. Each investigation must address the following elements: root cause, impact to the material or product, the immediate correction taken, the corrective action to prevent re-occurrence for specific product/operation, and the preventive action taken to prevent re-occurrence for all products/operations.

Once these elements have been investigated, results from the investigation must be documented. The written narrative should clearly explain what happened, when it happened, and who was involved or observed what happened. The narrative documents the solution and rationale for the root cause that was determined through the investigation process.

The key to any successful investigation is not stopping too soon and assuming you have the solution prior to completing the investigation. Ask questions until you can think of no more questions to ask and be sure to document the answers to your questions. If you follow your investigation procedure and thoroughly document your results, you should have an acceptable investigation regardless of whether you are manufacturing a traditional product or a biotech product. **PT**

Your opinion matters.

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

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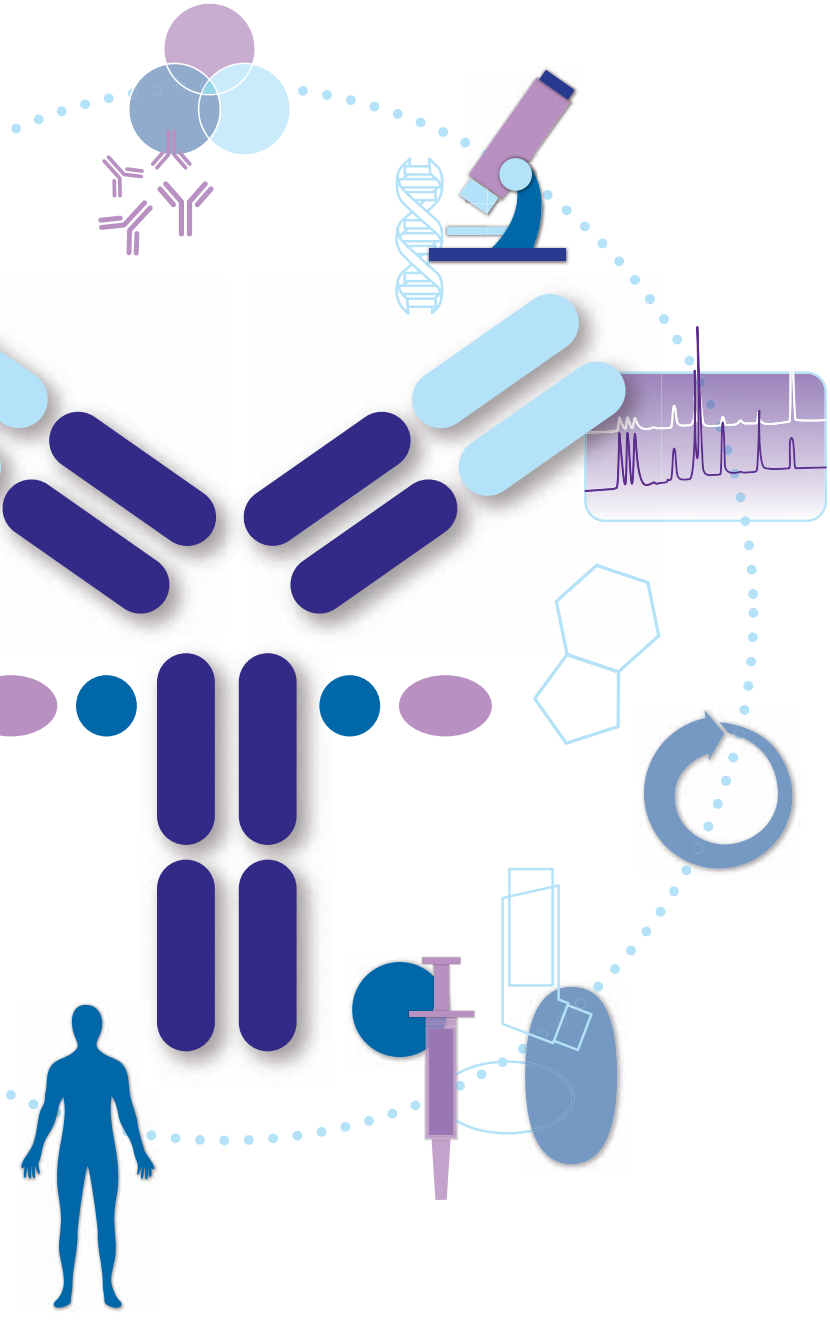

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