NOVEMBER 2013 Volume 37 Number 11

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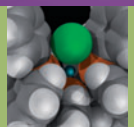

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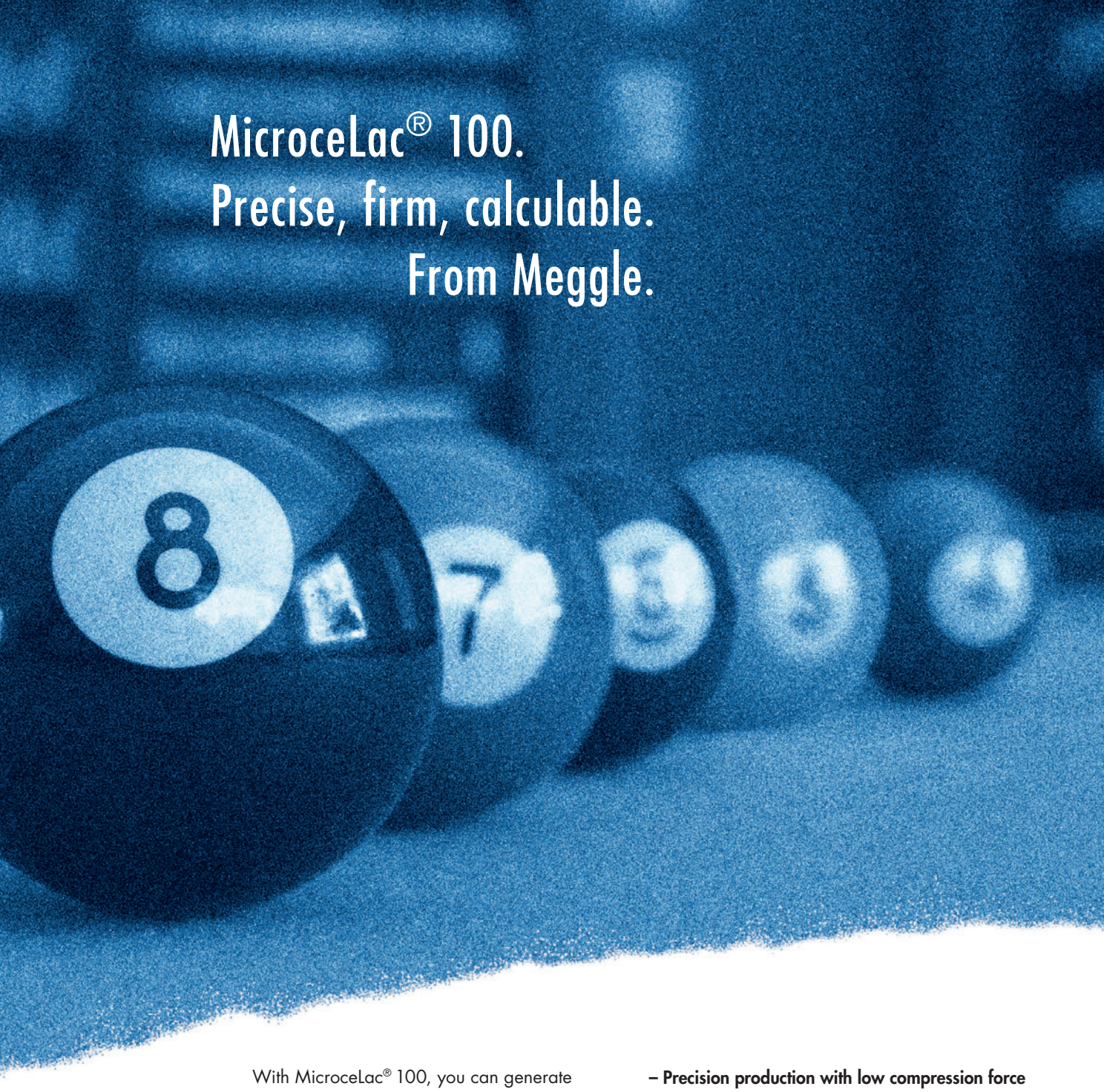

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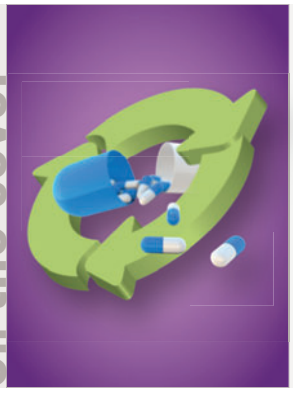

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Formulation strategies for product lifecycle optimization

Illustration by Dan Ward
Images: Bjorn Holland/Getty Images

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Preparing for Patent Expiry
Neal Hansen, managing director of the consulting firm Hansen Strategy, discusses the importance of solid planning when it comes to product lifecycle management.
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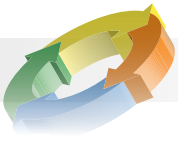

Correction: In the October 2013 issue of *Pharmaceutical Technology*, page 18, the first Product Spotlight headline should have read "RheocalcT Software Tests Parameters and Data Collection".

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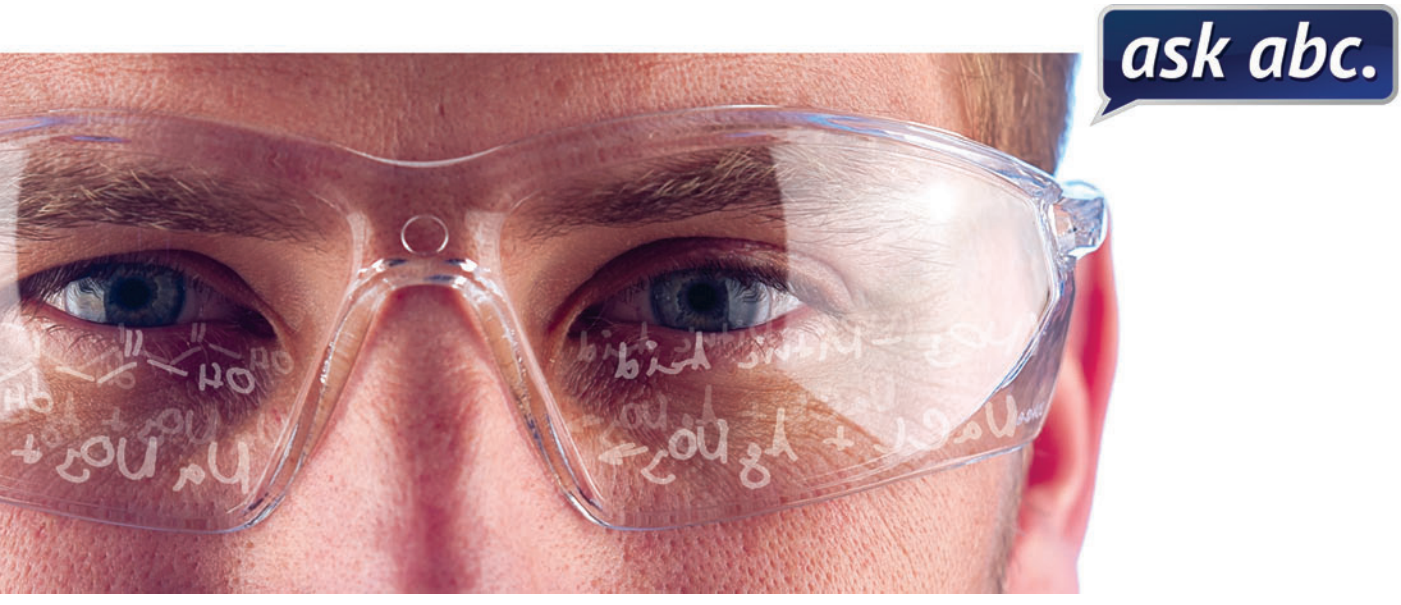

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New Funding and Approval Pathways Prove Popular

Rita Peters

The JOBS Act and FDASIA show early signs of accelerating drug development.

Compared to other manufacturing and technology industries, the bio/pharmaceutical industry has one of the longest product development timelines. The research, development, testing, and regulatory review process typically extends for more than a decade, often exhausting the financial resources and commitment of investors.

For patients with unmet medical needs, the wait for an effective therapy can be long, frustrating, and even life threatening. Late-stage failures of promising drugs can be devastating to the developer and patient alike.

Bio/pharmaceutical companies continue to explore different research, collaboration, and funding strategies in the search for ways to accelerate drug development. Assistance may be coming from an unlikely source: US Congress.

The 16-day shutdown of the US government demonstrated the divisiveness that has characterized Congress. More than half of all FDA employees were furloughed; research programs stalled at National Institutes of Health; and investigators at the Centers for Disease Control were not available to track outbreaks of infectious diseases.

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rpeters@advanstar.com.

However, two pieces of legislation that took effect in 2012 are showing signs of having a positive impact on bio/pharmaceutical development, encouraging business growth, and hopefully will result in improved patient access to effective drugs.

The JOBS Act and FDASIA passed with bipartisan support.

The Jumpstart Our Business Startups (JOBS) Act, signed into law in April 2012, gives emerging growth companies an easier path to raise capital privately or to seek public financing. It also reduces financial regulatory and compliance burdens on certain new public companies, enabling them to focus more on scientific research and less on financial reporting. The Biotechnology Industry Organization (BIO) reports that more than 40 biotech companies have gone public using provisions available to emerging growth companies through the JOBS Act (1).

The Food and Drug Administration Safety and Innovation Act (FDASIA), which included reauthorization of the Prescription Drug User Fee Act through September 2017, also provided for the timely review of new drug and biologic license applications. Since the legislation took effect in October 2012, Pharmaceutical Research and Manufacturers Association, BIO, and drug companies have commended FDA for improved communication and collaboration with sponsors.

FDA's breakthrough therapy designation was developed to expedite the development and review of drugs for serious or life-threatening conditions and provide more intensive FDA guidance on an efficient drug-development program. Other expedited programs are fast track designation, accelerated approval, and priority review. Although no drugs have been approved under the new designations, the pathways are proving to be popular.

In fiscal year 2013, the Center for Drug Evaluation and Research received 92 breakthrough requests, approved 27, and denied 41; the remaining requests are pending approval. For almost 98% of the requests, action was taken within 60 days of receipt of the request. The Center for Biologics Evaluation and Research denied 8 of the 10 requests it received through Aug. 31, 2013 (2).

Both the JOBS Act and FDASIA passed with bipartisan support, largely out of the public spotlight. In a few months, as members of Congress engage in the next round of budget and debt-ceiling debates, perhaps they should take a lesson from these bipartisan efforts and reach a consensus that makes sense for the nation as a whole.

Sources

1. BioTechNow blog, *Jobs Act Deconstructed*, www.biotech-now.org/tag/jobs-act-deconstructed, accessed Oct. 21, 2013.
2. FDA, *Frequently Asked Questions: Breakthrough Therapies*, www.fda.gov, accessed Oct. 21, 2013. **PT**

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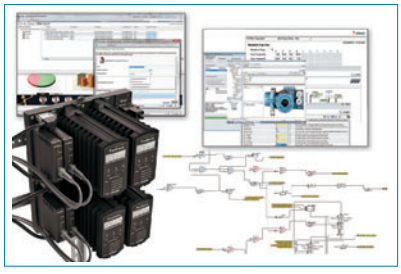

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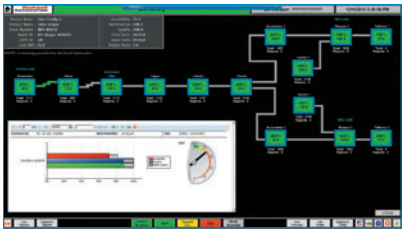

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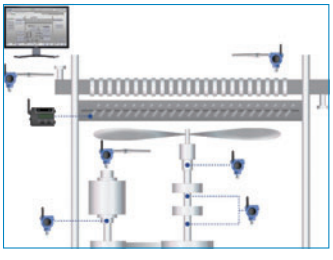

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Congress Revises Rules for Drug Compounding and Supply-Chain Security

Legislators agree on a limited bill affirming FDA authority over compounders while setting up a process for national drug tracking.

Public outrage over deaths from contaminated injectables produced by large compounding pharmacies, along with rising concerns about counterfeit and unauthorized drugs entering the US market, managed to lift the stalemate on Capitol Hill long enough to gain agreement on reform legislation. After years of heated negotiations and multiple public hearings, Democrat and Republican leaders of the House Energy & Commerce (E&C) Committee and the Senate Health, Education, Labor and Pensions (HELP) Committee unveiled a compromise bill on Sept. 25, 2013 (1). The Drug Quality and Security Act (H.R. 3204) provides more clarity and predictability to drug oversight and moves forward initiatives designed to enhance the safety and quality of medicines in the US.

Limited compounding oversight

The Compounding Quality section of the bill does little to actually extend FDA rules to ensure that products from large drug compounders meet quality standards. The main advance is to clarify the agency's authority to regulate pharmacy compounders in general under section 503A of the Food, Drug and Cosmetics Act. A series of court rulings over the past decade have undermined FDA authority in this area; the new legislation should make it easier for FDA to take action against violative firms and to defend the legitimacy of its rules.

Otherwise, the bill falls far short of giving FDA the means to identify those large compounders that operate as drug manufacturers, even those producing sterile injectables. Instead, Congress establishes a voluntary program for large "outsourcing facilities" to register with FDA and agree to meet quality standards. Outsourcing facilities would have to pay fees, report adverse events, and adhere to quality and reporting requirements. In addition, these firms—as with all compounders—could not routinely produce drugs that are "essentially a copy of a marketed drug," language important to drug manufacturers. But the limitation does not apply to drug shortage situations. There are curbs on outsourcers making certain products that raise safety issues and appear on an FDA no-compounding list, as well as limits on producing drugs subject to risk evaluation and management strategies (REMS) that carry limited distribution requirements.

By making registration voluntary, small-scale compounders escape new rules, which is important to pharmacists and the compounding community. But it's not clear that any compounders will opt for FDA oversight. The expectation is that large operators producing sterile drugs will want to demonstrate the quality of their products to gain an advantage over unregistered producers in marketing to hospitals and clinics. However, it remains to be seen if providers are willing to pay a premium for products from registered facilities. The voluntary program creates the potential for the market to drive high-quality standards, says Allan Coukell, senior director for drug and medical devices at The Pew Charitable Trusts. But he recognizes that this is tricky because quality compounders "will have to compete against those operating at lower standards," according to a letter to House and Senate leaders dated Sept. 26, 2013.

The legislation provides for enhanced communication between FDA and state pharmacy boards to better coordinate policies and oversight. The Government Accountability Office will assess the legislation's impact after three years.

Pharmacists praised the bill, while manufacturers remained largely silent on the measure. Harsh criticism came from Michael Carome, director of Public Citizen's Health Research Group, who declared that the measure will actually make it easier for unscrupulous compounders to produce substandard drugs (2). At the same time, the International Academy of Compounding Pharmacists complained that the bill gives FDA "sweeping, unprecedented authority" to determine what pharmacies can compound. Its beef is that there's no provision for anticipatory compounding to provide physicians in advance with therapies for "office use" (3).

But these complaints were lost in the loud applause for the measure and Congress' desire to show it can act to prevent future outbreaks of meningitis and other dangers from contaminated drugs. The measure may help FDA identify violative operators more quickly and encourage more collaborative scrutiny of compounders by state and federal agencies. FDA, however, will face many of the same hurdles as it does today in identifying bad actors and enforcing standards.

Pre-empting states

Manufacturers are much more invested in the drug supply-chain security section of the act, which takes the important step of pre-empting state pedigree laws, including the comprehensive California statute slated to go into effect in 2015. Pharmaceutical companies and wholesalers thus achieved their main goal of replacing the growing patchwork of state tracking and labeling requirements with a uniform federal system that promises to be more effective and less costly to implement.

The legislation generally follows the bill drafted earlier by the Senate in establishing a 10-year process for creating an electronic, interoperable, unit-level drug tracking system that includes manufacturers, wholesalers, repackagers, and dispensers (i.e., retail and hospital pharmacists) of prescription drugs. During

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the phase-in period, the legislation sets a schedule for providing pedigrees on drugs moving through the distribution system and for manufacturers to affix unique product identifiers to packages and cases.

First, manufacturers, wholesalers, and repackagers have to supply pedigrees on drugs they handle by Jan. 1, 2015; pharmacists have another six months to comply. In four years, manufacturers have to include on packages a unique, two-dimensional product identifier with a serial number up to 20 characters that includes data on product lot and expiration date. A lot-level electronic tracking system would go into operation in the fourth year, followed by unit-level tracking six years later.

There are provisions for notifying FDA of illegitimate products; for handling product returns and and recalls; for dealing with combination products and drug samples; and for tracking drop shipments from manufacturers to dispensers. All parties will need systems to verify that products are legitimate (i.e., not counterfeit, diverted, stolen, or adulterated) and to purge violative products from the supply chain.

FDA has a lot of work to do. The program requires guidance on dealing with suspect and illegal products, on unit level tracing, and on standards for an interoperable data exchange. The agency has to hold public meetings to get input on these policies and run pilot projects to test new systems. There will be a waiver process for small pharmacists and repackagers to seek exemptions from requirements, plus adjustments for drugs in the supply chain prior to the legislation.

Third-party logistics providers such as Federal Express and UPS have to be licensed, meet shipping and storage regulations, and submit annual reports to FDA. But they don't have to comply with recordkeeping and pedigree requirements, a caveat that raises fears about creating serious gaps in the tracking process.

Despite these and other concerns, the track-and-trace policy drew loud applause from pharma and biotech companies and other supply-chain parties. Cancer organizations chimed in with praise for gaining protections from substandard medicines. The Congressional Budget Office quickly calculated that the bill adds little cost to the government because new fees would offset outlays. And despite the budget battle on Capitol Hill, the legislation moved forward, largely because some of the provisions are important, and many new policies are sufficiently modified to satisfy pharmacists, compounders, and states.

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European Union Introduces GMPs for Excipients

Regulators hope new standards will stop illegal drug imports, but manufacturers fear they may stifle innovation.

The European Union is introducing a system for implementing standards of good manufacturing practices for medicine excipients after a long campaign for the imposition of GMP standards by excipient manufacturers in the region. The move follows the creation of new EU rules for GMP standards for imported APIs; full enforcement began this summer.

The imposition of the two sets of GMP standards, which is laid down in the EU's Falsified Medicines Directive (FMD), is seen by European manufacturers of active substances and excipients as necessary to stop the increasing numbers of substandard products imported into the EU in recent years, particularly from Asia.

Quality standards

In addition to the GMP initiative with excipients, the EU has also been tightening up rules on other quality issues, such as the use of certain phthalate ingredients because of their possible adverse effect on human reproduction and development. The London-based European Medicines Agency (EMA), responsible for centralized pharmaceutical regulation in the EU, has been drawing up stricter rules on information of excipients in labels and product leaflets.

Excipient manufacturers in Europe, while welcoming the tougher quality standards, reckon that the EU and national regulatory authorities are still not doing enough to encourage innovation, according to the International Pharmaceutical Excipients Council (IPEC). In particular, they are continuing to press for the introduction of an excipients master file system, the absence of which is putting the EU regulators out of line with those in the US, Canada, Australia, and other developed countries.

"There is a lot of regulatory activity in the EU at the moment with excipients with the objective of giving European producers more of a level playing field internationally," explains Kate Denton, a regulatory affairs manager at Novozymes Biopharma UK Ltd., Nottingham, UK, a maker of biopharmaceutical excipients and part of the Danish-based Novozymes group. "Now is a good opportunity to do something about the lack of an excipients master file, which has become a barrier to innovation in Europe," she tells *Pharmaceutical Technology*.

On GMP for excipients, the European Commission has been finalizing details of a guideline after issuing a draft with a consultation period that ended in April of this year. The finalized version looks likely to be similar to the Quality Management System of the International Organisation for Standardisation (ISO 9001:2008) and to a joint guideline of IPEC and the London-based Pharmaceutical Quality Group (PQG).

Under the FMD approved two years ago, marketing authorization holders have to ensure that "the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice is" (1). In the EU's draft guideline, the quality risk management principles of the International Conference on Harmonisation (ICH) would be used to categorize the excipients as being of "low," "medium," or "high" risk to determine the appropriate GMP. This risk assessment would take into account the potential for microbiological or viral contamination and for impurities originating from raw materials.

Third-party auditing

Mechanisms are now being put in place for third-party auditing schemes generating single certificates covering both GMP and good distribution practice (GDP), which are acceptable to pharmaceutical manufacturers and the regulatory authorities in Europe.

The main organizations carrying out the audits in Europe are likely to be the US-based Rx-360 International Pharmaceutical Supply Chain Consortium and EXCiPACT, Brussels. EXCiPACT has been set up by four groups—IPEC, PQG, European Fine Chemicals Group (EFCG), and the Federation of European Chemical Distributors (FECC). So far the organization has certified two auditing organizations to carry out its audits with two excipient producers in Germany already receiving certificates and three others for European manufacturers close to being issued. The GMP standard being used by EXCiPACT is based on the ISO 2001 and IPEC-PQG guideline and will be broadly similar to the one being finalized by the European Commission.

"We have got a momentum going," says Tony Scott, a UK consultant working for EXCiPACT. "An acceptable third-party auditing system for issuing single certificates is essential if the EU's requirement for GMP compliance is going to work. Otherwise excipient producers and suppliers will be overwhelmed with visits by auditors." The third-party auditing system will cover mainly low- and medium-risk excipients and some high-risk ones. "We'll be dealing with the 90% of excipients considered to be safe," Scott told *Pharmaceutical Technology*.

Novel excipients

In a virtual category of their own are novel excipients whose ingredients, modes of action, or other aspects of their performance manufacturers want to keep confidential. Also regulators have to cope with an absence of other products with which to compare them in order to assess their safety.

The major impetus behind innovation in excipients is the need to help with problems like poor solubility, absorption, and stability of active substances. "The development of new molecular structures in excipients can be a big challenge for excipient producers because they have to finance their own toxicity and tolerance studies, which can be very expensive," explains Professor Rainer Mueller, founder of Pharmasol, Berlin, a producer of solid lipid nanoparticle (SLN) excipients. "With classes of new chemical entities, excipient manufacturers are avoiding being the first ones on the market so that they have the responsibility to carry out the first safety studies," he continued. "If you're not the first, the costs would be lower."

Although marketed as nanoparticles, Pharmasol's lipid particles fall outside the official EU definition of "nano" because they

are larger than 100 nm. "If they were smaller we would also be required to carry out toxicity and other studies," he said.

Nonetheless, in a recent reflection paper, the EMA indicated that with nanoparticles falling within the EU definition and with other innovative excipient materials, there were possible advantages in not being the first on the market (2). This would particularly be the case if the product could be demonstrated to be similar to or a follow-on of a previously marketed product, the paper says.

"Formulation scientists prefer excipients that have a pre-approved functional role in drug products and a pharmacopeia monograph in order to avoid additional risks in the approval process," says Francois Scheffler, head of global marketing pharma ingredients at BASF. "In this situation, it is typical for the transition from novel excipient to commonly accepted excipient to take from 7-10 years," he adds.

The European branch of IPEC believes that the commercialization timeframe for novel excipients would be much shorter if the EU accepted a system for excipient master files (3). The files would consist of a closed part with confidential information accessible only to the regulator and an open part for the pharmaceutical manufacturer to enable it to ensure the efficiency, efficacy, and quality of the medicine.

A direct approval process based on a master file system would "simplify the overall drug approval process and as a consequence accelerate drug development and, therefore, drug launches," says Scheffler. "That would foster innovation and ultimately improve treatment options for patients," he adds.

The EMA has set up a working group to investigate possible improvements to the EU master file system for active ingredients. IPEC and other groups argue that the system of master files for actives could be extended to cover excipients (3).

The regulatory authorities acknowledge the arguments in favor of an excipient master file procedure but argue that the introduction of one is not a priority since improvements to other parts of the approval process are more urgent. Excipient producers, however, point out that novel excipients hold the key to making a wider range of drug more beneficial to patients by enhancing their delivery capabilities. "The European authorities are out of sync with the rest of the world with efforts to encourage innovation through harmonization of procedures," says Denton.

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Susanne Keitel, PhD, is head of the European Directorate for the Quality of Medicines of the Council of Europe. EDQM is responsible for the *European Pharmacopoeia*.

Control of Elemental Impurities

The European Pharmacopoeia Commission has decided to change its approach on elemental impurities.

The *European Pharmacopoeia* (*Ph. Eur.*) traditionally collaborates closely with European regulatory authorities. The Ph. Eur. Convention specifies that member states nominate their delegates for the Ph.Eur. Commission, the governing body of the *Ph. Eur.* Currently, all delegations include at least one representative from a health authority who normally also serves as head of the delegation. It is not surprising, therefore, that the texts of the *Ph. Eur.* are much aligned with regulatory developments in its 37 member states. This is a true benefit for users, as it ensures that compliance with the legally binding *Ph. Eur.* standards makes it easier to obtain marketing authorizations from competent authorities throughout the continent.

The Ph. Eur. Commission felt it important not to proceed with a revision of the chapter until limits had been harmonized.

Changing the strategy

The decision of the Ph. Eur. Commission to revise its strategy regarding control of metal catalyst or metal reagent residues is a recent example of the consistency between the approaches of European licensing authorities and the *Ph. Eur.* This revision followed a discussion at the Committee for Medicinal Products for Human Use (CHMP), the leading EU scientific committee involved in assessing marketing authorization applications coordinated by the European Medicines Agency (EMA).

In 2008, the CHMP adopted a EU guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000). CHMP's Safety Working Party developed this guideline in close collaboration with the Joint CHMP/CVMP Quality Working Party. It defines specification limits for 14 metal elements according to their route of administration and came into effect in September 2008 for new drug products while defining a five-year transition period for existing drug products. When it was adopted, it was intended that the requirements of the guideline would apply to existing products by September 2013 at the latest.

Revising compendia tests on heavy metals

The current compendia tests on heavy metals (Chapter 2.4.8 of the *Ph. Eur.*) have been criticized by users for not being adequate and state-of-the-art for the control of all relevant metal elements. A revision of these tests, therefore, has been included on the work program of the Ph. Eur. Commission. However, as methods and specifications are linked, the commission felt it important not to proceed with a revision of the chapter until limits had been harmonized and agreed upon. At the same time, to support the implementation of the CHMP guideline in line with what has been done in the past (e.g., related to the International Conference on Harmonization [ICH] guidelines on control of impurities in active substances [ICH *Q3A*] or on residual solvents [ICH *Q3D*]), the Ph. Eur. Commission decided to introduce the CHMP guideline as a general chapter for information only, as is the case for all general chapters that are not referred to by a monograph. This was done in *Ph. Eur.* Supplement 7.7, which came into effect in April 2013. As the final step, the commission decided at its 145th session in March 2013 to introduce a reference to this general chapter in the general monograph "Substances for pharmaceutical use" (2034), which would make the requirements of the general chapter mandatory for all substances used in the production of medicines for the European market, regardless of whether or not they are covered by an individual monograph in the *Ph. Eur.*

At the international level, in October 2009, the ICH Steering Committee endorsed a concept paper on the development of a harmonized ICH *Guideline for Elemental Impurities*, a project known as ICH *Q3D*. Step 2b of this guideline was completed in June 2013, and the document is currently published in the EU for comments until December 31, 2013. While the limits defined in the CHMP guideline referred to previously have been used as a basis for ICH *Q3D* discussions, the latter has a different scope in terms of both geography (which is normal for an ICH guideline) and the elements covered, notably in that it defines limits for the so-called "big four" contaminants arsenic, cadmium, mercury, and lead among the 24 elements it deals with. At present, these are not covered by the current CHMP guideline. In addition, certain limits proposed in the current version of the ICH document differ from those that have already been implemented via the CHMP guideline in Europe. For some of the elements the limits are wider (e.g., chromium, nickel, and platinum), while for others they are stricter (e.g., copper, molybdenum, and vanadium). A certain degree of disharmony between the current European and the future ICH guideline should be noted.

Harmonization

Being committed to international harmonization, European regulators and the Ph. Eur. Commission have stated from the inception of the ICH guideline that they would update their respective requirements in line with the outcome of the discussions at the ICH level. This means that the CHMP guideline

would be replaced by the ICH guideline once the CHMP adopts the latter, which according to EU procedures is the final step in the implementation in the EU of an ICH guideline adopted by the ICH Steering Committee. The Ph. Eur. Commission would do the same for its general chapter on metal catalyst or metal reagent residues (Chapter 5.20). The Ph. Eur. has always been clear that it will keep the European requirements for the time being and revise the respective chapter to align them with the ICH requirements once the discussions at the ICH level have been finalized. This strategy contrasts with what has been announced by the United States Pharmacopeial Convention, which has been developing its own specification limits for elemental impurities in parallel with the ICH discussions.

In the meantime, the ICH document has reached step 2b, but some of the limits are different from the ones previously defined by European regulators and applied by the Ph.Eur. Normally, according to the CHMP guideline, the latter requirements should have become applicable to existing products as well in September 2013. Likewise, the *Ph. Eur.* would have made these requirements legally binding for all substances for pharmaceutical use as of Supplement 8.1, which will come into force in April 2014. This would have created further disharmony for industry. To avoid this, the CHMP decided at its July 2013 meeting to postpone the application of its guideline to existing products and to await the outcome of discussions at the ICH level before taking any further measures. As an integral part of the European regulatory network and to ensure continued consistency between the policies applied by regulatory authorities and the pharmacopoeia, the Ph. Eur. Commission has decided to defer the addition of a reference to the general chapter in the general monograph "Substances for pharmaceutical use." This should not be confused with the decision of the USP Executive Committee of Council of Experts to postpone the implementation of its respective General Chapters <232> Elemental Impurities–Limits and <233> Elemental Impurities–Procedures, which was made for different reasons.

The decision to postpone the implementation of the full scope of the CHMP Guideline on the specification limits for residues of metal catalysts or metal reagents made by the CHMP and the Ph. Eur. Commission are an excellent example of the benefits of close collaboration between regulators and the pharmacopoeia authority, not only for themselves, but also for industry. Just imagine the situation if one party had decided to defer the extension of the scope of the CHMP guideline to existing products while the other had made them mandatory. **PT**

More on Elemental Impurities:

- A Risk-Based Approach to Monitoring Elemental Impurities in Leachable Studies
  PharmTech.com/monitoringelemental
- Modernization of the Standards for Elemental Impurities
  PharmTech.com/modernizingelemental

EMERGING MARKET REPORT

Report from: Brazil

Hellen Berger

New regulation offers patients in Brazil greater access to experimental drugs.

Brazil's Health Surveillance Agency (Anvisa) published a new regulation, Resolução da Diretoria Colegiada (RDC) 38/2013, on Aug. 14, 2013 that implements patient access to new drugs before they are officially approved and available for purchase. The new regulation offers drug options for patients with rare, severe, or debilitating illnesses for which there are no treatments available or where the existing medication is insufficient.

According to Anvisa, the resolution will provide promising access to new drugs without agency registration under a public health program that will be requested by the patient's doctor. Patients who previously would not have access to treatments before drug registration will now be able to get their medicines through three programs: compassionate use, expanded access, and post-study program.

Medicines access programs

The compassionate use program will benefit patients with serious or rare diseases. These cases can involve importing new, unregistered drugs if needed. Patients with serious life threatening illnesses may participate through the expanded access program in cases that lack satisfactory treatments, Anvisa told *Pharmaceutical Technology*. This program will offer new drugs that are not registered with Anvisa, but are undergoing, or have concluded, Phase III clinical trials. The post-study drug-supply program guarantees free drug supply to volunteers who benefited from the drug during clinical trials.

According to Anvisa, the authorization approval for the expanded access and compassionate use programs will be evaluated according to the severity of the illness. The current state as well as the absence of satisfactory treatment alternatives available for the patient's condition in Brazil will also be assessed before issuing an authorization. Anvisa says RDC 38/2013 will benefit patients in Brazil because it guarantees innovative drug supplies to those whose illnesses are chronic or severe according to medical request.

Access to unregistered drugs was already available previously by RDC nº 26/1999 to patients in Brazil through the expanded access program, Anvisa told *Pharmaceutical Technology*. The program, however, did not include compassionate use or post-study access and, therefore, had to be updated.

Patients who previously would not have access to treatments will now be able to get their medicines.

All three programs were, therefore, included and are regulated by RDC 38, dated Aug. 12, 2013. "The process for obtaining the drug authorization will not be complex or bureaucratical," says Anvisa. "The patient's doctor will need to make a formal request to obtain the drug from the company funding the assistance program and the company will place a request with Anvisa, following RDC 38/2013 ruling." Anvisa, however, points out that the negative point of the program from the industry's perspective is the high cost of the assistance

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The new regulation offers drug options for patients with rare, severe, or debilitating illnesses for which there are no treatments available.

program. On a more positive note, data collected through the program may be used by the company as additional information for product registration.

"It is important to note that the data collected though the expanded access and the compassionate use programs will not substitute clinical trials for drug registration or delay the development of clinical trials for such drugs," the agency adds.

Anvisa says the program would not pose any kind of risk or impact to the local pharmaceutical market and that patients will not have access to drugs without medical authorization and request. According to RDC 38/2013, chapter VIII section 18, the company funding the treatment will offer the complete treatment and medication at no cost for the patient under the expanded access, compassionate use, or post-study programs. The company will also be fully responsible for the products used in the program, including adequate stocking and distribution processes, according to the new rules.

Considerations for patients requesting access to new drugs

This improved medicines-access initiative has been positively viewed by many industry players and patients; however, patients should bear in mind some key considerations before requesting authorization to access new drugs. Firstly, the efficacy and benefits of these drugs have not been proven considering that they have not been registered with Anvisa. Secondly, the risks and complete range of side effects of experimental drugs are unknown. Also, while physicians in Brazil tend to be open to patients' requests, the doctor may not grant access to the new drug if he/she believes that the experimental drug could be dangerous for a specific condition, for example. It is always important to seek advice and ask for a second opinion on specific medical cases, if needed. **PT**

—Hellen Berger is a business correspondent based in São Paulo, Brazil.

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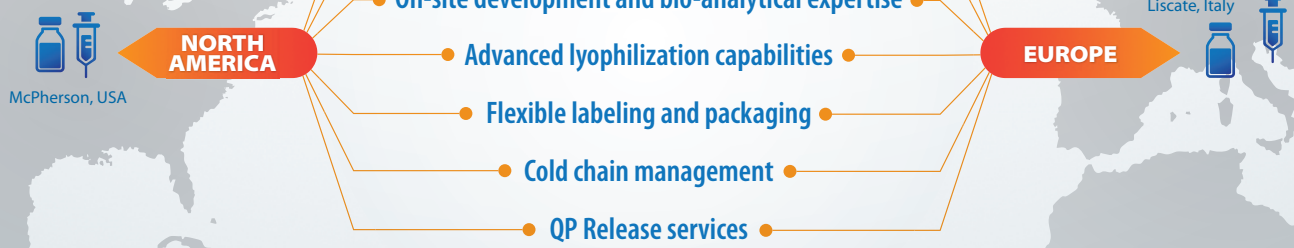

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Can Pharma Defy Gravity at the Patent Cliff?

Formulation strategies for product lifecycle optimization

Adeline Siew, PhD

Generic-drug competition has become increasingly aggressive, especially in an environment where healthcare policies are placing stronger emphasis on pharmacoeconomics and demanding better treatment outcomes at a lower cost. A 2012 analysis by IMS Health estimated that patent expiries will reduce brand spending in developed markets by $127 billion through 2016 (1). With drug-development expenditures escalating at an alarming rate while R&D productivity continues to decline, branded drug-makers are under pressure to maximize the value of their products throughout their lifecycles.

"Although the development of new drugs to address unmet patient needs remains the single most important goal of any pharmaceutical company, effective lifecycle management (LCM) is invaluable for getting the greatest possible value from existing brands," says Anil Kane, PhD, executive director and global head of formulation sciences, Patheon.

"The challenge, however, is in the development of creative and unique strategies that will generate intellectual property and provide additional mid- to long-term exclusivity for the product," notes Ninad Deshpanday, PhD, president, R&D, Cirrus Pharmaceuticals, a Kemwell company. "The competition among innovators developing similar strategies has increased, and generics have become smarter; therefore, the window to succeed with novel lifecycle products has become much narrower today."

LCM strategies include identifying new indications, developing modified formulations, finding new routes of administration, combining more than one drug into a single product, producing the drug as a single enantiomer if the original drug substance was a racemic mixture, and switching from a prescription product to over-the-counter (OTC) status, among others. According to Kane, the key issue facing pharmaceutical companies is the selection of one or more of these LCM options by understanding the opportunities and competitor landscape, potential return on investment, and the ability of timely implementation. "Adopting a proactive LCM strategy, such as line extension into pediatrics, changing the dosing regimen by using modified-release formulations or improving clinical benefits and patient compliance by combination products, can offer a broad patent coverage and enhance the value of the brand," Kane adds.

Thomas Hein, PhD, director of sales & business development, at Hermes Pharma, emphasizes that LCM should start as early as possible and be part of an overall product portfolio strategy. "However, from our experience, most companies tend to consider line extensions after the product has been marketed for several years with the aim of prolonging the product lifecycle when it is under threat or when looking to target new customer segments such as children or the elderly."

Formulation strategies

Over the years, pharmaceutical companies have found formulation strategies to be an effective LCM tool in preserving revenue streams following patent expirations of their blockbusters. "Formulation strategies fall into two core groups based on their target patient populations," says Neal Hansen, managing director of the consulting firm Hansen Strategy. "Switch-and-grow formulations seek to bring improvement to core user populations, for example, greater convenience, better compliance, improved outcomes, and/or reduced side effects. These formulations will typically need to compete head-to-head with generic versions of the original formulations and, therefore, must deliver demonstrable advantage to drive switching and minimize back-leakage. Examples of the switch-and-grow strategy include once-weekly bisphosphonates for the treatment of osteoporosis, once-daily attention deficit hyperactivity disorder agents and new device/formulation combinations in diabetes, asthma, chronic obstructive pulmonary disease, and inflammatory diseases."

"Expand-and-grow formulations seek to unlock either new or unsatisfied patient pools that are not well addressed by available market formulations. As such, these approaches are already well differentiated from the original, generic-threatened formulations, and therefore, have a degree of competitive protection although such approaches offer no protection to the mass-market side of the business," continues Hansen. "Classic examples of this approach include pediatric and geriatric formulations, fast-melts for 'on-the-go' patients, and intravenous/intramuscular forms for acute use in hospitals."

Modified-release formulations

Developing and patenting new modified-release formulations, which include

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controlled-release, sustained-release, extended-release, and long-acting preparations, has been a route favored by pharmaceutical companies in their quest to extend the lifecycle of their products. These formulations are mainly designed to increase the duration of drug action by providing a gradual and continuous release of a drug substance from its dosage form, and thereby, decrease dosing frequency. The advantages of modified-release drug delivery include enhanced patient compliance, improved treatment efficacy, and a lower incidence of adverse reactions due to more uniform drug levels in the blood or plasma, among others.

A well-known case is with Pfizer's cardiovascular drug, Procardia (nifedipine), when it lost its patent. Pfizer went on to introduce Procardia XL, an extended-release formulation designed for once-daily administration as opposed to three times a day with the conventional tablet. The improved formulation consists of a semipermeable membrane surrounding an osmotically active drug core. The drug core is divided into two layers: an active layer containing the drug and a push layer containing osmotically active but pharmacologically inert components. Once ingested, water enters the tablet and the increased pressure in the osmotic layer pushes against the drug layer, releasing the drug through a laser-drilled orifice at a constant rate over 24 hours (2).

Another LCM example is Bristol-Myers Squibb's extended-release formulation of its oral antihyperglycemic drug, Glucophage XR (metformin), which permitted once-daily dosing (instead of twice-daily) in the management of Type II diabetes. Glucophage XR consists of a dual hydrophilic polymer matrix system. Metformin is combined with a polymer, which controls drug release, to form an inner phase. This inner phase is then incorporated as discrete particles into an external phase of a second polymer. Following administration, gastrointestinal fluids enter the tablet, causing the polymers to hydrate and swell, thereby releasing the drug slowly by diffusion through the gel matrix. Drug release is independent of pH, and the hydrated polymer system is broken down by peristalsis of the gastrointestinal tract (3).

Similarly, after the patent of Eli Lilly's blockbuster antidepressant drug, Prozac (fluoxetine), expired, the company developed a once-weekly sustained-release formulation. Prozac Weekly capsules contain enteric-coated pellets that resist dissolution until the lower region of the gastrointestinal tract where the pH is more than 5.5. The enteric coating delays the onset of absorption of fluoxetine for 1 to 2 hours compared with the immediate-release formulations (4). Compliance with the weekly formulation was better than with once-daily fluoxetine (5).

Janssen Pharmaceuticals also used modified-release formulations to optimize product lifecycle by introducing a once-daily paliperidone palmitate tablet (Invega) and an extended-release injectable suspension for intramuscular use (Invega Sustena), administered once every four weeks, for the treatment of schizophrenia. Invega Sustena incorporates Alkermes' proprietary technology for nanoparticles. Janssen is now developing a three-month depot injection, and in June 2012, the company initiated a Phase III trial to evaluate the efficacy, safety, and tolerability of the three-month formulation (6).

Combination products

Combining two or more drugs into a single solid dosage unit and marketing it as a whole new product is also becoming increasingly popular as an LCM strategy to extend intellectual property and minimize generic exposure of mature brands. "According to a recent study from IMS Health, about half a trillion dollars could be avoided by improving the use of medicines, which equals to 8% of annual total healthcare costs worldwide," comments Stefania Barzanti, marketing manager at IMA Active. "These costs are due to many reasons, but nonadherence to prescription regimen and mismanaged polypharmacy account for more than 60% of this avoidable cost opportunity. This is where fixed-dosed combinations (FDC) can offer convenience to patients and encourage compliance and adherence with their medications. At the same time, FDCs allow product differentiation and containment of generic exposure for mature pharmaceutical products."

For example, Eli Lilly launched Symbyax (olanzapine and fluoxetine) as a means to stall sales erosion following the patent expiry of its antipsychotic blockbuster, Zyprexa (olanzapine). Merck & Co. also pursued this strategy with the development of Fosamax Plus, which is a combination of a bisphosphonate and vitamin D for the treatment of osteoporosis in postmenopausal women, and Juvisync, the FDC formulation of the cholesterol-lowering agent, simvastatin, and the antidiabetic drug, sitagliptin. Other examples include GlaxoSmithKline's combination treatments for HIV, Combivir (lamivudine and zidovudine), Trizivir (abacavir, lamivudine, and zidovudine), and Epzicom (abacavir and lamivudine); and Gilead's Truvada (tenofovir and emtricitabine).

FDCs can be developed in different forms, for example, layered tablets, hard gelatin capsules filled with multiple products or multiparticulate tablets, formed through the compression of multiparticulates. In terms of formulation considerations for FDCs, Barzanti explained that the first issue is the challenge of bringing together different pharmacokinectics and target release profiles, which becomes more complex with higher number of actives. "From the manufacturing point of view, however, one of the most common challenges is combining two chemically incompatible actives that need to be kept separated but included in a single dosage form," says Barzanti. "This issue is particularly crucial for layered tablets, where sometimes, an intermediate placebo layer has to be placed to avoid any interaction. Constant check and frequent replacement of the scraper blade are of the utmost importance to avoid the mixing of the different powders comprising the various layers."

Another critical issue for all forms of FDC is the in-line control of the single dosages of each drug. "In a layered tablet, the single layers can be sampled and checked individually but it is not possible to check them separately in the final complete unit dose," notes Barzanti. "On the contrary, manufacturing of FDC in hard gelatin capsules can be easily achieved through subsequent filling unit, and many technical solutions are available for in-line check of each drug dosage."

Fast-dissolve formulations

Recently, there has been a growing interest in user-friendly dosage forms, particularly formulations that dissolve quickly in the mouth without water as they eliminate the need to swallow pills. "User-friendly medicines are easier to take, taste better, and can reduce the number of doses required in a day," says Hein from Hermes Pharma. "These are factors that attract the interest of patients. Adherence is still a major problem today, limiting the effectiveness of treatments, and anything that makes administration easier has the potential to offer significant benefits."

"Applications of fast-dissolve formulations are expanding across therapeutic areas," observes Steve Hamlen, global group product manager, Catalent. For example, conventional selegiline tablets had to be taken more than once daily. Not only did the conventional formulation have less than optimal efficacy, but it also presented a safety risk due to first-pass metabolite formation. The fast-dissolve formulation of selegiline, Zelapar, developed using Catalent's Zydis orally disintegrating tablet technology, is absorbed buccally, thereby, avoiding first-pass metabolism and significantly reducing the potential for side effects. The ability to disintegrate in less than 3 seconds allows for increased bioavailability and a faster onset of action for Zelapar. The maximum blood levels of the drug (T_{max}) were achieved in 15 minutes for Zelapar compared with 1 hour for the conventional selegiline pills. Moreover, dosing frequency could be reduced (i.e., 1.25 mg or 2.5 mg once daily compared with 5 mg twice daily for the conventional formulation).

"In one recent case, we were asked to redesign a life-saving medication that required delivering large quantities of the API. The original medication is administered as multiple tablets taken three times a day," says Hein. "We reformulated the medicine from a series of solid tablets into three single packages of orally disintegrating granules, allowing us to encapsulate more API per dose, and therefore, simplify the treatment regimen. This innovation not only improved patient compliance but also provided our client with the opportunity to extend patent protection as the new formulation significantly improved the product."

Conclusion

In the past, drug-makers have only dedicated modest resources to their off-patent strategies but the changing landscape of the industry, especially with the increasing focus on value, budget management and outcomes in today's healthcare systems, means that LCM is essential for sustained revenue generation and margin improvement. "The future for successful formulation strategies will most likely lie in hypersegmentation as with the much-hyped death of the blockbuster. Companies that can hypersegment their markets and deliver solutions to the specific needs of different patient and healthcare professional groups will be those that succeed," comments Hansen. "To win will require both a level of true market insight and continuing innovation in the formulation and services sector to optimize product performance." With fewer compounds in the development pipeline and more products edging towards the patent cliff, strategies that can extend the commercial life of mature brands are crucial to the success of pharmaceutical companies.

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Preparing for Patent Expiry

The importance of solid planning when it comes to product lifecycle management is gaining increasing attention among specialty pharma, biotech, drug-delivery companies, and even generic-drug players. Companies now see it a necessity to protect their market position long before their products come off patent. Neal Hansen, managing director of the consulting firm Hansen Strategy, notes that preparing for and surviving through patent expiry is a key challenge for pharma given that generics are a necessary reality. "Branded players must accept that generics are a valuable tool to support healthcare budget management in a constrained financial environment," Hansen says. "Without a healthy generics market, there would be no budget room for innovation, which would lead to an even greater challenge than is already faced by new drug launches."

According to Hansen, pharmaceutical companies classically face three core challenges:

- *"Short-term focus.* Companies often tend to focus on the short-term outlook (i.e., one to two years). As such, effective and early-enough planning remains one of the most challenging aspects of lifecycle management.
- *"Market diversity.* Companies have to deal with a widely diverse therapeutic landscape and stakeholder environment. This diversity is exemplified at patent expiry when the stakeholder balance of power varies hugely between countries, creating a complex matrix of different tactical needs that must be explored to maximize potential.
- *"Lack of innovation.* Pharma is always seeking the 'magic bullet' that will drive growth for the next 10 years or enable them to differentiate so well from generics that patent expiry will pass with barely a whisper. However, innovation in lifecycle management is not about putting all the eggs in one basket but about effective coordination of a portfolio of tactics that will synergize to maintain competitiveness."

The full interview is available at **PharmTech.com/lifecycle**.

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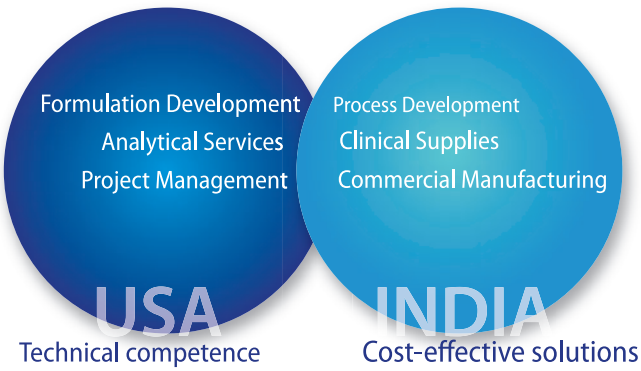

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Solvent-Free Coating of Traditional and User-Friendly Dosage Forms

Detlev Haack, PhD and Martin Koeberle, PhD

Considerations when selecting a coating technology for user-friendly solid oral-dosage forms

Tablets and capsules are often coated for various reasons such as to improve their appearance or to make them easier to swallow. Coatings also play an important role in maintaining drug stability, activity, and effectiveness. This article reviews the benefits of solvent-free processes and techniques specifically optimized for coating new dosage forms such as orally disintegrating granules (ODGs).

Coating technologies and methods

Coating is usually achieved with one of a variety of techniques but regardless of the equipment and coating process used, there are several common challenges and considerations that will influence coating success. Firstly, the coating should be immediately stable (e.g., without the need for a curing step), reproducible, and cost efficient. Secondly, the coating process used during formulation development must be easy to transfer to manufacturing conditions and ready for scale-up, using excipients that can be easily and safely stored in bulk amounts.

In terms of the coating itself, some approaches can lead to structural polymorphism within the coating, which can render it difficult to consistently predict drug-release profiles, bioavailability, and efficacy while also affecting intellectual property (IP) protection and infringement. Such variations can arise during the coating process or develop over prolonged storage; hence, it is important to select a method where these factors have been studied and are well understood.

Liquid coating using solvents

Liquid coating is a reliable and well-established technology that is still the industry standard for coating many APIs but it has several disadvantages. Firstly, liquid coatings must be dried to form a solid final product, a time-consuming process that often requires an increase in temperature that incurs additional cost. The use of heat may also cause thermal stress, leading to API degradation. When using liquid coating, it may also be necessary to spray the tablet core or seed particle with several layers to create the final dosage form or intermediate with the desired characteristics. This step adds time and complexity to the procedure and can have detrimental effects on the quality of the final product by causing variability in the crystalline form or an uneven, heterogeneous coating, thereby, leading to unwanted polymorphism or defects. Besides affecting stability, performance, and efficacy, such structural variations can also have important IP implications. For example, it may be that certain polymorphic forms of the API are protected by patents, and thus, must be avoided. For these reasons, solvent-free coating technologies are of interest.

Solvent-free coating

Solvent-free coating offers several advantages over the use of solvents by reducing the time and costs associated with drying liquid coatings. It can also reduce the thermal stress imposed on the API and simplify the coating process by reducing the number of steps required to reach the final product. These methods include compression coating, electrostatic spray powder coating, supercritical fluid coating, photocuring, and hot-melt coating (HMC).

Compression coating. Generally, when coating tablets, the APIs are initially granulated before being blended with further excipients, compressed into tablets, and finally coated. It is also possible to use these uncoated tablet cores in a second compression step designed to surround them with an additional layer containing certain functional excipients, such as a second API or an additional dose of the same API. The method is well suited for producing multi-stage treatments that combine two or more APIs, particularly if they are incompatible and must be physically separated within the dosage form, or if their mode of action requires that they are administered to different parts of the digestive system.

Perhaps the biggest drawback of compression coating is that in the second compression step, it can be difficult to position the tablet core accurately in the center of the tablet, which is important for reproducible formulation and reliable pharmaceutical performance. Various efforts have been made to circumvent this problem, leading to the development of new approaches such as the one-step dry-coated (OSDrC) tablet manufacturing system, which can reduce the likelihood that the compaction process will negatively affect tablet performance (1). The excipients must also be carefully selected. Using appropriate fillers and/or binders is essential to successfully creating a solid dosage form by compression. Finally, because many APIs and excipients are simply not compressible in their crystalline or amorphous forms, an alternative solvent-free coating methodology must be selected.

Electrostatic spray powder coating. An advantage of spraying liquid coatings onto tablet cores is that the final product is visually appealing, creating a clean, polished,

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and homogenous coating. To pseudo-replicate the process but without the need for solvents, researchers have developed ways to replace liquids with dry powders. One such approach, electrostatic spray powder coating, uses powdered raw materials that have been electrostatically charged through the application of high voltage. These materials are sprayed onto a neutrally charged seed pellet and will adhere to the surface by electrostatic forces. The coating is then fixed in place by temperature or exposure to infrared radiation for approximately 1 to 2 minutes (2, 3). The main advantage of the process is that the coating forms and hardens quickly while the final product can easily be customized in terms of properties and thickness by adjusting the composition and amount of mixture sprayed on the tablet core prior to fixation.

For the process to work, however, the coating and tablet core must possess certain conductive properties, or be modified using additional steps to introduce electric charge. To circumvent this issue, the conductivity of the core particle can by increased by wetting it with water to decrease resistance, although this method introduces moisture into the tablet and can lead to instability. Another way to improve conductivity is to modify the surface of the API substrate using polar groups. This method is usually achieved by dissolving the polar groups in a volatile solvent before spraying the solution onto the tablet core, thereby, reintroducing a solvent step into the process. Either way, the electrostatic attraction between the solid substances tends to be weak, hence, making it difficult to produce a thick coat without multiple rounds of spraying and fixing. The fixing step also requires moderate heating, hence, increasing the energy required to carry out the method, which potentially leads to API instability. Current research is focused on finding new ways to increase the conductivity of the tablet core and lower the glass transition temperature of the coating polymer (4).

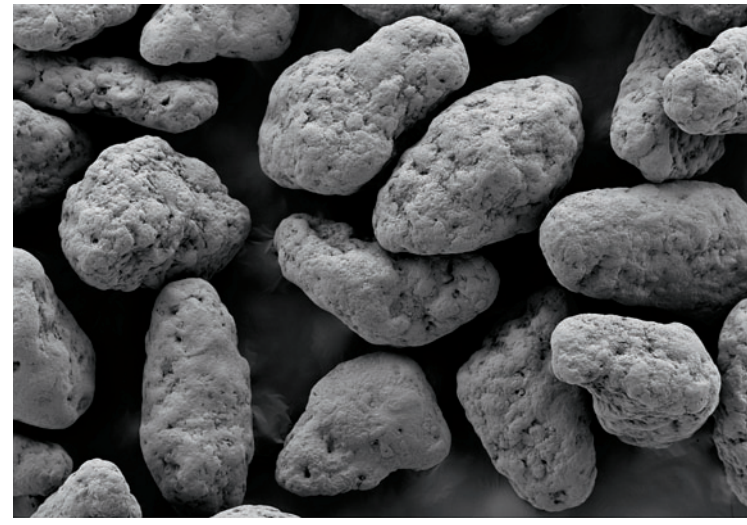
Photocuring. A fundamental stage in the coating process is the fixation of the coating to form a solid, protective layer. In many cases, this step involves the use of heat. This increase in temperature requires costly energy and many APIs become more susceptible to degradation as temperature increases. Photocuring attempts to avoid these problems by employing a method of fixation dependent on light energy rather than heat. As such, it does not require any heating or drying steps and is ideal for temperature-sensitive APIs. The process hinges on the use of light energy to trigger a polymerization reaction to convert a liquid or granulate surface coating into a solid material. The technique has been successfully used in pharmaceutical coating to create immediate and sustained-release dosage forms (5).

While coating can proceed rapidly, oxygen in the ambient atmosphere can slow or halt the reaction and in some cases, must be purged from the formulation or manufacturing system using nitrogen, which adds complexity and cost to the process. While this technique has clear applications for heat-sensitive compounds, it is unsuitable for excipients or APIs that are photosensitive. Moreover, the process is expensive and is still in early phase development.

Supercritical coating. One way to avoid the downsides of traditional liquid coating is to use supercritical liquids, which have properties between liquids and gases along a continuum that can be manipulated. Like liquids, they can be used to dissolve the excipients and API, thereby facilitating the mixing and formation of a homogeneous coating. Carbon dioxide is most widely used because of its low critical temperature (31 °C) and pressure (74 bar), making it easy to manipulate under manufacturing conditions. The major benefit compared with standard liquid coating is that supercritical liquids can be rapidly transitioned to the gaseous phase by a reduction in vessel pressure, causing the excipient mixture to precipitate and form a solid. Unlike solvent-based methods, the technique leaves no residue and does not require any heating or drying steps.

Supercritical liquid coating has so far proven to be effective for coating of fine particles. The supercritical liquid solvating power can be controlled by small changes in temperature or pressure, thereby, enabling the fine-tuning of coating properties (6). However, for the process to work effectively, the core particle onto which the coating forms must be insoluble in the supercritical fluid. In addition, high-pressure equipment is required to carry out the process, which adds further cost to an already expensive approach.

Figure 1: A scanning electron microscope image of taste-masked, fast-acting API particles coated with a mixture containing lipids produced using hot-melt coating.



Hot-melt technology for coating ODGs

Despite the various methods available for coating traditional dosage forms that improve taste, mouth-feel, and ease of swallowing, many patients still complain that swallowing tablets and capsules is pain-

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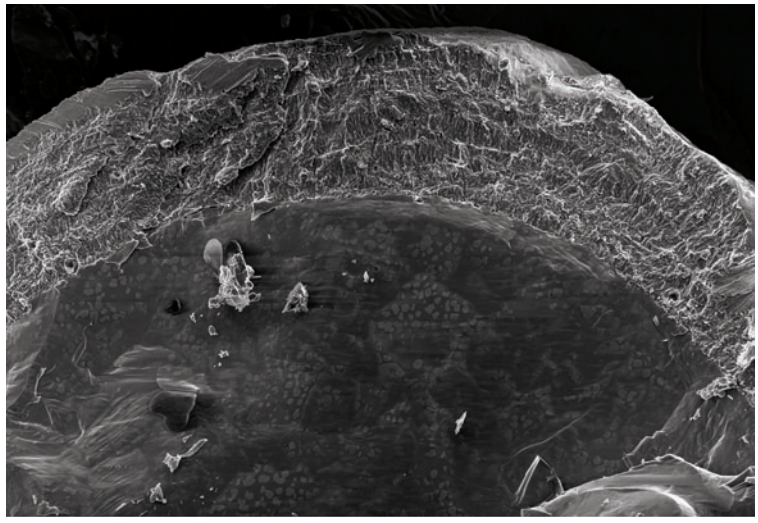
Figure 2: With hot-melt coating, molten mixtures are sprayed onto solid particles. Upon cooling, the mixture solidifies to form a protective coating around the seed particle containing the API. This image is an enlargement of a cross-sectioned particle.



ful and unpleasant. According to a large pan-European study, more than 25% of a particular general practitioner's patients complained of swallowing difficulties (7).

Orally disintegrating granules (ODGs) are user-friendly dosage forms designed to meet patients' needs, improve adherence, and increase treatment effectiveness. ODGs provide value for patients as they rapidly dissolve in the mouth, thereby circumventing any issues with swallowing. They can also be quickly and easily administered without the need for water and are much simpler to administer to children and the elderly. As they are not constrained by physical size, ODGs can also be formulated to contain larger amounts of API and/or multiple APIs in a single dose, simplifying treatment regimens.

The effective coating of APIs for ODGs is dependent on many factors. Solvent-based coating is applicable for ODGs, but suffers from heating, drying, and potential stability complications while most organic solvents inherently pose various health and environmental risks. Although several solvent-free approaches have been used with some success for coating ODGs, especially electrostatic spray powder coating, most of them are time-consuming and expensive, often leading to a final product that does not adequately mask the bitter taste of most APIs. In addition, many approaches are not practical for coating large numbers of small granules. For example, compression coating is better suited for coating larger tablets. While new approaches such as supercritical liquid coating and photocuring may offer an effective way to coat ODGs, both methods are still experimental, expensive, and impractical for scale-up.

In an effort to avoid the use of solvents and identify coating methods that might be suitable for ODGs, there has recently been significant research and development into novel methods of pharmaceutical coating. One such technology, hot-melt coating (HMC), is gaining popularity as it offers short processing times (typically under 1 h) and significantly lowers costs compared to other solvent-free methods. HMC avoids the use of solvents by instead utilizing molten mixtures, which are sprayed onto solid particles usually using a fluid bed coating setup. This mixture then solidifies upon cooling to form a protective coating around the seed particle containing the API. The excipients most suitable for HMC include lipids, waxes, fatty bases, and hydrogenated vegetable oils, as they are easy and quick to process, cost-effective, and have relatively low melting points (below 100 °C).

Compared to other solvent-free coating methods, HMC is particularly well suited for taste masking and careful manipulation of API release (8), making it ideal for formulating ODGs. By carefully selecting excipients based on molecular flexibility, hydrophobicity, melting point, molecular weight, and rigidity, as well as optimizing their relative concentrations, it is not only possible to fine-tune the release profile of the API to provide sustained or delayed release but also to provide immediate release products (see **Figure 1**) (9, 10).

Although HMC can be carried out using a variety of methods and common manufacturing equipment including fluidized bed and spray coating, optimization of the protocol for each API/excipient mixture takes skill, knowledge, and experience. Air-flow, spray rate as well as spray and product temperature must be carefully controlled during the process to enable to successful melting and solidification of the excipient mixture to create a pleasant tasting, homogenous coating with the desired API release characteristics. These parameters are important and when the process is carried out correctly, dosage forms coated using HMC do not suffer from some of the polymorphic variations (and associated challenges) that other coating methods may exhibit.

It is important to create formulation and manufacturing processes that embody quality-by-design (QbD) principles to enable a seamless transition during scale-up, and at the same time employ process analytical technology (PAT) that measure HMC parameters, such as coating thickness, to enable their accurate correlation with final product characteristics. Offline methods, such as scanning electron microscopy, can also be used to assess product quality, because they enable the surface and coating layer of ODGs to be visualized (see **Figure 2**).

Optimizing HMC

While HMC is a suitable API-coating method for producing ODGs with delayed- or sustained-release profiles, optimizing the process for producing rapid-release medications such as analgesics has proven to be a challenge. A team at Hermes Pharma is collaborating with the Research Center Pharmaceutical

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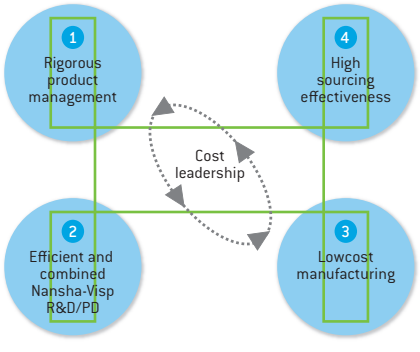

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Defining and Presenting Overkill Cycle Validation

John Anderson

Autoclave overkill cycles should be validated by correlating lethality data to support chosen critical process parameters.

When sterilization validation comes up in an audit of a moist steam-sterilization autoclave, the quality assurance manager will be asked to explain how autoclave loads were validated. The conventional, easy answer is the term "overkill," which is understood to mean that all items were steamed beyond all hope of anything surviving a grossly exaggerated load cycle—and that would be the end of it. This "overkill cycle" entails increasing the temperature or lengthening the time of the sterilization cycle with little understanding of what is occurring within the load items. All bioindicators (BIs) are inactivated at some undetermined but early point in the validation cycle, and temperature profiles are presented separately. In this approach to overkill sterilization cycle validation, no attempt is made at correlation of the biologic and physical data. Temperatures recorded by thermocouples are used to calculate the accumulated lethality at various load points. Bioindicators are placed beside each of these thermocouples to comply with well-established sterilization methods. In this scenario, BIs are considered as mere binary factors, either alive or dead. The data would be presented as just that: all BIs were inactivated.

A key component when presenting any autoclave validation package, however, is to be able to clearly defend how the requirement to correlate biologic and physical lethality data from the validation reports is satisfied (1). Fulfilling this requirement can provide sound justification for autoclave critical process parameters (CPPs) and how they were validated, no matter what type of production cycle is run.

The data demonstrated by the inactivation of the BIs have a numeric value, because the D-value (i.e., the decimal reduction time or time required to kill 90% of the BIs) and population are known through compendial testing. Because the F_0 number (i.e., lethality level) represented by the physical data is derived by an equation of probable microbial death rates, actual kill must be demonstrated as well. Although less precise by nature than data generated by calibrated thermocouples, the BI data can be enumerated and are relevant when compared to the physical data to demonstrate a real versus theoretical kill. It is this one-two punch that makes the validation an assurance of the routine sterilization process.

Defining overkill

The key point to remember is that overkill is a process description of the programed autoclave cycle parameters and not a validation description. In the Parenteral Drug Association *Technical Report 1*, an overkill cycle is defined as: "a sterilization cycle that is demonstrated to deliver an F_{phy} and F_{bio} of 12 minutes to the items being sterilized" (2). Overkill is differentiated from process-specific autoclave cycles for which the incoming bioburden load is not known. An overkill cycle addresses the worst possible routine manufacturing conditions and will assure that autoclaved items will meet the definition of sterile at the end of the routine autoclave cycle. It is for this reason that the *United States Pharmacopeia (USP)* General Chapter <1035> states that, with an overkill cycle, the need for incoming bioburden enumeration may be reduced (3). Referring to the manufacturing process, then, an overkill sterilization program for an autoclave describes the cycle, not the word validation.

Validation requirements

Validation for autoclaves is just like any other validation in that the executed test scripts must demonstrate a reliable, repeatable process. Because the process in question is one of microbial kill, which is based on probability, sterilization validation has the requirement of additional proof by means of testing using compendial BIs.

An overkill cycle addresses the worst possible routine manufacturing conditions, which should be challenged by the validation load conditions (2). The validation represents a known, worst-case demonstration of a successful cycle; hence the most resistant organisms (e.g., *Geobacillus stearothermophilus*) with a high population count are placed in the most difficult locations for steam penetration within a given load.

An overkill production cycle may be an appropriate choice to satisfy the numerous and sometimes conflicting regulatory requirements for delivered leathality to assure sterilization by claiming a CPP for F_0 of greater than a certain value, but the choice does not absolve a manufacturer from applying appropriate validation principles in demonstrating CPPs are met. If one of these methods of demonstration is

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biological data, these data should be relevant to the test being conducted.

Assessing bioindicators

BIs, if used as per *USP* <1035>, contain a known population of organisms. The range of possible BI D-values is 1.5–3.0 minutes and the population per indicator must be 10^5–10^6. Whether BIs are made in-house or purchased, these attributes of the BIs are documented. It is this known population that must be correlated to the actual F_0 measured at the adjacent thermocouple to give the test results meaning and justify the cycle conditions of the autoclave for the worst-case loads under test.

When claiming an overkill sterilization, one must still have a good scientific rationale for the choice of cycle parameters.

For example, inactivating a BI with a D value of 1.5 and a population of 10^6 should take an F_0 of 18 min. When the adjacent thermocouple accumulates 40 F_0s, a margin of error greater than 100% has been built into the biological portion of the test. This is an example of a bad test, not of "overkill sterilization validation." If, however, the BI has a D value of 36, the maximum allowable for a compendial indicator, then an F_{phy} of 40 would seem appropriate.

Justifying load parameters

When claiming overkill sterilization, one must be careful to still have a good scientific rationale for the choice of cycle parameters. Just choosing the time and temperature on a cycle without detailed assessment does nothing to demonstrate control or knowledge of the critical operating parameters of the autoclave cycle or how those are affecting your particular load conditions. Theoretical values cannot be assured throughout a load before mapping with thermocouples is done to assure air removal, and equilibration times support these assumptions.

It is crucial to determine appropriate cycle parameters. This author has repeatedly found autoclave cycles programed by the autoclave manufacturer and accepted by the plant owner without running development studies prior to operational and performance qualification. The program parameters were assumed to provide a predetermined sterility assurance level within all load items without any testing prior to the validation runs of an overkill cycle. It is necessary to compare theoretical F_0s with the actual F_0s delivered in an actual cycle. This real development testing will give a good idea of performance and capability of the autoclave and allow for realistic program-parameter settings.

It may be appropriate to add some time or temperature as a safety factor to account for all of the variables inherent to autoclaving items needed in a manufacturing process. Unknown incoming bioburden load is a reasonable driver to choose an overkill sterilization cycle. However, gross overage indicates a lack of control of the process and a lack of understanding of the appropriate lethality being delivered to load items. Delivered lethality should be well understood from development runs and applied judiciously, even in overkill cycles, in order for validation to be a credible assurance of process functionality.

Fractional cycles as a method of validating overkill cycles

Once actual F_0s throughout loads have been determined in development studies, program parameters may be defined for the autoclave cycles. At this stage it may be appropriate to use fractional validation load programs, for which the validation cycle program delivers an F_0 close to values needed to inactivate the BIs. The successful completion of this fractional cycle then gives a baseline to which a rational overage may be added for routine manufacturing cycles and justifies the term overkill (4).

By defining a fractional (i.e., partial) cycle time and temperature for validation loads based on an understanding of the autoclave capabilities in conjunction with particular load limitations, an excellent rationale can be made, and manufacturing cycles can be programed as overkill cycles. The overkill compensates for deviations in time or temperature caused by calibration faults in controlling thermocouples, chamber leaks, variability in packaging and assembling components, or other production events.

Conclusion

A cavalier approach to sterilization validation is no longer enough to satisfy most regulatory inspectors, who have grown accustomed to control strategies based on risk assessment and scientific rational for the mitigation of the identified risks. A more robust, quality-by-design philosophy based in sound science and process understanding is more appropriate and defendable.

Any autoclave validation, for either overkill or product-specific load cycles, must demonstrate the delivered lethality to the most difficult locations using biological and physical data. More than being just a "dead or alive" reading, the BI does enumerate delivered lethality when assessed appropriately. By knowing the D value of the BIs used and setting the fractional validation cycle to accommodate this value, inactivation can be achieved in the BIs and correlated to the thermocouple readouts. This validated cycle can then be appropriately increased to account for minor process variations to support a robust, validated process. This validation method, firmly based in the accepted tenets of sterilization science and a rational scientific approach, will provide a sound basis for an autoclave sterilization program.

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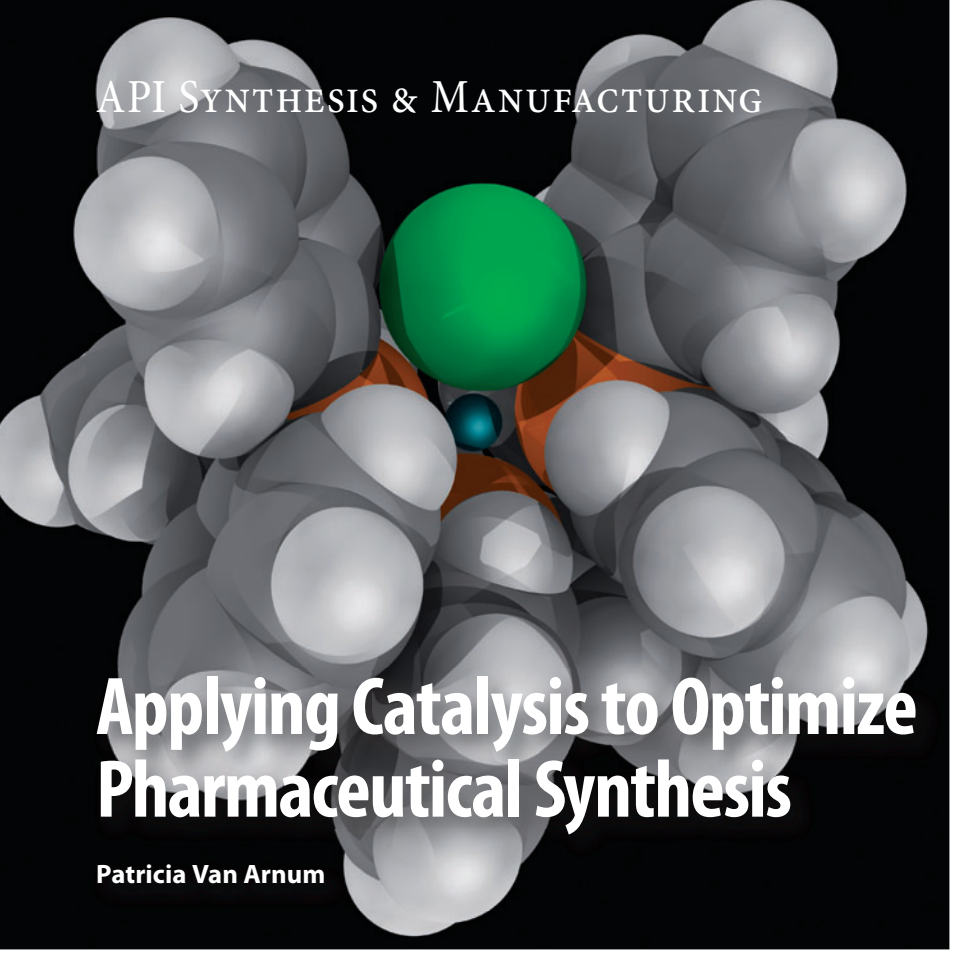


Applying Catalysis to Optimize Pharmaceutical Synthesis

Patricia Van Arnum

Fine-chemical companies, contract manufacturers, and researchers advance chemocatalysis and biocatalysis.

Organic chemists are tasked with optimizing synthetic routes for pharmaceutical compounds. Catalysts, both chemical catalysts and biocatalysts, play a crucial role in improving reaction efficiencies and conditions, increasing yield, and achieving desired stereoselectivity. Fine-chemical companies, contract manufacturers, and other researchers are advancing this field for producing pharmaceutical intermediates and APIs.

Company activity

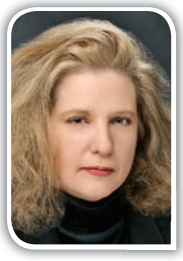
Codexis, a company specializing in biocatalysis, recently reported on its development of industrial biocatalysts for sulfide oxidation and Baeyer–Villiger-type monooxygenations (BVMO). These BVMO enzymes can be used to improve methods to manufacture chiral sulfoxides, which are important molecules for pharmaceutical synthesis. Codexis used these enzymes to develop biocatalytic processes for producing esomeprazole and armodafinil to improve enantiometric purity and reduce sulfone impurity, according to an Oct. 3, 2013 Codexis press release. The enzyme and API manufacturing processes are currently being scaled up for commercial supply. Codexis' BVMO enzymes are commercially available as a screening kit that process chemists can use to develop new biocatalytic oxidation processes.

Earlier this year, Codexis partnered with Purolite, a provider of ion-exchange, catalyst, adsorbent, and specialty resins, to develop and market immobilized enzymes for the pharmaceutical industry. The enzymes are immobilized through binding to inert resins to allow for easier separation from a reaction mixture, and immobilization allows the enzymes to be used under different reactions conditions and re-used at a commercial scale. The collaboration is focused on immobilized transaminase enzymes.

Codexis also partnered earlier this year with the CMO AMRI in a nonexclusive, two-year agreement focused on identifying and implementing new and improved manufacturing routes for select APIs. Codexis is providing its directed evolution technology for enzyme discovery and optimization, and AMRI is providing process development and manufacturing capabilities, including using AMRI's proprietary microbial strains.

Johnson Matthey Catalysis and Chiral Technologies (JMCCT) business unit, which provides heterogeneous, homogeneous, chiral, and biocatalytic technologies, is expanding its existing specialty ligand-manufacturing capability to include commercial-scale manufacturing up to 100 kilograms. The expansion is largely focused on the Buchwald ligands from the Massachusetts Institute of Technology. The Buchwald ligands offered by JMCCT are a class of dialkylbiaryl monophosphine ligands, which are used for the *in-situ* generation of active catalysts for coupling reactions in the manufacture of pharmaceuticals and specialty chemicals. The XPhos and SPhos ligands are used for Suzuki–Miyaura reactions, in particular with hindered aryl substrates and heteroaryl halides. In addition, the combination of Buchwald ligands, such as XPhos, SPhos, RuPhos, and BrettPhos with several palladium catalyst precursors, such as $Pd(OAc)_2$, $Pd(dba)_2$ and $Pd2(dba)_3$, are used in combination for the *in-situ* generation of active catalysts. These catalysts can be applied in carbon–carbon, carbon–nitrogen, carbon–oxygen, carbon–sulfur, and carbon–born bond formations, including the Suzuki–Miyaura, Negishi, Sonogashira, Buchwald–Hartwig amination and carbonyl alpha-arylation reactions.

The biocatalysis company evocatal is relocating to Monheim, Germany, to a facility that doubles the company's laboratory and production area to add additional capacity for research, process development, and production. The expansion adds new industrial fermenters to optimize the



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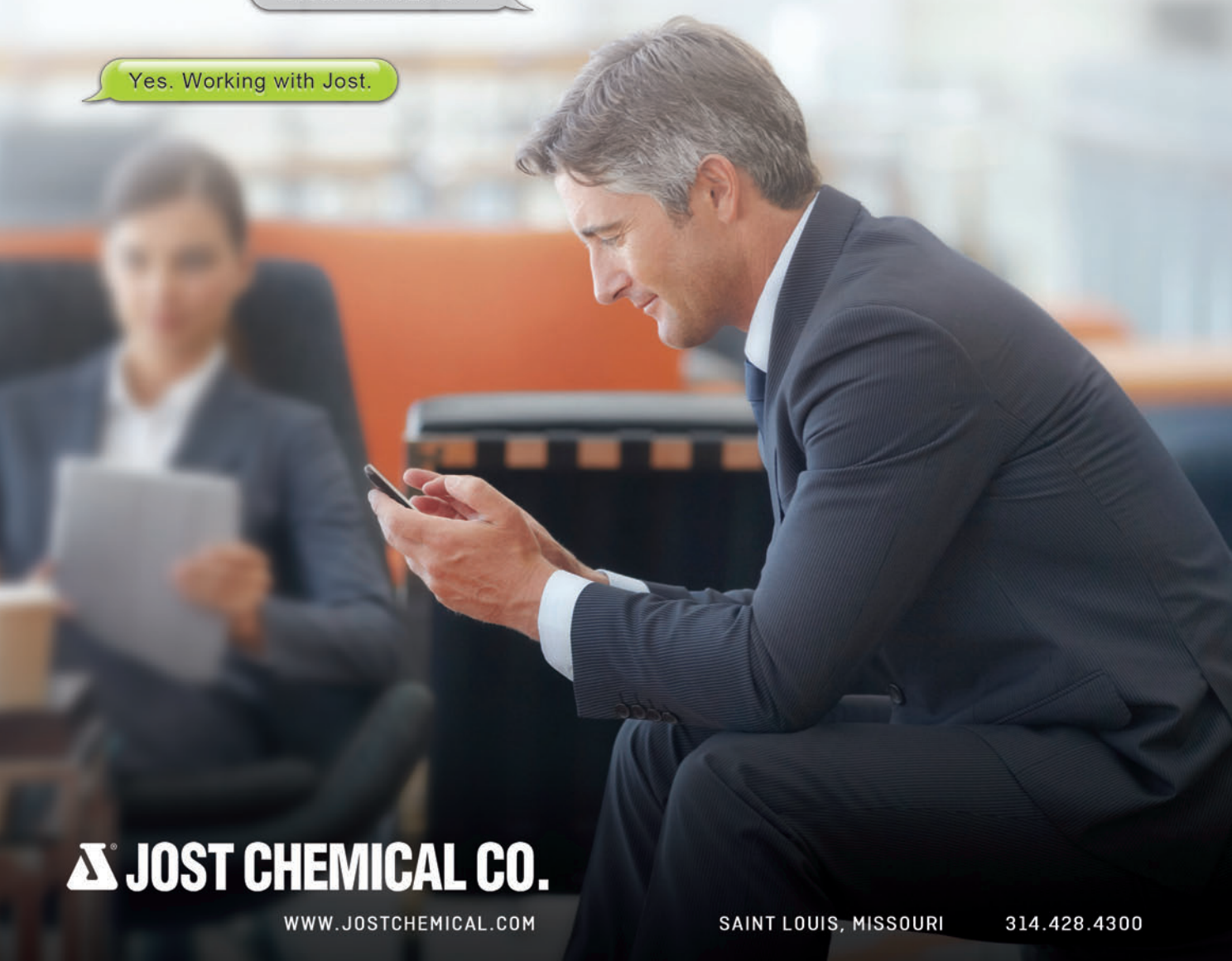

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manufacture of biocatalysts up to the 100-L pilot scale. In addition, the new location will house multipurpose equipment for the synthesis of fine chemicals up to the kilogram scale.

Almac recently reported on its collaboration agreement with DSM Pharmaceutical Products in biocatalysis, which includes the successful transfer of enzymes for enzyme screening, process development, and scale-up manufacture. The agreement grants both companies access to their enzyme platform technologies, services, and expertise for API manufacturing. Almac is bringing expertise in enzyme identification, scale-up, and implementation into early-phase projects, and DSM is providing commercial-manufacturing expertise, which gives Almac a preferred partner for large-scale production. Since forming their agreement in 2012, Almac and DSM have initiated and completed multiple projects in the fields of ketoreductases, transaminases, bio-oxidations, and hydrolases. Almac also recently completed a knowledge transfer partnership with Queens University Belfast to develop, improve, and embed bioprocesses.

Advancing catalysis

Researchers at Max–Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany recently reported on their work in immobilizing various catalysts on nylon and applying them in pharmaceutical synthesis among other reactions. Working in collaboration with scientists from the Deutsches Textilforschungszentrum in Krefeld, Germany and Sungkyunkwan University in Suwon, Korea, the researchers at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr developed a process for immobilizing different organic catalysts on textiles with the help of ultraviolet light. The fabric acts as a support for the substances on which a chemical reaction occurs.

The researchers used three organic catalysts: a base (dimethylaminopyridine, DMAP), a sulfonic acid, and a catalyst that functions as both an acid and a base, according to a Sept. 13, 2013 Max–Planck-Institut für Kohlenforschung press release. To attach the catalysts to the nylon fibers, the chemists irradiated the textile to which a catalyst was applied with ultraviolet light for five minutes. All three catalysts converted approximately 90% of the source materials to the desired products.

Compared with other ways of immobilizing catalysts, organotextile catalysis has several advantages. In particular, it provides the reagents with a larger surface than other supports, such as plastic spheres or foils, with the larger surface enabling a more efficient reaction. Moreover, the nylon is flexible and inexpensive. In the approach for immobilization of organocatalysts on the textile nylon using ultraviolet light, the catalyst and the textile material require no chemical modification for the immobilization (1). All of the prepared textile-immobilized organocatalysts (a Lewis basic, a Brønsted acidic, and a chiral organocatalyst) showed "excellent" stability, activity, and recyclability for various organic transformations, according to the researchers (1). They reported good enantioselectivity (> 95:5 enantiomeric ratio) that was maintained for more than 250 cycles of asymmetric catalysis. The researchers asserted that textile organocatalysis may be beneficial for various fields by offering inexpensive and accessible functionalized catalytic materials (1).

In another development, researchers at Boston College in Massachusetts reported on the enantioselective silyl protection of alcohols promoted by a combination of chiral and achiral Lewis basic catalysts. The researchers noted that catalytic enantioselective monosilylations of diols and polyols provide alcohol-containing molecules in high enantiomeric purity, but that these transformations require high catalyst loadings (20–30 mol%) and long reaction times (2–5 days) (2). To resolve those challenges, the researchers used an achiral cocatalyst structurally similar to a chiral catalyst. A combination of Lewis basic molecules served as an achiral nucleophilic promoter and the other molecule performed as a chiral stereoselectivity base. On the addition of 7.5–20 mol% of a commercially available *N*-heterocycle (5-ethylthiotetrazole), reactions typically proceeded within one hour, with high product yields and enantiomeric ratios (2). In certain examples, there were no reaction in the absence of the achiral base, but the presence of the achiral cocatalyst facilitated product formation in high enantiomeric purity (2). Overall, the new approach reduced the reaction time to less than an hour, down from a period of two to five days, reduced catalyst loading, and produced a more efficient transformation for enantioselective alcohol silylation, according to a July 2013 Boston College press release.

"The use of cocatalysts can be tricky, especially in procedures intended to deliver handedness in the molecules you want your reaction to produce," said Amir Hoveyda, the Joseph T. and Patricia Vanderslice Millennium Professor of Chemistry at Boston College, in the Boston College press release. "What we've shown is that in this procedure, you can take two cocatalysts, which on the surface are competing with one another, and effectively keep them from interfering with one another."

Hoveyda and Boston College Professor of Chemistry Marc Snapper have worked since 2006 on this method of catalysis. These catalysts, originally developed in their laboratories seven years ago, are valued for producing reactions that offer a high level of enantioselective purity. The relatively slow reaction time of two to five days was a key problem, but which was mitigated by applying a computational approach. The researchers used the cocatalyst model involving two Lewis base molecules, adding an achiral molecule to an already present chiral molecule. These cocatalysts operated in concert, with the chiral molecule activating alcohol and the additional achiral molecule (from commercially available 5-ethylthiotetrazole) activating silicon. Identification of the positive influence of ethylthiotetrazole proved to be the key component of the discovery, giving the team the ability to fine-tune the reaction and effectively control the interplay between the cocatalysts. Together, the Lewis bases served as a closely related Brønsted base to allow the catalyst to work faster while retaining high enantioselectivity.

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Predicting Long-Term Storage Stability of Therapeutic Proteins

Simon Webster

An increasing desire to deliver therapeutic proteins as liquid formulations for self-administration by patients has led to an increased need to develop molecules and formulations that are stable for several years when stored in solution in a refrigerator. Formation of protein aggregates during storage is of increasing concern to developers and regulators. Measurements that predict how stable a given protein and formulation will be during long-term storage are desirable to effectively screen and optimize candidate proteins and formulations early in the development process. The author reviews the scientific literature and examines multiple routes to aggregation during storage to suggest that multiple measurement types should be made to probe different aspects of protein behavior.

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Therapeutic proteins are a powerful and versatile way to treat a wide range of diseases. Commercial products such as Remicade (infliximab), Avastin (bevacizumab), and Humira (adalimumab) treat a wide range of indications, and a significant proportion of drugs currently under development are proteins. When compared to conventional small-molecule drugs, however, the delicate nature of proteins makes them difficult to use as commercial pharmaceutical products. To be a successful pharmaceutical, efficacy alone is not sufficient; the medicine must also be robust enough to retain this efficacy and remain safe for patients during extended periods of storage over multiple years.

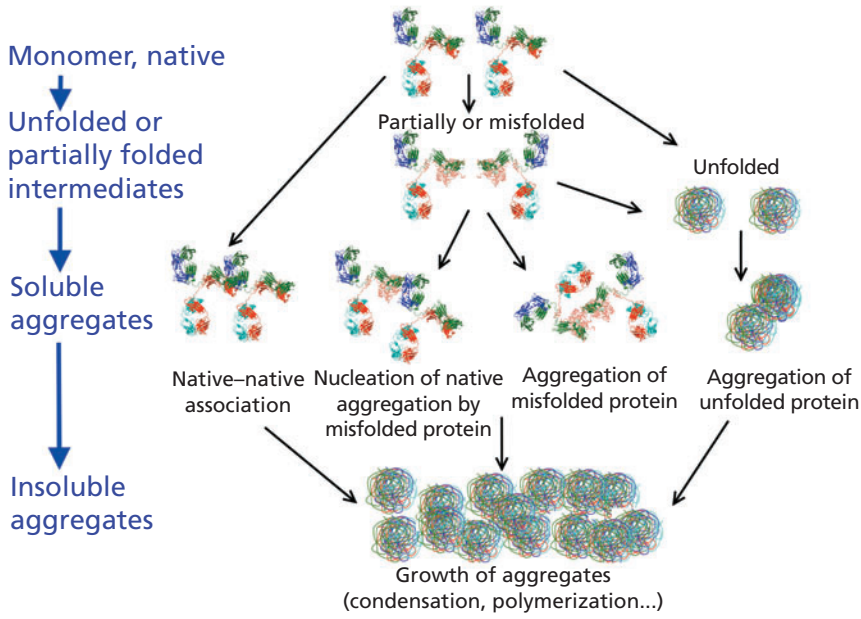
The challenge to produce protein medicines that are stable over extended periods has further increased in recent years due to pressure to move away from lyophilized formulations, which need reconstituting by the patient, toward more convenient liquid formulations, which can be directly injected. In addition, an increasingly competitive commercial landscape means that there are considerable pressures to bring products to market faster and for these products to have longer shelf lives.

Aggregation as a degradation route

Proteins in solution can degrade by means of several mechanisms during extended storage, and a common degradation route is aggregation of the protein over time. Recently, this route has been a particular focus for biopharmaceutical developers and regulatory authorities due to increasing concerns that the presence of even relatively small amounts of aggregated protein may lead to unwanted immune responses in patients, thus potentially resulting in adverse reactions or loss of efficacy over time.

Biopharmaceutical developers have two main strategies at their disposal to create liquid biopharmaceutical formulations with long shelf lives and a resistance to the formation of aggregates: engineering of molecules for aggregation resistance and the inclusion of additives that inhibit the formation of aggregates in the solution (i.e., formulation). There are, however, many possible ways to engineer a protein, as well as many different additives and combinations of additives that could potentially be used. How should a development scientist determine which of these many options will be the most effective at ensuring aggregation resistance during extended storage? One option

Figure 1: Schematic illustration of the multiple pathways by which monomer protein in solution can form aggregates.



is to try a range of protein engineering and formulation options, store them in the refrigerator, and come back in three years to measure the level of aggregates formed. Three years, however, is a long time to wait, especially if none of the protein engineering or formulations provide adequate aggregation resistance. What is needed is a rapid means of predicting at the start of the study, with a reasonable level of confidence, which molecules and formulations will resist the formation of aggregates. Such a method could be used by protein engineers and formulation scientists early in the development process to screen many molecules and formulations to identify the best options and ensure those taken forward will ultimately be suitable for use in a commercially viable product. Real-time storage-stability studies of the selected molecules and formulations will still need to be performed to satisfy the regulators, such as FDA and the European Medicines Agency, but early use of a predictive screening tool has the potential to dramatically reduce the risk of such studies failing.

Biopharmaceutical developers have historically performed a range of activities to try to predict and optimize the long-term aggregation stability of therapeutic proteins early in development. The scope and reliability of these efforts, however, have been restricted somewhat by the lack of suitable technologies and a limited understanding of aggregation processes. For example, methods such as differential scanning calorimetry (DSC)—traditionally used to experimentally screen the stability of proteins in a range of buffer compositions—use a relatively large amount of often scarce protein sample, which limits the number of conditions that can be tested. Additionally, DSC only probes one of a number of possible routes to aggregate formation and therefore may not be predictive if an alternative mechanism dominates.

Predicting aggregation during long-term storage

In an ideal world, a computational tool would be available to predict which molecules and formulations will have optimal stability and how they will behave over extended periods of time. There are a range of computational tools available that aim to help predict the aggregation propensity of proteins. These are undoubtedly useful. Therapeutic proteins, however, are typically large and complex molecules, and industry's knowledge and understanding of aggregation mechanisms, the effect of the solvent environment on these molecules, and the exact mechanism of action of many excipients remains incomplete. This incomplete knowledge currently limits the practical use of such computational tools.

Empirical methods that can be applied early in the development process and that will provide the information necessary to make predictions about long-term storage stability must, therefore, be used. A fundamental question is: what experimental measurements of candidate molecules and formulations will, for example, predict the level of aggregation in solution after multiple years stored at 4 °C? Unfortunately for the biopharmaceutical development scientist, there is currently not a single, unambiguous answer to that question. There are, however, a number of attempts to tackle the problem reported in the scientific literature.

A comprehensive article by Weiss *et al.* from the University of Delaware reviews the state of the art in 2008 and reveals that the science of predicting the long-term storage stability of proteins was something of a work in progress at the time (1). Despite some progress in the intervening years, it remains so today. A number of more recent publications, however, have tackled this difficult question and proposed some answers. This article presents a short review of some of the most notable proposed approaches to predicting long-term aggregation propensity of protein solutions.

Aggregate formation route determines predictive measurements

There are a number of routes by which monomer proteins in solution can come together to form aggregates and, to

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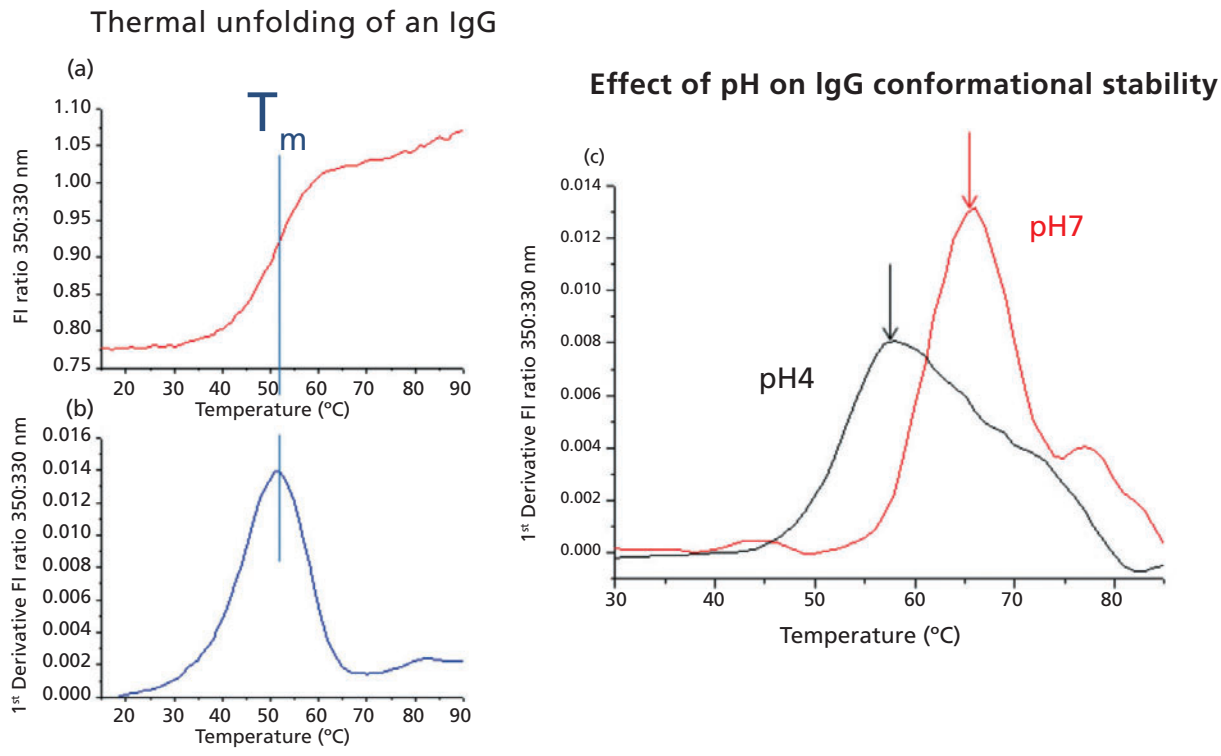
Figure 2: Example of the use of intrinsic protein fluorescence to determine protein thermal unfolding temperature, T_m. Figure 2(a) shows that cooperative unfolding of the immunoglobulin G (IgG) protein results in a change in the wavelength of maximum emission. As shown in Figure 2(b), the midpoint of this transition may be identified as the maximum of the first differential of the fluorescence unfolding curve. Figure 2(c) compares the thermal conformational stability of an IgG sample at two different solution pHs and indicates that the protein is substantially less stable at pH 4 than it is at pH 7.



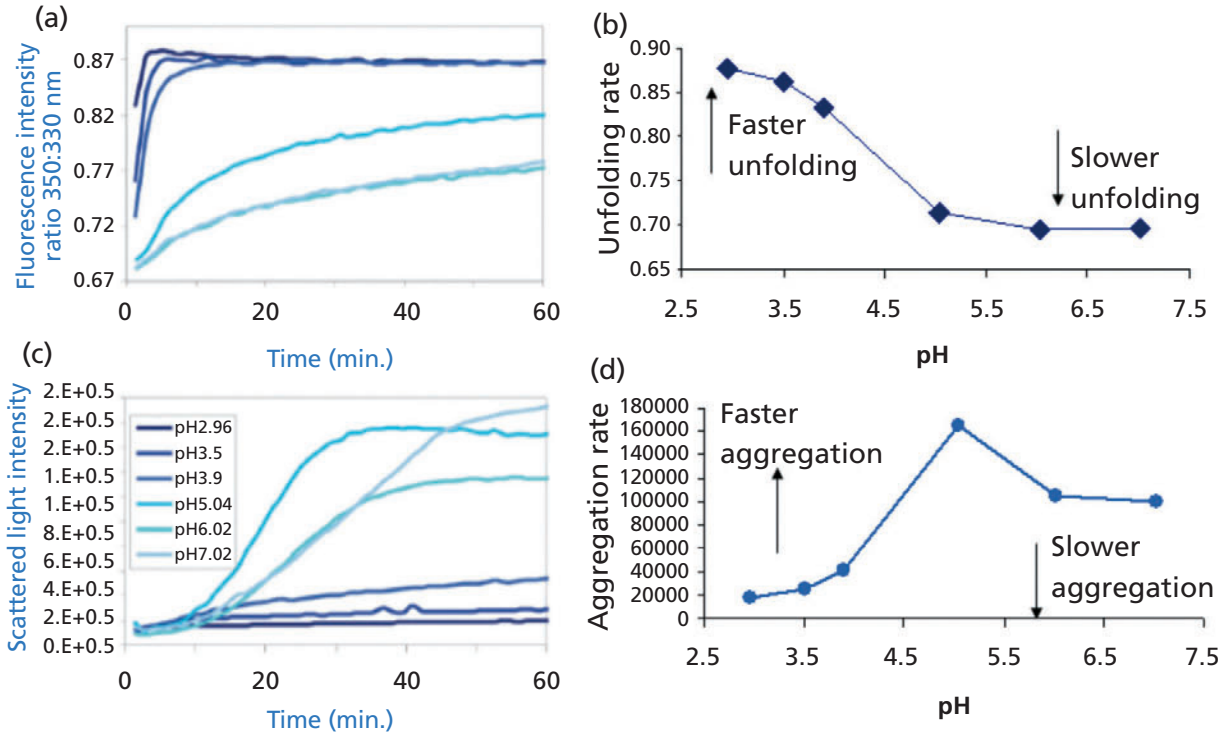
make accurate predictions of long-term aggregation behavior, measurements must be found that probe in some way the crucial steps along this pathway to aggregation. Two pathways by which protein molecules can aggregate are illustrated schematically in **Figure 1**. In the first pathway, some of the proteins in solution unfold either partially or fully so that aggregation-competent regions, such as hydrophobic residues, are exposed and cause the proteins to stick together—this is described as "non-native aggregation." In the second pathway, the protein molecules retain their correctly folded, native conformation, but have aggregation-competent regions on their surface, such as localized charged regions or hydrophobic patches, that cause the proteins to stick together and aggregate. The aggregation rate-limiting steps for these two different pathways are quite different, and, therefore, different experimentally measurable parameters may be potentially useful, depending on which pathway is dominant for a particular molecule or formulation.

Lack of conformational stability in aggregation

First consider the case of non-native aggregation processes, in which the conformational stability of the protein may play a role. One of the most widely used, experimentally determined parameters for screening molecules and formulations for stability is the temperature at which the protein is observed to unfold, which is the protein melting temperature (T_m). T_m may be determined experimentally by applying a temperature ramp to the protein in the solvent of interest and identifying the temperature at which the protein unfolds using either calorimetric methods, such as DSC, or spectroscopic methods, such as intrinsic protein fluorescence, as illustrated in **Figure 2**.

T_m has been used as a crucial stability-indicating metric for candidate screening and formulation development by the majority of large biopharmaceutical developers for a number of years, and many reports of its application in high-throughput formulation screening have been presented (1–9). Conceptually, a higher T_m will mean that, in a refrigerator at 4 °C, there will be statistically fewer unfolded protein molecules in solution and, therefore, less chance of the formation of non-native aggregates over time. As a means of predicting long-term storage stability, this may be useful in cases for which the T_m of the protein is particularly low, but for comparing proteins or formulations for which the T_m

Figure 3 (a) and (b): Examples of the use of protein intrinsic fluorescence to monitor the time-dependant rate of thermally-induced unfolding of an IgG protein as a function of solution pH and simultaneously acquired time-dependent aggregation behavior. Figure 3(c) and 3(d) show data obtained using static light scattering.



is relatively high, the number of unfolded proteins predicted by this parameter will be very low indeed. An interesting illustration of both the potential—and the limitations—of the predictive powers of T_m was reported by Goldberg *et al.* from MedImmune, who observed a correlation between T_m and aggregation stability during storage at 40 °C for two monoclonal antibodies, but not for a third (2). The stability of the third antibody appeared to be predicted by its rate of aggregation when heated to 70 °C. T_m is, therefore, a useful prescreening tool to identify particularly conformationally stable or unstable molecules or formulations, but may not, on its own, be predictive of long-term storage stability for all samples. It is worth noting, however, that T_m may be useful in understanding other aspects of protein stability relevant to its use as a biopharmaceutical, such as how the protein will behave at temperatures higher than 4 °C, due to unplanned temperature excursions during storage, the higher temperatures experienced during manufacture, and the elevated temperatures *in vivo*.

High-temperature aggregation kinetics as a predictive tool

An alternative or additional approach to the use of T_m as a predictor of storage stability (summarized in **Table I**) is to observe the kinetics of aggregation when the sample is held at a temperature that accelerates the formation of aggregates. Such measurements essentially probe a combination of the time-dependent rates of unfolding and the aggregation of these proteins. Christopher Roberts and his group at the University of Delaware have demonstrated the value of measuring aggregation rates at elevated temperatures for rapid formulation and candidate screening (1, 10–12), and these authors emphasize that understanding the rate-limiting step in the non-native aggregation pathway is important to predicting behavior at lower temperatures and longer times. One approach to identifying the aggregation rate-limiting step is to try to fit various mechanistic aggregation models to accelerated (elevated temperature) aggregation data to identify the model that fits best. Once this best fit has been established, the selected model may be used to predict behavior at lower temperatures and longer times. Kayser *et al.* have also demonstrated the application of this approach (13).

The Delaware group of Roberts *et al.* have also described a practical method which predicts the aggregation behavior for an immunoglobulin G (IgG) molecule of interest (11, 12). A thermal ramp was applied to the IgG in a range of solution conditions, and the amount of aggregation was monitored as a function of temperature. The authors determined that the temperature at which the rate of increase in aggregate content exceeded a certain set value (obtained in an experiment taking approximately an hour) was a useful predictor of aggregation behavior of the same sample when stored at 40 °C for 40

Table 1: Measurements with the potential to predict long-term storage stability.

Probes of protein conformational stability		
Type of measurement	**Measured parameter**	**Experimental method**
Equilibrium thermal unfolding	Thermal unfolding mid-point, T_m	Fluorescence, differential scanning calorimetry
Equilibrium denaturant unfolding	Denaturant unfolding midpoint, $D_{1/2}$	Fluorescence, circular dichroism (CD)
Time-dependent thermal unfolding	Thermal unfolding rate(s), K_T unfolding	Fluorescence, CD
Time-dependent denaturant unfolding	Denaturant unfolding rates, K_D unfolding	Fluorescence, CD
Probes of protein colloidal stability		
Type of measurement	**Measured parameter**	**Experimental method**
Protein–protein interaction	Second virial coefficient, A_2	Static light scattering, self-interaction chromatography
Protein solubility by precipitation	Precipitation midpoint, [precipitant]	Ammonium sulfate or polyethyleneglycol precipitation with static light scattering, turbidity
Protein diffusion interaction	Diffusion interaction parameter, k_D	Dynamic light scattering
Probes of combined colloidal and conformational stability		
Type of measurement	**Measured parameter**	**Experimental method**
Thermal scanning aggregation	Aggregation onset temperature, at which aggregation rate exceeds a certain value	Static light scattering, size-exclusion chromatography–high-performance liquid chromatography (SEC–HPLC)
Time-dependent, thermally induced aggregation	Aggregation rate(s)	Static light scattering, turbidity, SEC–HPLC

days. Experimentally, there are a number of possible routes to obtaining this kind of data in a high-throughput screening environment, with optical methods being particularly well suited to this type of application. **Figure 3** shows typical data obtained using intrinsic protein fluorescence to monitor time-dependent unfolding and static light scattering to monitor the corresponding rate of aggregation.

Protein-protein interactions as a predictive tool

The experimental approaches described so far largely probe non-native aggregation mechanisms arising due to attractive forces between fully or partially unfolded protein molecules in solution. As discussed earlier, attractive interactions between native proteins in solution can also potentially lead to the formation of aggregates, and it is therefore interesting to measure the strength and nature (attractive or repulsive) of these interactions for candidate proteins or formulations. The resistance to aggregation due to native protein–protein interactions in solution is often referred to as the "colloidal stability" of the protein. A number of experimental methods are available to determine this stability, including self-interaction chromatography and dynamic light scattering. Static light-scattering arguably provides the most accessible and developed method for measuring protein-protein interactions in solution and requires only the protein concentration-dependent light-scattering intensity from the protein of interest in the solution of interest. By combining these data with suitable physical and instrumental constants, one can generate a graph, known as a Debye plot, from which a value called the second virial coefficient (also known as A2 or B22) can be extracted (14). The sign of this value indicates whether the protein–protein interactions are attractive (a negative value) or repulsive (a positive value) while the magnitude of the value indicates the strength of the interaction. Generally, one might expect that molecules or formulations with net repulsive protein-protein interactions will be more resistant to aggregation. A number of studies have integrated use of the second virial coefficient, or its equivalent, into their formulation screening approaches (7, 14–16) and, like T_m, it has proven to have a useful predictive value for some proteins, but not for all.

It is also worth noting that the aggregation rates of unfolded monomer proteins will be determined, in part, by the nature of interactions between these species. For example, attractive hydrophobic forces caused by exposure of the hydrophobic residues could potentially be overcome by repulsive electrostatic forces if all the molecules carry a significant net charge.

Protein solubility might hold the key

An alternative approach to investigating the effect of native protein–protein interactions is to determine the solubility of the candidate protein in the solution of interest. An interesting study was recently presented by Banks *et al.* from Amgen, which experimented with two strategies to formulate an IgG (17). One approach sought to stabilize the conformation of the protein, and the other sought to improve its colloidal stability. The effects of the formulations on conformational stability were

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evaluated with DSC, and the effect on protein solubility was investigated using ammonium sulfate precipitation. Importantly, the formulations were also stored at 4 °C for nearly a year, and the rate of aggregate formation was measured to directly assess the effectiveness of the formulation in preventing aggregation during long-term storage. The key result of this study was that, for the molecules and formulations studied, the effect of the formulation on the solubility of the protein, rather than the effect on the conformational stability, was key to improving the long-term aggregation resistance of the protein at 4 °C.

Complications at high protein concentrations

To be delivered subcutaneously, many therapeutic proteins need to be supplied at very high concentrations, often 100 mg/mL or more. At these high concentrations, the protein molecules are very close to one another, and the nature of the dominant forces acting between them can change from long-range forces to shorter-range forces. This change has the potential to further complicate the process of predicting shelf life because, in some instances, there may be different processes limiting the rate of aggregation for dilute and concentrated solutions.

An interesting example of this phenomenon was reported by Kumar and colleagues from Abbott, who studied two molecules, a monoclonal antibody (IgG1) and a dual variable domain antibody (DVD-Ig), and obtained a range of analytical data at low and high (up to 150 mg/mL) concentrations (18). The data were correlated with the rate of aggregate formation when the samples were stored at 5 °C for an extended period. The results suggested that, for the monoclonal antibody studied, the second virial coefficient (A2) was a good predictor of aggregation behavior for both the low and high concentration samples. However, for the DVD-Ig molecule, although the second virial coefficient was a good predictor at low protein concentrations, it failed at high concentrations, for which the thermal conformational stability was found to be a better predictor. The authors rationalized this as being due to the interactions leading to aggregation of the IgG at both high and low concentrations and of the DVD-Ig at low concentration being electrostatic and, therefore, relatively long-range in nature. In contrast, at high concentrations of DVD-Ig, short-range, attractive hydrophobic forces became the dominant interactions, leading to aggregation during quiescent storage. The authors hypothesized that, in conditions where the DVD-Ig molecule had low thermal conformational stability, there may be a greater chance of the normally buried hydrophobic residues becoming more exposed. This would enhance attractive hydrophobic interactions and explain the apparent correlation between T_m and aggregation at high concentrations.

Conclusion

As can be seen from the previous discussions, a number of rapid analytical measurements have been used to successfully predict protein-aggregation behavior during long-term storage at refrigerator temperatures (2–8 °C). Currently, however, no single measurement can be considered predictive of long-term storage stability for all proteins in all formulations and at all protein concentrations. To improve the predictive capabilities of early-stage protein candidate and formulation screening, multiple measurement types are needed to probe different potential pathways to aggregation. These measurements can be used to optimize protein candidates and formulations. In addition, these measurements can be used to investigate the dominant mechanisms that lead to aggregation for a particular molecule, so that strategies to alleviate these may be rationally designed. Measurements probing conformational stability, such as T_m and time-dependent rates of thermal unfolding, as well as measurements probing colloidal stability (e.g., second virial coefficients from static light scattering or solubility from ammonium sulfate precipitation) should all be performed to give a full picture of the mechanisms which may have an impact on long-term storage stability. Some measurements, such as aggregation rates at elevated temperatures approaching the T_m of the protein, might be expected to contain a convolution of information about conformational and colloidal stability (e.g., rates of unfolding and rates of aggregation of unfolded species).

Conveniently, recent advances in analytical instrumentation mean that many of the measurements described above and in the literature referenced in this article can be rapidly performed in an automated, high-throughput manner using modest protein- sample volumes. Some of these instruments can obtain multiple conformational and colloidal stability parameters from a single sample, further streamlining the process of obtaining the empirical information needed to make accurate predictions. These technologies make it feasible to obtain a wide range of potential predictive parameters routinely and cost-effectively as part of the protein candidate and formulation screening and optimization workflow. Although this still may not provide guaranteed predictions of what will happen to every product after three years in a refrigerator, it should greatly reduce the risk of any unpleasant, and expensive, surprises in the future.

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Implementing Risk Management for Regulatory Compliance

ON-DEMAND WEBINAR

REGISTER FREE at http://www.pharmtech.com/regcomp

EVENT OVERVIEW:

The pharmaceutical industry is facing a new benchmark for quality and compliance as risk management becomes a crucial approach for measuring and monitoring compliance activities. This 60-minute webcast will explore the strategy behind risk in compliance, define the various ways and terms associated with risks, and how business processes incorporate risk to drive a proactive approach to continuous improvement. Learn from leading industry experts on the relationship between risk management and risk assessment, the use of risk tools in common compliance processes, and the importance of risk reporting.

Key Learning Objectives:

- Understand the growing industry trends in risk management and best practices in defining risk factors for an organization
- Learn why risk is an integral part of the compliance process
- Outline the paths for success for implementing a risk-based strategy

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- Directors, group leaders, managers, and senior staff of information technology (IT) operations
- CMC (chemistry, manufacturing and controls) staff
- Senior scientists

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Patricia Van Arnum
Executive Editor
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For questions contact Sara Barschdorf at sbarschdorf@advanstar.com

JONATHAN EVANS/PHOTODISC/GETTY IMAGES

Disposable Applications in Demand by BioPharma

Eric S. Langer

Interest in chromatography innovation continues to decline.

It's becoming harder to ignore the rapid emergence and impact of single-use devices on biomanufacturing. Data from BioPlan Associates' *10th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* suggest that the interest in disposable devices has begun to extend to biopharma operations beyond basic single-use bags and connectors (1).

BioPlan Associates asked more than 200 biopharma industry decision-makers to identify the top areas they want their suppliers to focus their new product development on. Four disposable device categories top the list, each cited by more than one-third of respondents (see **Figure 1**): disposable products, bags and connectors (43.8%); disposable probes and sensors (39.6%); disposable bioreactors (34%); and disposable purification products (also 34%).

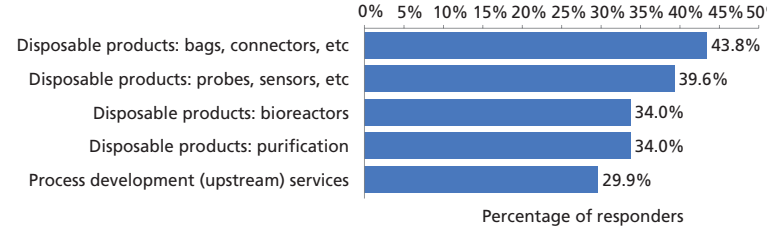
Rounding out the top five innovation areas were process development (upstream) services (29.9%), followed by analytical assays (27.1%), process development (downstream) services (26.4%), and analytical development (26.4%).

It's not a surprise to see bags and connectors top the list. This area has been a growing trend over the past five years. While many respondents separately said they expect to see fully disposable facilities in the next five years, the predominant single-use paradigm still involves dropping multi-layer plastic laminated bags/liners into what are basically classic-design stainless-steel bioreactors, mixers, and other fluid containers. The majority of vendors are behind this approach, particularly as they invested heavily in expensive bag-making facilities in the past few years. This approach, though, may actually stifle long-term innovation—as vendors won't be focusing as much on other more innovative product lines in the near future.

Aside from bags and connectors, there is continuing demand for improvements in single-use bioprocessing sensors and probes. Currently, few single-use sensors are sufficiently robust, and sensors are restricted to relatively few analytes. Relatively few single-use sensor products are currently available, and there are often issues regarding ports and how to pass single-use sensors through bioreactors and other vessels and their bag liners.

The industry is likely to see innovation in tubing and connectors, many targeted to replace and/or be cheaper than silicone, including fluoropolymers tubing, fluoropolymer-lined tubing, and new thermoplastics blended tubing. Many of these new tubing options will provide improved performance compared with silicone, likely by being heat-sterilizable at higher temperatures, lasting longer, and resulting in less leaching from plastics.

Figure 1: The top new product development areas cited by biomanufacturers and CMOs.



**Source: 10th Annual Report and Survey, Biopharmaceutical Manufacturing and Capacity, www.BioPlanAssociates.com, April 2013*

Single-use innovation

Several trends are driving innovation interest in single-use equipment. Greater application of quality-by-design (QbD) principles in manufacturing stimulates interest in probes and sensors. Similarly, innovation in probes and sensors is fueled by commercial interest in biosimilars and biobetters, which require the ability to demonstrate rigorous, extensive, and robust comparability.

Results from BioPlan's study show that disposable innovation is growing. Interest in new disposable products is up in this year's survey, and bags and connectors represent the highest level in at least the past four years at 43.8% of respondents (up from 38.9% in 2010). The same is true for disposable probes and sensors, up from 29.3% of respondents in 2010 to 39.6% in 2013.

Interest for improved cell-culture media is down to 25% this year from 35.4% in 2010, suggesting that these products have improved sufficiently relative to the hurdles in other areas of bioprocessing, such as downstream processing. The

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FIGURE 1 IS COURTESY OF THE AUTHOR.

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pendulum may be swinging back from downstream problems, as other product areas experiencing a relative decrease this year in demand for improvements include: process development (downstream) services (26.4% this year versus 34.9% in 2010); chromatography products (25% vs. 36.7%); and general separation products (16.7%, from 20.5%).

Disposable purification product innovation

BioPlan evaluated the differences between how respondents at biotherapeutic developers and CMOs viewed the need for innovation. The two groups' perspectives were quite different.

The most dramatic differences were seen with disposable purification products, with 61.1% of CMOs citing this as an area of innovation interest, more than twice the rate for developers, at 30.2%. CMOs are generally involved with many more and diverse products compared to innovator companies and see more issues with purification than developers.

Aside from disposable purification products, CMOs expressed slightly less interest than developers in disposable product innovation (most notably for probes and sensors), surprising given that disposables provide the flexibility and rapid turnaround required by CMOs. Areas where CMOs had more interest compared to product developers included process development and downstream services, analytical development, process development and formulation, validation, and instrumentation.

On a regional basis, interest in disposable bags and connectors was fairly consistent across the United States (47.7%) and Western Europe (45.7%). US respondents were more attracted to innovation in disposable probes and sensors compared with Western Europeans (46.5% and 31.4%, respectively) and disposable bioreactors (38.4% vs 31.4%), while the opposite was true with respect to disposable purification products (34.9% and 42.9%, respectively).

Respondents in the rest of the world in general were less interested in disposable innovation and more interested in services. Bioprocessing products are marketed and readily available worldwide, while many countries lack bioprocessing critical mass and infrastructure and have fewer CMO and CRO services available.

Downstream innovation

Improvements in upstream manufacturing have greatly improved yields in recent years, much of this due to improved cell lines and expression systems. With enhancements in these and other areas, users are now expressing desires for comparable improvements in downstream purification.

BioPlan's study suggests that upstream improvements are now more highly desired than downstream improvements despite downstream still being very much a problem area compared to upstream bioprocessing. Why users desire better bags and connectors over better downstream technology, where most of the bottlenecks are, is up for debate. Users are generally experienced in the bag-in-a-vessel paradigm, not seeing any substantial technological changes or progress with these products since their launch about a decade ago while advances in upstream manufacture are more common and are moving more into the mainstream, such as tangential flow filtration chromatography and new Protein A products and alternatives.

Nevertheless, downstream purification processes remain little changed and are increasingly the major limiting factor in commercial-scale biopharmaceutical manufacture. It would be expected—certainly if CMOs are to be seen as leading indicators—that purification will become a more highly sought area for which product improvements are desired.

Reference

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Solutions in Pharmaceutics – *contin. from page 34*

Engineering GmbH (RCPE), INNOJET Herbert Hüttlin, CREMER Oleo GmbH & Co. KG, and the Karl Franzens University to identify and develop HMC parameters for producing such fast-acting medicines. The goal of the project is to develop new pharmaceutical formulations and manufacturing processes, and engineer new approaches and manufacturing controls for effective masking of the unpleasant tastes and smells associated with most APIs.

Preliminary results from the ongoing project have highlighted that the production of fast-release medicines using HMC is feasible and amenable to scale-up. The transfer of the technology into production is underway. In several proof-of-principle studies, the parameters for formulating ODGs containing fast-acting APIs were successfully identified. The proof of concept studies included many different lipids, such as mono-, di- and triacylglycerides with varying carbon chain length (C14 to C22). In addition, more than 10 emulsifiers were tested. The resulting dosage forms provide rapid dissolution characteristics, similar to those of film-coated immediate-release tablets. Importantly, the granules are pleasant tasting and easy for patients to ingest. The HMC approach at Hermes is being extended to formulate other fast acting medicines such as ODGs, with the method expected to be fully validated and available for use by pharmaceutical developers in the near future.

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Ensuring USP Compliance with Revised Chapters on **Weighing**

LIVE WEBCAST:
Tuesday, December 3 2013
11:00 EST; 16:00 UTC (GMT)

REGISTER FREE AT **www.pharmtech.com/USPcompliance**

EVENT OVERVIEW:

The United States Pharmacopeia (USP) revisions to General Chapters <41> Balances and <1251> Weighing on an Analytical Balance become official on December 1, 2013. This 45-minute webcast will inform you about the details of these latest changes, explain the impact on your weighing processes and advise how you should update your standard operating procedures (SOP's) to remain compliant.

General Chapter <41> now states that accurate weighing must be performed using a calibrated balance. Repeatability and accuracy requirements are clarified and updated, with new acceptance limits and permissible test weights.

General Chapter <1251> has undergone major revisions focusing on balance qualification and operation, including the importance of "minimum weight". A daily balance check, typical in the pharmaceutical industry, is not actually a requirement. Instead, the type and frequency of balance checks should be determined by the risk and process tolerance of the application. Performing the right tests at the right intervals will ensure quality results and can potentially save time and money by eliminating unnecessary testing!

General Chapter <1251> also introduces "gravimetric dosing", a state-of-the-art weighing methodology for analytical standard and sample preparation. This method involves weighing of the sample and diluent, resulting in concentration units of mg/g.

In this webcast, Gregory Martin, President of Complectors Consulting LLC and Chair of the USP Expert Panels on "Balances", explains the implications of the latest USP revisions for balance users. Weighing and compliance experts from Mettler Toledo help you to understand what changes you need to make to your standard operating procedures (SOP's) to comply. Take advantage of this unique opportunity to obtain expert advice during a live question and answer session after the presentation, allowing you to verify that your weighing procedures are up to date before your next audit.

Who Should Attend:

- Laboratory Managers
- Compliance Managers
- Regulatory Affairs Managers
- Engineering Managers
- Production Managers
- Quality Assurance Managers
- Metrology Personnel

Key Learning Objectives:

1. Based on USP changes, discover which tests have to be periodically performed on balances used for quantitative analysis and which acceptance criteria apply from 1st Dec
2. Recognize that a daily balance check is not a requirement and get insight into the risk-based approach recommended by USP General Chapter <1251>
3. Learn how to assess and calculate the minimum weight of your balances
4. Find out more about gravimetric sample preparation and how to implement this method

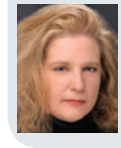
Presenters

Gregory P. Martin
President of Complectors Consulting LLC; Chair of the USP Expert Panel on "Balances"; Former Director of Pharmaceutical Analytical Chemistry at Merck Research Laboratories

Dr. Martin Huber
Head of GWP Competence Center Mettler-Toledo AG

Dr. Joanne Ratcliff
Communications Project Manager, Laboratory & Weighing Technologies, Mettler Toledo AG

Moderator



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Product labels

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Compliance in Quality Systems

Siegfried Schmitt of PAREXEL discusses regulation requirements for quality systems.

Q. What's wrong with compliant quality systems?

A. Reading healthcare regulations for pharmaceutical products, the key to compliance and product quality is a quality management system (QMS) that meets expectations of GMP guidelines. What we continue to observe as an industry, however, is a constant stream of warning letters, import alerts, and recalls. FDA's Rick Friedman delivered a presentation on Sept. 30, 2013 at the Regulatory Affairs Professional Society (RAPS) Annual Conference in Boston on sustainable compliance, in which he explained that compliance requires a quality system that meets the letter of the law and sound science-based decisions. In short, they need to go together hand-in-hand (1).

There seems to be an overreliance on thousands of standard operating procedures (SOPs) and work instructions, rather than on process and product understanding within the context of good practices. Friedman also said that without the right subject matter experts (SMEs), organizations would lack the necessary understanding, expertise, and knowledge to support quality and compliance at expected regulatory levels. In addition, industry restructuring will likely eliminate the expertise needed to reduce quality and compliance failures.

Quality systems are often large collections of documents that must be rewritten with each organizational or procedural change. Rarely, if ever, is this done proactively or (at least) in a timely manner. The mere structure of these quality systems, and their associated documentation, prevents them from being agile, effective, robust, culture-focused, and mature.

To fix this problem, organizations must take a process-oriented approach to designing and documenting quality management systems. The basic principles of a tableting process are universal, but attempting to integrate the quality systems of two tablet manufacturers would reveal few SOPs that could be used interchangeably (allowing for equipment differences) because they are generally too complex, too wordy, and not derived from common process flows. Process flows are added almost in hindsight at the end of SOPs, driven by document text, not the other way around.

A large number of compliant QMSs in their current state do not deliver product quality. They merely establish a framework of often difficult-to-maintain documents. It is the interpretation, expertise, and mental capacity of SMEs that transform these systems into tangible quality and compliance outputs. For example, how often do we see "Preventive action: update SOP." Is this really preventive? The question should have been: Why was the SOP not appropriate in the first place?

If we want mature, agile, and compliant quality systems that deliver every time, we must re-examine how to design and build them, and have them interpreted, applied, and continually improved by SMEs. This won't make regulatory inspections superfluous, but it would make them much happier events. In addition, it will provide companies with an important competitive advantage.

Reference

1. R. Friedman, "Moving from QC to QA: How to Assure Consistent Quality (Sustainable Compliance)," RAPS Annual Conference, Sept. 30, 2013, www.raps.org. PT

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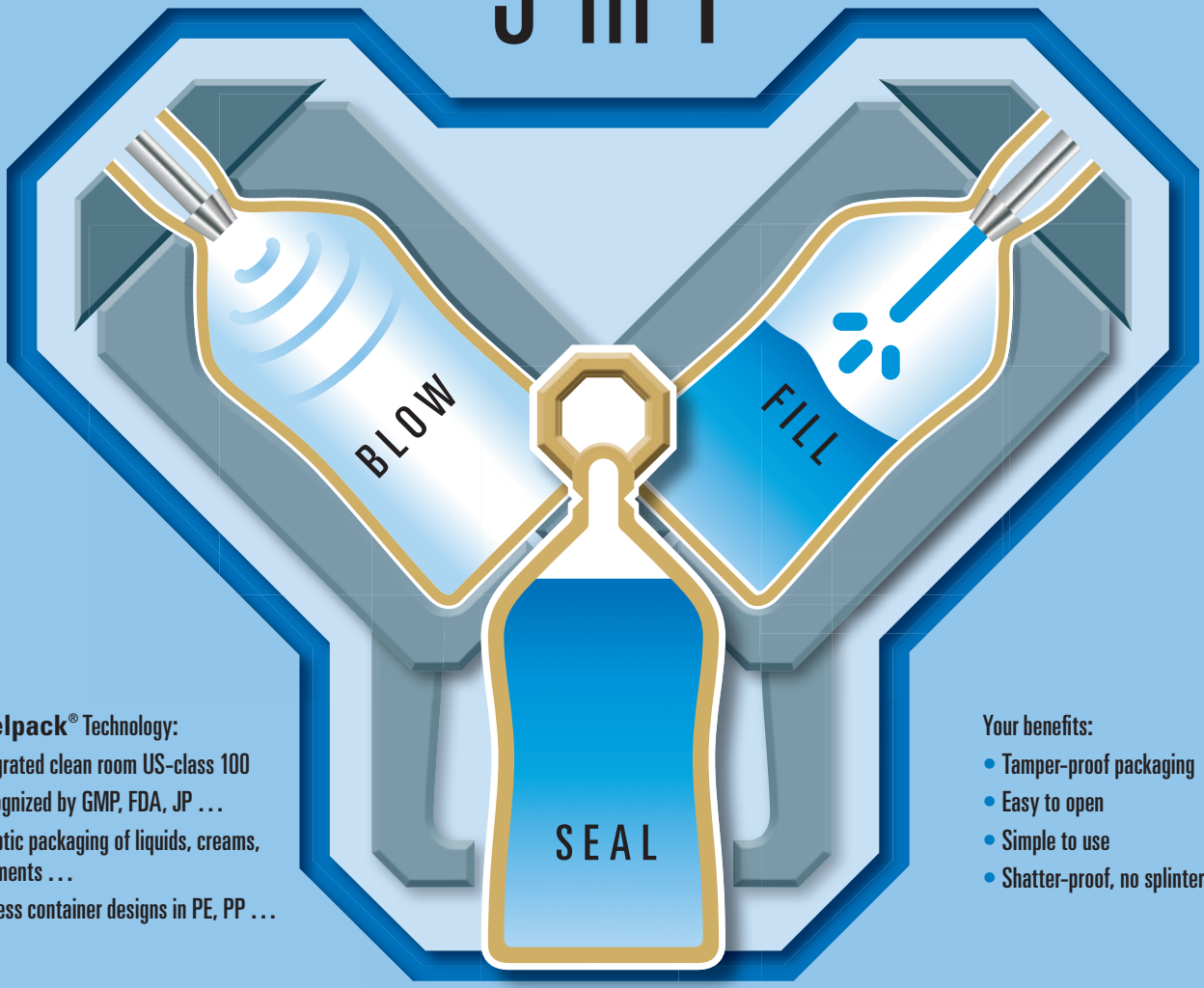

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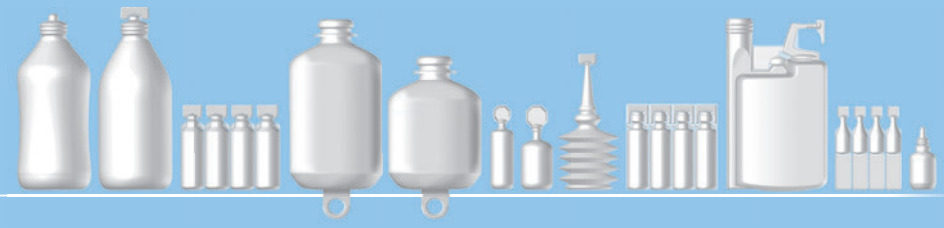

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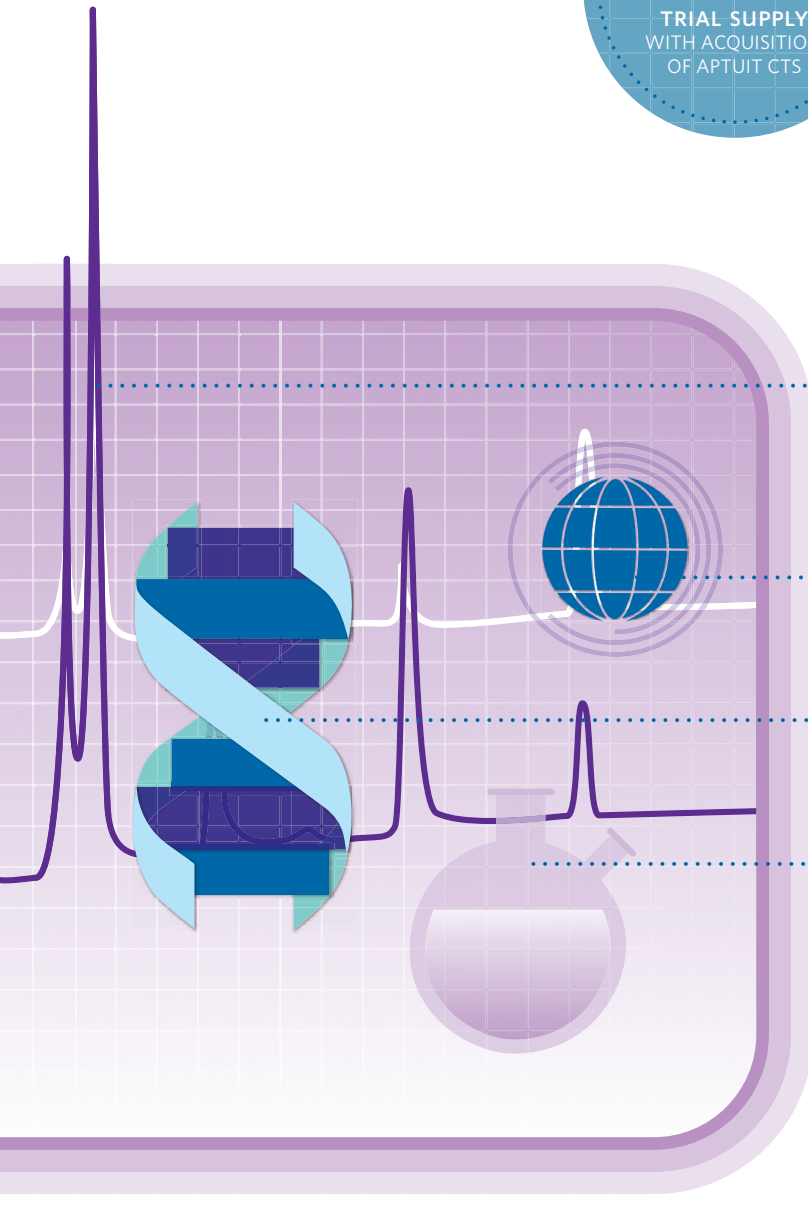

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