MAY 2019 Volume 31 Number 5

Advancing Development & Manufacturing

Pharmaceutical Technology® EUROPE

PharmTech.com

CELEBRATING 30 YEARS ANNIVERSARY

Enhancing Bioprocessing

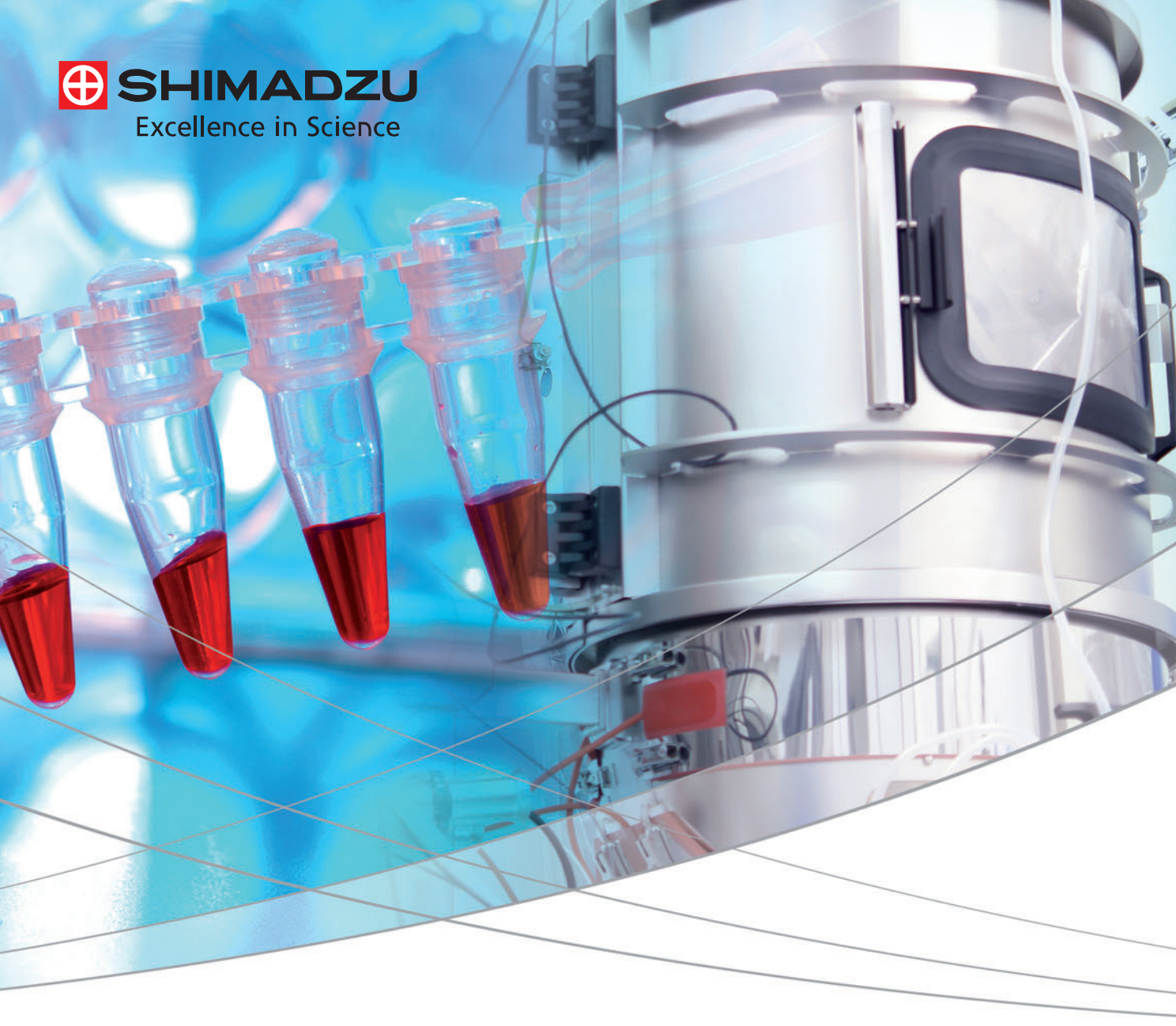
Searching for novel ways to improve biologics productivity

FORMULATION
Particle Morphology

PEER-REVIEW
Testing for Water in DMSO

MANUFACTURING
Aseptic Fill and Finish

SHIMADZU
Excellence in Science



Don´t prepare. Just be ready.

C2MAP-2000 – 1 method, 17 mins, 95 media components

The new C2MAP-2000 automates all steps from pretreatment to measurement without any human intervention. It simplifies the workflow for optimizing cell culture conditions. There is no need to prepare. Just be ready.

Complete LCMS solution for cell culture analysis
combining the C2MAP-2000 pretreatment module with ultra-fast LCMS-8060

Highly efficient
through cutting culture media analysis time by 80 percent

Monitoring of up to 95 components
including amino acids, metabolites, sugars, vitamins and organic acids

Changes at a glance
with C2MAP-TRENDS viewer software visualizing temporal changes of components

C2MAP-2000 – Complete LCMS solution

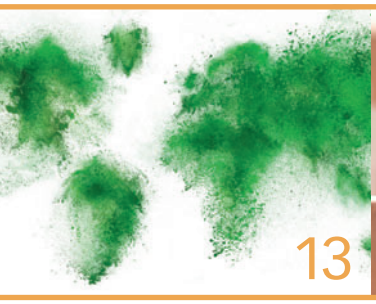
www.shimadzu.eu/c2map

Pharmaceutical Technology Europe is the authoritative source of peer-reviewed research and expert analyses for scientists, engineers, and managers engaged in process development, manufacturing, formulation and drug delivery, API synthesis, analytical technology and testing, packaging, IT, outsourcing, and regulatory compliance in the pharmaceutical and biotechnology industries.

May 2019

Advancing Development & Manufacturing
Pharmaceutical Technology EUROPE
PharmTech.com

Cover: Paulista/Anusorn/stock.adobe.com
Art direction: Dan Ward



PharmTech.com

Features

Peer-Reviewed

Columns and Regulars

Join *PTE's* community

Join the *Pharmaceutical Technology Europe* group on LinkedIn™* and start discussing the issues that matter to you with your peers.

Go to PharmTech.com/linkedin

LinkedIn

*The linkedIn logo is a registered trademark of LinkedIn Corporation and its affiliates in the United States and/or other countries

Alliance for Audited Media

Pharmaceutical Technology
EUROPE

PharmTech Group
Editorial Director
Rita Peters
RPeters@mmhgroup.com

PharmTech Europe
Editor
Felicity Thomas
FThomas@mmhgroup.com

Senior Editor
Agnes Shanley
AShanley@mmhgroup.com

Managing Editor
Susan Haigney
SHaigney@mmhgroup.com

Manufacturing Editor
Jennifer Markarian
JMarkarian@mmhgroup.com

Science Editor
Feliza Mirasol
FMirasol@mmhgroup.com

Associate Editor
Amber Lowry
ALowry@mmhgroup.com

Contributing Editor
Cynthia A. Challener, PhD

Global Correspondent
Sean Milmo
(Europe, smilmo@btconnect.com)

Art Director
Dan Ward

Publisher
Michael Tracey
MTracey@mmhgroup.com

Sales Manager
Linda Hewitt
Tel. +44 (0) 151 353 3520
LHewitt@mmhgroup.com

Senior Sales Executive
Stephen Cleland
Tel. +44 (0) 151 353 3647
SCleland@mmhgroup.com

Sales Operations Executive
Barbara Williams
BWilliams@mmhgroup.com

C.A.S.T. Data and List Information
Michael Kushner
MKushner@mmhgroup.com

Published by
MultiMedia Healthcare LLC
Hinderton Point
Lloyd Drive
Cheshire Oaks
Cheshire CH65 9HQ, United Kingdom
Tel. +44 151 353 3500
Fax +44 151 353 3601

President,
MultiMedia Healthcare LLC:
Thomas W. Ehardt

VP & Managing Director,
MultiMedia Healthcare LLC:
Dave Esola

EDITORIAL ADVISORY BOARD

Above is a partial list of the *Pharmaceutical Technology* brand editorial advisory members. The full board, which includes advisory members of *Pharmaceutical Technology* North America, can be found online at www.PharmTech.com/pharmtech-editorial-advisory-board. *Pharmaceutical Technology* publishes contributed technical articles that undergo a rigorous, double-blind peer-review process involving members of our distinguished Editorial Advisory Board. Manuscripts for editorial consideration should be sent directly to Susan Haigney, managing editor, shaigney@mmhgroup.com.

Broadening Europe's Research Horizons

Horizon Europe gains parliamentary endorsement, bringing it closer to becoming a reality.

In June 2018, the European Commission proposed a new future programme for European funding, Horizon Europe, with an increased budget on its predecessor programme, Horizon 2020 (1). Key objectives of this €100-billion research and innovation programme have now been agreed upon by the European Council (2), news that has been applauded by many in the European pharmaceutical and health industries.

Six undersigned European health industry associations, including the European Federation of Pharmaceutical Industries and Associations (EFPIA), noted in a joint statement, "We welcome the overall structure and ambition of Horizon Europe. Europe has been at the forefront of life-science research, and a health mission is a palpable signal that it intends to keep on striving for excellence and impact" (3).

Evolution, not revolution

The purpose of Horizon Europe is to strengthen the European Union's science and technology sectors and thus help the region maintain a robust position within research and innovation. If fully confirmed and approved, the programme will go live as soon as Horizon 2020 expires and will run through 2021 until the end of 2027.

Based on the mantra of 'evolution, not revolution,' Horizon Europe will build upon the successes of the Horizon 2020 programme, maintaining some key aspects and introducing a few new features. One of the main new features is the European Innovation Council (EIC), already running in a pilot phase, which is aimed at bridging research and market application by funding and helping innovative start-ups and companies.

"While only an idea a couple of years back, we're now setting up a fully operational EIC based on the experience of the already successful pilot, which is funding promising innovators," said Carlos Moedas, commissioner for research, science, and innovation in a statement (2). "The EIC will not only boost funding for innovation but also crucially help to create a whole innovation system linking early research and market application. The commission will also launch research missions with bold and ambitious goals to tackle issues that affect our daily lives."

Brexit: The 'elephant in the room'

Obviously, Brexit has been a major consideration for all those involved in Horizon Europe. So much so, in fact, that there was a workshop held in November 2018 to assess the impact of Brexit on the programme in more detail (4).

One of the speakers during the workshop was Elizabeth Kuiper, executive director public affairs at EFPIA, who specifically focused on the potential impact of Brexit on European pharmaceutical R&D. In her presentation, Kuiper highlighted the fact that the United Kingdom makes up 10% of the European Union's total pharmaceuticals production and contributes to approximately one-fifth of the region's total R&D (4). She surmized that the level of contribution by the UK to global research means a preferred future scenario is one where the country can continue to access EU funding and participate in region-wide collaboration programmes for science, such as Horizon Europe.

Additionally, during the debate on 'Establishing Horizon Europe,' which took place in the European Parliament on 16 April 2019 (5), the minister for European Parliament for South East England, John Howarth stated, "Mr President, the 'elephant in the room' during many of the discussions on this Horizon programme has been, of course, the position of many UK institutions that contribute in such a major way to the predecessor programmes. It's not the fault of the rapporteurs or the negotiators that the situation over Brexit is yet to be resolved, but it is at last now clear that even this UK Government will seek closely to associate whatever the outcome of Brexit with this programme.

"I'm glad to see, however, scientific excellence maintained as a key criterion for Horizon Europe funding," he continued. "Excellence is not enhanced by throwing money around, it is enhanced by collaboration with excellence. The contribution of the UK's world-class research community makes Horizon Europe a bigger, better, and more successful programme."

References

1. European Commission, "EU Budget: Commission Proposes Most Ambitious Research and Innovation Programme Yet," *Europa.eu*, Press Release, 7 June 2018.
2. European Commission, "Statement by Commissioner Moedas on the European Parliament's Vote on Horizon Europe," *Europa.eu*, Press Release, 17 April 2019.
3. EFPIA, "Health Industries Welcome Unprecedented Progress Leading to an Adoption of Horizon Europe, its Areas for Missions and Partnerships," *efpia.eu*, Press Release, 17 April 2019.
4. European Parliament, "Brexit and Horizon Europe," *publications.europa.eu*, Workshop Proceedings, January 2019.
5. European Parliament, "Establishing Horizon Europe—Laying Down its Rules for Participation and Dissemination," *europarl.europa.eu*, Debate, 16 April 2019.

Felicity Thomas
Editor of *Pharmaceutical Technology Europe*
FThomas@mmhgroup.com

EUROPEAN
REGULATORY WATCH

Sean Milmo
is a freelance writer based in Essex, UK, seanmilmo@btconnect.com.

Playing the Waiting Game with GMP Guideline Revisions

Delays in revisions to guidelines by the European Union are impeding the pharmaceutical industry.

The European Union has a lengthening queue of revisions and other changes to good manufacturing practice (GMP) guidelines, which is worrying industry because of the impact the delays are having on pharmaceutical businesses, particularly investment decisions. The guidelines comprise key sections of the EU's GMP guide, which also includes good distribution practice (GDP).

Among the areas covered by the revised or new guidelines are sterile products, imported medicines, data integrity, drug device combinations (DDCs), investigational medicinal products, and streamlining of information on the GMP responsibilities of marketing authorization holders (MAHs). In a joint letter to the European Medicines Agency (EMA), sent in October 2018 on behalf of 13 trade associations and professional associations, Sini Eskola, regulatory, drug development, and manufacturing director at the European Federation of Pharmaceutical Industries and Associations (EFPIA), said the topics covered by the guidelines were 'urgent' (1).

Disruptions to operations

The delays have been exacerbated by the disruption to the operations of the EMA's expert committees, particularly the GMP/GDP inspectors working group (GMDP IWG) as a result of Brexit. The planned withdrawal of the United Kingdom from the EU has forced EMA to move its headquarters from London to Amsterdam to ensure it was based in an EU member state.

The IWG and other specialist committees have had to confine their work on revisions to four guidelines on the manufacture of sterile medicinal products, guidances for medicine importers, a reflection paper on GMP and MAHs, and on quality requirements for DDCs. Scheduled activities on other guidelines were temporarily suspended in October 2018, and are anticipated to last for at least a year according to EMA. Even with those guidelines on which revision work is continuing, activities have been slowed down without any new target dates for completion or meetings with industry representatives being announced.

"More transparency on the actual status of these few projects shortlisted (for continued work) would be more than welcome as currently industry has no idea when the IWG would communicate back or when it foresees further actions," Koen Laenen told *Pharmaceutical Technology Europe*. Laenen is regulatory affairs and quality manager at Medicines for Europe, which represents generics and biosimilars producers and was one of the signatories of the joint letter to EMA. "For 2019, no stakeholder meetings with industry are foreseen by IWG," he continued. "This is a long period for no official meetings with different stakeholders."

Despite the hold-up in the IWG's operations, the industry is pressing for a continued dialogue with the group, preferably through face-to-face meetings on some issues. The need for consultations with stakeholders, especially industry representatives, is a major reason for the length of time it can take to revise or draw up new versions of GMP guidelines. A consultation period after the publication of a draft, the processing of comments and then the finalization of the guideline, can extend to one-to-two years.

The potential for further delays

Once a guideline is completed, there can be further delays while the industry and EMA or the European Commission—the EU executive to which the agency is accountable—sort out how the new or modified guideline should be implemented.

This is what has happened on a new, lengthy guideline on the manufacture of sterile medicinal products, work on which started in 2014 with a draft being published late in 2017, and a consultation period being completed in March 2018. However, its finalization has been held up because of disagreement of how it should be implemented, which is unlikely to be resolved until the IWG is fully operational again.

The new guideline, which comprises Annex 1 of the EU GMP guide, has tripled in size from its 16-page original document, which was introduced in 1971, to a 50-page document. The enlargement contains the principles of quality risk management to "ensure that microbial, particulate, and pyrogen contamination associated with microbes is prevented in the final product (2)."

Other additions include details on the use of new technologies, also mainly to provide protection against particulates and microbes. Another expanded area is the training and skills required of personnel to ensure they have the appropriate engineering and microbiological knowledge.

The complexity and detail of the guideline is expected to lead to the closure of sterile capacity serving the European market in anticipation of its extra costs. "[On the basis of] the current draft, we expect that for several sterile manufacturing sites, the capacity for some

GLOBE: ZOONAR RF/GETTY IMAGES

SMA MicroParticle ICS
Non-Viable Particle Counters

THE NEXT LEVEL OF PARTICLE COUNTING

UNMATCHED ENVIRONMENTAL CONTROL

STERILE.COM

For more information, visit our website at **sterile.com/particlecounters**

vai
VELTEK ASSOCIATES, INC.

products will be reduced by 50% during the (guideline's) implementation phase," Laenen explained. "This implementation phase could be lengthy, amounting to several years. Hence, reduced sterile production capacity could occur for products that are already on [the World Health Organization's] WHO's shortage list. It's important also that once the new Annex 1 is adopted, inspectorates are treating and interpreting it in a uniform way to prevent differences in audit findings and outcomes."

The additional work the industry is wanting EMA to perform on the guideline could postpone its full implementation even further. In their joint letter to the agency, the trade associations and professional organizations have asked for the opportunity to provide further feedback to the IWG before the document is finalized. This is because of the large number of comments submitted during the first consultation round.

The industry wants workshops, seminars, and training sessions to be held to achieve a clearer understanding between the pharmaceutical sector and the inspectorate on the purpose, scope, and expectations of the guideline's risk-based approaches. There is a need to understand more clearly how the risk control measures in the guideline help to enhance levels of sterility, according to the joint letter. To enable a "harmonized understanding and implementation" of the new guideline, industry suggests in the letter that training materials be developed for both pharmaceutical companies and regulators.

Finally, industry wants at least parts of the guideline to be implemented gradually over a period of up to five years because of risk assessment requirements and the complexity of the changes. One area likely to cause complications, for example, is the risks created by poor quality control of filters, which may necessitate pre-use, post-sterilization integrity testing.

Impact of new technologies

A large proportion of guideline revisions have been triggered by the establishment of new technologies, which indicates that there will be an increasing number of new versions of guidelines over the next several years. Much of the impetus behind the drawing up of the new guideline on sterile manufacturing has come from the use of new technologies, particularly in dealing with microbial contamination.

EMA published in November 2018, with a consultation period due to end in May 2019, a draft guideline on the quality of water for pharmaceutical use because the two existing guidelines on the subject, issued in 2001 and 2002, were out of date (3). The existing guidelines allowed only distillation for purification of water for injection. The new guideline permits the use of new technologies such as reverse osmosis coupled with techniques like electrodeionization, ultrafiltration, and nanofiltration.

In a draft document on EMA Regulatory Science to 2025, published in December 2018, the agency outlines how it is aiming to keep pace with technological advances (4). "The pace of innovation has accelerated dramatically in recent years," said Guido Rasi, EMA executive director, in the document. "Regulators need to be ready to support the development of increasingly complex medicines."

Among the agency's strategic goals will be the facilitation of the introduction of novel manufacturing technologies by taking a 'flexible approach' in the application of GMP. This policy has already run into difficulties with controls of advanced therapy medicinal products (ATMPs). Instead of issuing new up-to-date guidelines on the manufacture of active biological substances, the EC adopted, in November 2017, a standalone regulation of GMP for ATMPs (5).

This action raised accusations of a lowering of GMP standards. The Geneva-based Pharmaceutical Inspection Co-operation Scheme (PIC/S), which aims to develop common GMP standards among inspectorates worldwide, claimed that the EU guideline risked leading to divergencies in GMP internationally, particularly with ATMPs.

Participants in PIC/S include EMA, the US Food and Drug Administration (FDA), and WHO. EMA's guideline on sterile manufacturing was, for example, drawn up in close collaboration with PIC/S and the WHO. PIC/S now comprises 52 authorities mainly in Europe and North America but also including Asia-Pacific, South America, and Africa so that it provides a global network of inspectorates.

The primary aim behind efforts to achieve harmonization of GMP standards is to make efficient use of inspection resources by avoiding the necessity for duplicate inspections of pharmaceutical plants across the world, especially those exporting their products into the global pharmaceuticals market. A joint report last year on an international inspection programme of API plants in 2011–2016, involving EMA, FDA, WHO, and approximately 10 other authorities, mainly in Europe, concluded that more work was needed to be done to avoid duplication. National legislation requiring unnecessary inspections was, for example, still to be left unamended.

The dispute between the EU and PIC/S over the ATMP guidance underlines the challenges facing the EMA and other regulators in both keeping in step with new technologies while also ensuring that guideline revisions and changes remain consistent with international GMP standards.

References

1. EFPIA and other organizations, "Letter to Brendan Cuddy, EMA's Head of Manufacturing and Quality Compliance, from Sini Eskola, EFPIA's Director of Regulatory, Drug Development and Manufacturing" (Brussels, 31 October 2018).
2. European Commission, *EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft)* (Brussels, 20 December 2017).
3. EMA, *Guideline on the Quality of Water for Pharmaceutical Use* EMA/CHMP/CVMP/QWP/4986873/2018 (London, 13 November 2018).
4. EMA, *EMA Regulatory Science to 2025—Strategic Reflection (Draft)* EMA/872479/2018 (London, December 2018).
5. European Commission, *Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products* (Brussels, 22 November 2017). **PTE**

The Search for Bioprocess Productivity Improvement

Large biopharmas, emerging biotechs, and CMOs are looking for novel ways to improve the productivity of biologics in a rapidly evolving biotherapeutics market.

Feliza Mirasol

The biopharmaceutical industry has long been working to refine and improve the biomanufacturing process to improve monoclonal antibody (mAb) productivity. Some success has been achieved in upstream bioprocessing where cell titre has been greatly increased as the result of better cell-culture methods and improved bioreactor performance, as well as optimized nutrition in cell-culture media and supplements. Biomanufacturers, however, continue to seek new and improved ways to increase productivity, including innovations in bioprocessing.

Obstacles to mAb production

The biggest challenge in mAb production is improving mAb titre without impacting product quality, which is dependent on the stability of the source cell lines and the expression systems with which the mAbs are produced. In upstream processing, determining the duration of the cell-culture process, the relative low density of the cells, and/or accumulation of stress-generating byproducts such as lactate or ammonium are also critical challenges.

In addition, there still remains quite of bit of work to be done on the upstream side to increase yields, including work to fully characterize all the materials going into upstream processes. Currently, three grams of API per litre is traditional for mAbs, but some biomanufacturers are claiming higher concentrations at 10 g/L and up to 50 g/L, which, from a scale-up perspective, sounds aggressive, notes Claudia Berrón, vice-president of global commercial development, biopharma, at Avantor, a manufacturer and distributor of products, services, and solutions to the life-sciences and advanced technologies industries. Depending on their characteristics, each raw material can react differently with the drug molecule, and many raw materials going into upstream cell-culture processes have not been fully characterized or optimized for the target molecule, Berrón explains. Thus, upstream optimization needs better characterization of all media components, and, more specifically, anything going into the cell-culture supplement with that particular molecule is crucial.

Improving productivity has largely been a question of progress in three areas, adds Nigel Darby, advisor to the CEO, GE Healthcare Life Sciences. First, mAbs were expressed at low levels in early bioprocessing in the early 1990s, typically 10- to 20-fold lower product titres than today, which necessitated the use of large bioreactors to manufacture sufficient product quantities. Second, downstream purification was limited by chromatography resins with four to five-fold lower capacity than today, particularly in the Protein A capture step, which necessitated the use of large volumes of resin to bind the product and wide-diameter chromatography columns to cope with the large volumes of dilute, clarified cell-culture supernatant coming out of the process. Third, both aspects of low productivity required big complex factories to manufacture significant quantities of mAb, which required high capital investments, long construction times, and significant financial risks if products failed in clinical trials.

To tackle these challenges, technology has fortunately been rapidly evolving to provide solutions. In the past 10 years, significant improvements in cell culture titres have been achieved, with 5–10 g/L being achieved and around five-fold improvement in Protein A resin capacity, Darby asserts. "The net effect of these improvements has considerable impact. Bioreactors have shrunk from 20,000-L volume to 2000 L, and two-metre

chromatography columns are replaced with 50–80-cm columns … all to achieve the same production output," he states.

Today, the most advanced biomanufacturing facilities are running with smaller unit operations and reduced infrastructure because of single-use technology, which is driving significant reduction in capital investment and construction times. Furthermore, the financial risk profile is much more favourable with scaled-down, right-sized facilities using single-use technology, Darby notes.

Engineer fixes

To meet the challenges of improving mAb productivity, design and development engineers are employing several methods or approaches to resolve these issues. For example, at Agenus Inc., an immuno-oncology company specializing in antibodies, vaccines, cell therapies, and adjuvants, the company's design engineers and scientists look into ways of developing efficient and high expressing vectors for cloning cell lines and sometimes may be sub-cloning for optimization. Agenus now has cell lines with excellent growth rates and high specific productivity for both fed-batch and perfusion cultures for several immunoglobulin G (IgG) isotypes, says Al Dadson, head of Global Biologics Manufacturing, Agenus.

"Our development engineers and scientists are working on both upstream, downstream, and analytical/formulation development platform processes to increase aspects of robustness, scalability, and reproducibility to complement high expression systems to reduce COGS [cost of goods sold]," Dadson says.

Meanwhile, Avantor has been focusing on dramatically improving materials characterization for upstream processing, specifically working with mAb producers to find the right combination of cell-culture components. The company recently implemented new laboratories, one focused on mammalian upstream cell culture and another focused on microbial fermentation, at its Bridgewater, New Jersey, US, site according to Berrón.

Avantor has process engineers working on optimizing three downstream parameters: yield, process time, and purity. "Depending on the target protein molecule and other factors, we can optimize various parameters such as resin chemistry, buffer type, and specific additives that can modulate separation performance to get higher yield or higher purity, or we can reduce the number of process chromatography steps. In addition, we can optimize buffer conditions and flow rate through the columns to decrease processing time," says Dr. Nandu Deorkar, vice-president of research and development, Avantor.

"One area where we are having success is more targeted ligands. Certain feedstock may contain closely related product impurities that may require multiple traditional chromatographic steps. It is a common challenge we see in recombinant protein, beyond traditional mAbs," Deorkar further states. "To address this challenge, we have been engineering mixed-mode, multimode, and hydrophobic chromatography resins that help optimize the removal of these closely-related impurities. This method has mainly been applicable to any recombinant protein that is produced in a microbial fermentation process."

Process engineers and scientists are also developing refined processes, including perfusion steps, adds Melanie Diefenbacher, PhD, scientific consultant, Genedata, a data intelligence company. To achieve this refinement, they try to take a broader, integrated view on the overall process from the development of the manufacturing cell line up to the downstream and formulation steps. Process engineers and scientists are also using miniaturized, automated approaches to study factors influencing manufacturing success. "Therefore, digitalization methods, such as artificial intelligence and deep learning, are becoming increasingly important to support these efforts," Diefenbacher says. "Using cyber-physical systems, the Internet of things, and cognitive computing, supported by smart laboratories and integrated and scalable information technology (IT) systems, R&D operations, and manufacturing systems are becoming decentralized, and at the same time intelligent, flexible, and highly integrated."

Innovation advancement

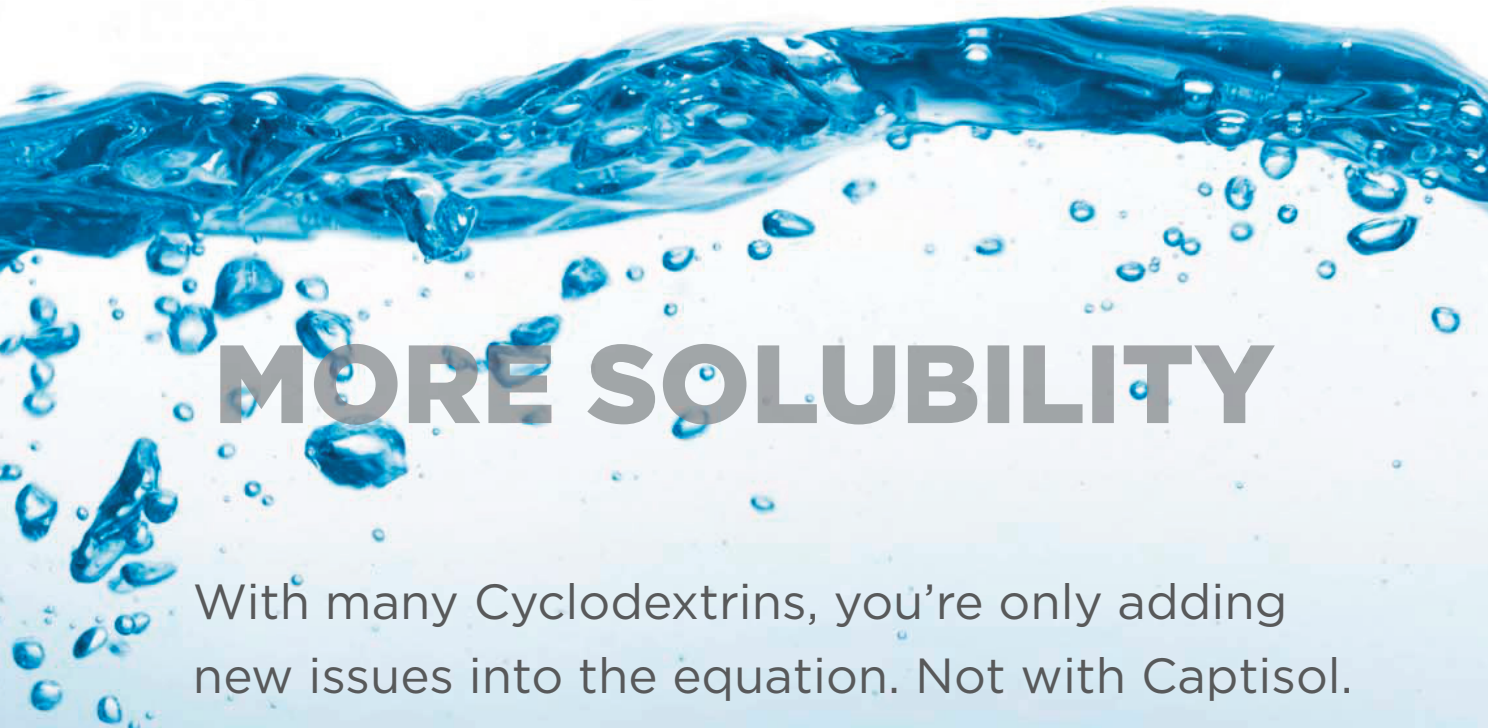
For the most part, the biopharma industry still has some challenges with assimilating the advances made in recent years to improve mAb productivity. Many operations have not yet started to use the best technologies that are available today, according to Darby. "Given the lifecycles of many processes, it can be difficult to assimilate new technology quickly because of the constraints of regulation and cost as well as risk of change," he says. Darby points out, though, that progress in technology continues, nonetheless. "For example, in the challenging downstream area, we are moving to consider new higher productivity technologies in purification, such as the use of nanofibre products as an alternative to chromatography beads. On the other hand, there are things we can do better with the resources we have today, [such as] better use of manufacturing process and raw material data to optimize manufacturing output and quality."

Another area for potential bioprocessing productivity improvements is in downstream processing, where single-use technology can be combined with process chromatography columns, says Deorkar. "Using single-use systems has the potential to move from a batch-based approach to something approaching a connected continuous process. It will be possible to minimize the large storage tanks and use single-use systems to streamline how you collect the samples, how you load the samples, and so forth. There are single-use systems that make it much more of a continuous process and remove the time required to clean, dry, qualify, and validate sampling and storage systems between chromatographic steps," he states.

Single-use systems have the potential to improve productivity across the entire mAb production process, especially in terms of sampling, adds Berrón. "Drug producers have to sample for quality and process control purposes many, many times continuously. Typically, to effectively sample, you sample more than what is needed, and, in some cases, it isn't possible to sample exactly what is needed."

The industry is using approaches like perfusion or some sort of continuous manufacturing to increase volumetric output and increase yield, in addition to developing high-producing cell lines, confirms Dadson. "Systems like the ATF [alternating tangential flow] and

MORE TECHNOLOGY.



MORE SOLUBILITY

With many Cyclodextrins, you're only adding new issues into the equation. Not with Captisol. With revolutionary, proprietary technology, Captisol is rationally engineered to significantly improve solubility, stability, bioavailability and dosing of active pharmaceutical ingredients.

SOLVE PROBLEMS WITH CAPTISOL SOLUTIONS.

CAPTISOL®
A Ligand TECHNOLOGY

CAPTISOL.com

other tangential flow systems have been known to increase productivity by several fold. The use of PAT [process analytical technology] in platform facilities is another avenue being explored by industry," he says.

Dadson also notes that certain approaches in cell-line engineering are using Chinese hamster ovary (CHO), nonsecreting null (NS0), Sp2/0, HEK293, and PER.C6 cell lines as host systems, although more than 70% of industry today is using CHO cells. New approaches also include transgenic plant and animal systems for host cells.

The Agenus West team in Berkeley, California, US, for example, is working with Agenus' cell line-development team in Cambridge, UK, and its Discovery/R&D teams in Lexington, Massachusetts, US, to ensure cell lines are developed with the required product quality attributes and commercial manufacturability. "The availability of desired cell lines for commercial production shortens manufacturing time for drug development. Coupled with this fully integrated approach, Agenus West thrives on the latest cutting-edge technology platforms in-house, making us self-reliant and giving us the advantage of manufacturing speed, cost efficiency, operational flexibility, and manufacturing technology transfer to commercial scale partners—all with desired product quality," Dadson states.

Approaches to improving mAb productivity have included increasing throughput and reducing cycle times using new automation equipment, says Diefenbacher. Another approach involves using new and refined bioprocesses that include the application of fully or at least partially continuous processes, such as upstream perfusion process steps. "In terms of newer innovation, the biggest push right now in productivity improvement is expected to come from the digitalization of the biopharma industry, which will improve process robustness and product quality and result in a more efficient use of resources," Diefenbacher states.

Future mAb enhancement

Future mAb production facilities are expected to see the implementation of a broad range of technologies, including the use of nanofibre technology in place of chromatography beads, increased automation and digitization of processes, and single-use systems. A few facilities are already exploring the use of some of these technologies today with many new facilities under construction, Darby observes. Meanwhile, innovations such as the nanofibre technology are still in development.

"The smaller highly flexible facility with a high content of single-use technology seems to be the future for much of the industry. Instead of scaling up, many now talk of scaling-out—building capacity as needed by rapid construction of new small-scale facilities rather than taking the risk to build a single large facility," Darby says.

As the mAb production process continues to intensify, the lack of "downtime" that used to occur naturally as a consequence of the greater demands of cleaning and maintenance in standard infrastructure puts ever more pressure on manufacturing teams and extended supply chains to become more efficient, Darby also points out. "The burden of some activities will be transferred to suppliers, as we see with the implementation of single-use technology, and this is expected to increase. We are still undergoing a significant transition in implementation of single-use technology with more operator training required to ensure these technologies can be applied successfully, particularly as productivity increases," he states.

"Right now, the biggest push is expected to come from the digitalization of the biopharma industry, which will improve process robustness and product quality and result in more efficient use of resources," Diefenbacher adds, noting that most big pharmaceutical companies today are already looking for ways to directly capture the huge amounts of data produced in R&D and manufacturing, such as cell-line selection, process optimization, or media development.

"The implementation of a central data backbone for sharing all data and driving digitalization across all development groups to connect information from upstream, downstream, formulation, and analytics development units is essential for every biopharma organization," she says.

"We think there will be more use of single-use technology, although there will still be plenty of need for stainless-steel, fixed production systems," Berrón interjects. Blockbuster drugs would still need stainless-steel production systems, she explains, because they have long production runs, and using stainless-steel is the most efficient way to produce a blockbuster drug. For faster change and faster turnarounds where smaller-volume drugs are involved, single-use technology continuously gains ground in this space.

"We also see greater investment and greater use of advanced data tools, and this is something that Avantor is making significant investments in—digital tools for process optimization," adds Deorkar. Compared to other industries, even small molecule, the biopharmaceutical industry is lagging in terms of how data are captured, what kind of data is captured, and how it is mined and used productively, he says.

There is also a push for future bioprocess facilities to build efficient continuous processing facilities, Dadson states. The push for facilities that use high-expression cell lines in combination with end-to-end single-use systems to build smaller, cost-effective footprint facilities versus conventional stainless-steel facilities has become an industry focus. "One drawback is the maximum size of single-use systems (2 kL–3 kL) to handle high product demand, especially in oncology, versus >20 kL stainless-steel facilities," he says.

Finally, the increase in automation to replace low-value activities, such as buffer management, and an increase in real-time data analytics in the management of processes will also require whole new skill sets in the workforce, Darby points out. "Time pressures will likely drive towards more analytical work being performed at- or on-line during manufacturing, with paperless workflows. These innovations are just emerging in the most advanced operations but will require changing approaches from plant operators." **PTE**

Avoiding Excipient Variability

Knowing the source and understanding the impact on CQAs is crucial to optimum drug formulation and processing.

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

Excipients are essential components in drug products. Although sometimes defined as "functional" or "inert," each has a specific role within the formulation that is necessary for the overall function of the medicine. Variability in the properties and performance of excipients may, depending on the nature of the variability and the role and quantity of the excipient, have a significant impact on the safety and/or efficacy of the final drug product. Managing—minimizing—excipient variability is, therefore, an essential part of drug product development and manufacture.

Sources of variability

Excipient variability depends on many factors. One important determiner relates to whether the excipients are prepared from natural materials or via chemical synthesis, according to Liam Cullen, an engineering specialist with Servier. For example, he points to cellulose-based materials, which are derived from wood pulp that is then chemically treated. "Natural materials, particularly those that are grown, can be subject to environmental conditions such as soil type, weather, and the use of fertilizers. Secondary processing steps can also provide further material variability," he explains.

Materials that are manufactured by chemical synthesis alone tend to have less variability, but changes in the manufacturing environment, including the raw materials used, processes, and manufacturing locations can occur. For instance, Cullen notes that suppliers may elect to move the manufacturing of an excipient from one plant to another for cost reasons, and then replace some or all of the raw materials with locally sourced alternatives. "While the overall material specification ranges do not change, the once-typical values may be impacted," he says.

Variability is most commonly encountered at ACD/Labs in the impurity profiles of excipients, according to Andrew Anderson, the company's vice-president of innovation and informatics strategy. Generally, excipient attributes such as rheology, granulometry, viscosity, and impurity profiles have been better indicators of change compared to more specific material characteristics such as purity, appearance, or loss on drying, according to Cullen.

Because both changes in the raw materials and processes used to manufacture excipients can impact final drug product performance, Mike Tobyn, research fellow in the materials science and engineering group at Bristol-Myers Squibb (BMS) stresses that it is important to understand the sources of variability for any excipients used in drug formulations.

In addition, he observes that the analytical methods used to generate results for certificates of analyses (CoAs) and by pharmaceutical companies upon receipt of excipients are often an unappreciated source of variability. "When debating whether a material is 'different' based on these results, it is necessary to consider whether the variability is in fact due to the different capabilities of the methods being used. In some cases, a change in the analytical results may be due to analytical 'noise' and not because the attributes of the material have changed," states Tobyn.

Impacts from development to commercial production

Understanding the impact of variability in excipient properties or specifications on the critical quality attributes (CQAs) and performance of the final drug product is key to developing a robust strategy for selecting the right formulation and process that will result in a robust drug product, according to Anil Kane, executive director and global head of technical and scientific affairs at Thermo Fisher Scientific. "Challenges (and failures) start in development. Hence it is key to evaluate variability in the excipients, the API, and the process parameters during the development and pilot stages before pivotal clinical trials," he states.

Excipient variability can impact product consistency, stability, and dissolution profiles, among other properties. Most often these impacts occur with excipients that have functional roles, such as in drug release. Variability in inert excipients (diluents, fillers, etc.) can have an impact on product performance, but the impacts may be more difficult to detect at the development stage, according to Cullen.

At both the development and commercial stage, excipient variability

can result in a batch failing to meet specifications, which equates to a loss of time and money, according to Tobyn. "Failure could be obvious, such as sticking or tablet breakage for oral solid dosage products. Or it could be more subtle, such as interference with an established analytical method. In the latter case, the process understanding and control provided by the method may no longer be in place, which slow down release or threaten the batch," Tobyn says.

While all levels of development and commercial production can be affected by changes in the performance of excipients, some stages may not display any negative effects. "It is important to take a holistic approach that considers all of the information gathered from various sources and includes comparison with historical data as well as computer modelling of the data gathered," Cullen asserts.

He notes as an example issues that can develop with particle segregation that typically aren't detected at development scale but become noticeable in the plant. In development, the distance from the feed intermediate bulk container to the tablet press feeder is approximately one meter; in commercial production, the feed IBC can be on the floor above the tablet press, and the acceleration involved when the material is released from the IBC to the press can result in a de-mixing phenomenon called segregation that affects smaller particle sizes in the feed mixture. "This issue is not immediately obvious in production but is normally identified during validation or standard product testing," Cullen adds. As a result, he suggests that design-of-experiment (DoE) and quality-by-design (QbD) models currently used in smaller-scale development should be expanded to commercial-scale activities.

Lack of variability at the development stage can also be a problem when processes are scaled up, according to Tobyn. "It is important during development to establish potential excipient variability issues that might occur and how they might affect product quality and performance. Tales abound of products developed using unusual or atypical batches throughout the development stage with no issues observed that fail in the plant due to an unexpected change. The formulator must work to avoid this situation," he comments.

Special considerations for continuous processes

In continuous manufacturing, material characterization of each and every excipient is extremely crucial because continuous processes rely completely on uniform continuous blending and feeding to tabletting or encapsulation machines, according to Kane. Physicochemical properties such as particle size distribution, densities, flow properties, surface morphology, and other characteristics play a critical role in developing an efficient continuous process.

Unlike for conventional processes where the first step is usually blending, Tobyn adds that in a continuous process there is a period where the excipient is not blended but is transported via a feeder to the blender. "The flow of this powder is a consideration that does not exist for batch processes. Although loss-in-weight feeders can cope with changes in flow and feed rates, it is still beneficial to keep these changes to a minimum," he notes.

Here again, employing QbD for continuous manufacturing is an effective approach to risk mitigation, according to Anderson. He also notes that the use of process analytical technology is imperative for QbD implementation.

Challenges abound

Drug makers face many challenges when approaching the management of excipient variability. One basic issue is the locations of excipient production, according to Cullen. Excipients are often not manufactured nearby or even in the same country or on the same continent, particularly for specialized materials. "Issues of distance, language, and time zones make it challenging to maintain concurrent or even regular contact," he notes. Online help desks often provide limited support due to insufficient staffing or unwillingness of suppliers to share process or material sensitive information, even where dedicated secure client accounts have been created, adds Cullen.

There are also different types of suppliers, according to Cullen. Some are dedicated to the pharmaceutical industry and understand the extensive requirements of the industry. Others serve multiple sectors with the pharmaceutical industry comprising a significant part of their businesses. These suppliers generally recognize the special requirements of their pharma customers, but may need some additional support. There are also suppliers for whom the pharmaceutical industry is a small percentage of their business. These suppliers may not fully understand the specific needs of pharma companies and communication may be difficult.

As one specific example, Cullen notes that some suppliers will indicate on CoAs that a specific attribute "complies" with the specification rather than providing an actual value, which makes it difficult to identify variations and to use data for trending analyses to determine patterns of variability that can assist in understanding the subtle changes in the CQAs of an excipient.

A deeper understanding of how variability in excipients can affect drug product performance and proposed control strategies is essential for improving drug product development, according to Kane. Gaining that understanding can be difficult, however, because pharma companies don't have the internal capability to manipulate excipients and their manufacturing processes. "Variability in excipients is a function of the control strategy used by the suppliers of these materials, and it can be challenging for drug makers to obtain ideal sets of samples for adequate investigations," he observes.

Furthermore, the number of excipient material properties combined with the number of excipients in a drug product formulation present cost and logistics challenges for executing manageable experimental designs. "Risk-based approaches may be helpful for identifying the excipient material properties (typically functional) that have the greatest impact on product performance," says Kane.

In addition to finding sufficient time to run a systematic DoE to evaluate the influence of excipients, Thermo Fisher is often also challenged by the need to work with minimal quantities of API at the clinical and pilot scale, according

to Kane. For ACD/Labs' customers, data analysis and reviews are a challenge, and the company is working with a variety of customers to address this issue, according to Anderson.

Tobyn agrees that there are business and quality barriers to completing the processes necessary to ensure that excipient variability is minimized from the start. "The technical processes to establish which materials have low variability exist. We currently need the business processes to exploit that," he adds.

Management strategies

One of the most common tactics for pharma companies is to, where possible, choose excipients that have worked well in the past and to purchase them from reliable suppliers with a track record of providing excipients with minimal variability.

For instance, BMS uses platform formulations that allow the company to work closely with and gain a greater understanding of a limited number of materials. "Because the platform is known, and how those materials interact has been demonstrated, the only material 'variable' is the API," Tobyn remarks. He adds that the platform utilizes high-volume, widely available excipients that are expected to demonstrate lower variability.

BMS has also used a range of techniques to identify vendors with proven track records in producing low-variability materials. "Use of these vendors, along with ongoing monitoring of the variability of their products, provides a stable base for the platform," Tobyn explains. Other vendors can be introduced, along with more variability, at key stages if the business requires.

Beyond the use of well-known excipients, the most basic step at Servier is to monitor and analyze the data from both CoAs and on-site testing results, according to Cullen. Functional excipients are monitored more closely than less functional materials, but all can have an impact. The data are trended along with the performance data of the finished product, and over time it is possible to identify which materials have the greatest effect on finished product. Servier also conducts regular supplier audits.

Once the most impactful excipient material properties are identified, this understanding can be combined with knowledge of the API properties and the process parameters used to manufacture the drug product to develop an appropriate control strategy that ensures consistent supply of safe and efficacious drug product, according to Kane. He also stresses that the experience of formulation scientists is essential for developing robust optimized formulations.

In addition, employing a QbD approach, and specifically accounting for each material's CQAs, can help with developing appropriate procedures and mitigating the risk of commercial production failures when any excipient has attribute variability, according to Anderson.

Suppliers can contribute

Of course, suppliers play a crucial role in reducing excipient variability. In general, BMS has found that the more experience a vendor has with a material the less variable it is likely to be, according to Tobyn. "A major excipient that has been produced for 50 years on a tonne-per-day basis and is in thousands of products is less likely (although not totally free from risk) to have variability that will influence final drug products," he says. On the other hand, suppliers of niche, specialist, novel materials may need some time to develop process and product consistency.

Cullen would like excipient suppliers to openly discuss planned and unplanned process changes with their suppliers,

provide specific values of CoAs, not just "Complies", and prepare annual summaries of CQAs for their processes and finished materials that also include timelines for any changes. He would also like to see more direct communication and opportunities for site visits to suppliers, such as workshops and plant tours, so pharma companies can gain a greater understanding of excipient manufacturing processes.

Excipient suppliers should, in fact, be open to sharing their data, with appropriate controls, on the variability of their products, according to Tobyn. He notes that some vendors, mainly the ones who are aware that their products are low variability, do so, but others are reluctant. "Data sharing would allow customers to make informed decisions about which materials are low and high variability and potentially provide pressure for vendors with high variability to improve that variability," he observes.

BMS would also like to monitor excipient properties in real time with vendors in order to be able to select batches during the purchasing process, either in a regular process or opportunistically when suitable batches became available. "This type of purchasing, however, will require new processes for our company and the vendors," Tobyn notes. In addition, he would like to see more focus on analytical methods and reduction of analytical "noise" so that "real" variability can be readily probed, identified, and minimized.

Both Kane and Anderson would like to see more excipient suppliers adopt and apply QbD principles in the manufacture of their excipients.

Relationships are central

Essential to minimization of excipient variability is the building of relationships with suppliers, according to Cullen. "Waiting to commence a dialogue with suppliers until an issue arises or until it is time for an audit does not provide good results. It is important to establish and maintain contacts within supplier organizations so that issues can be discussed freely and directly as they occur or ideally in advance of their occurrence where issues during the manufacture of an excipient have arisen. It is an area for constant development. Drug manufacturers must work closely with their excipient suppliers at all times," he asserts. **PTE**

Suppliers in the news

Cambrex Expands API QC Testing

Cambrex Corporation announced the opening of a 120-sq.-m quality control (QC) laboratory at its site in Paullo, Milan, Italy, expanding the existing QC facilities to analyse and test generic API products during development and manufacturing (1). The additional laboratory space, which is operational following authorization by the Agenzia Italiana Del Farmaco, features a new polarimeter and infrared spectrometer, along with electronic data capturing software for traceability in line with regulatory requirements.

"Our facility in Milan is the centre of the Cambrex's generic API business, and this investment is the latest in a number of steps we have taken at the site to increase its efficiency and flexibility as we look to grow the portfolio of products that we offer," commented Aldo Magnini, managing director, Cambrex Milan, in a 23 April 2019 press statement.

Cambrex manufactures more than 70 generic APIs, which are produced to cGMP standards at the Milan site; seven production departments are supported by a pilot plant, kilo scale plant, and development and analytical laboratories.

Catalent Adds Softgel Encapsulation Lines

Catalent has announced a US$14 million [€12.52 million] expansion to expand integrated turnkey softgel capabilities at its facility in Eberbach, Germany, including two new encapsulation lines for Catalent's proprietary Vegicaps technology (2).

The new Vegicap lines will be completed by September 2019, Catalent reported in a 23 April 2019 press statement. Other aspects of the investment—including new printing technology, a vision inspection system, expansion of the facility's softgel coating capabilities, and the additional packaging capacity—are scheduled for completion by mid-2020.

The site will also increase the workforce by more than 10% across operations, quality control, and related supporting functions. The 360,000-sq.-ft. facility offers integrated softgel manufacturing services for prescription pharmaceuticals, over-the-counter pharmaceuticals, nutritional supplements, medical devices, and animal health products, as well as highly potent and cytotoxic compounds within an isolated, self-contained cytotoxic suite.

Pharma Suppliers Recognized with Queen's Awards

The Queen's Awards for Enterprise are announced annually and are granted to United Kingdom businesses deemed to have demonstrated 'outstanding achievement' in the fields of innovation, international trade, sustainable development, and promoting opportunity through social mobility. Two companies supporting pharmaceutical development announced they were award recipients.

Sterling Pharma Solutions has been recognized in the field of International Trade for the short-term growth in its overseas sales of its API development and manufacturing services, which has increased by 80% over the past three years. Recently, the contract development and manufacturing organization acquired a facility in the United States, enabling it to service a global customer base (3).

Biocatalysts was recognized for its MetXtra bespoke software system, which is capable of screening millions of sequences to identify new enzymes in hours (4). Rod Sears-Black, Biocatalysts' managing director, commented in a press release, "We are very proud to receive the Queen's award for Innovation. It recognizes the dedication and commitment of the Biocatalysts team to create this unique offering to the market."

References

1. Cambrex, "Cambrex Completes New Quality Control Laboratory for Generic API Development in Milan," Press Release, 23 April 2019.
2. Catalent, "Catalent Invests $14 Million At Its Eberbach, Germany Softgel Facility," Press Release, 23 April 2019.
3. Sterling Pharma Solutions, "Sterling Pharma Solutions receives Queen's Award for International Trade," Press Release, 23 April 2019.
4. Biocatalysts, "Biocatalysts Win Prestigious Queen's Award for Enterprise," Press Release, 23 April 2019.

—*The editors of* Pharmaceutical Technology Europe

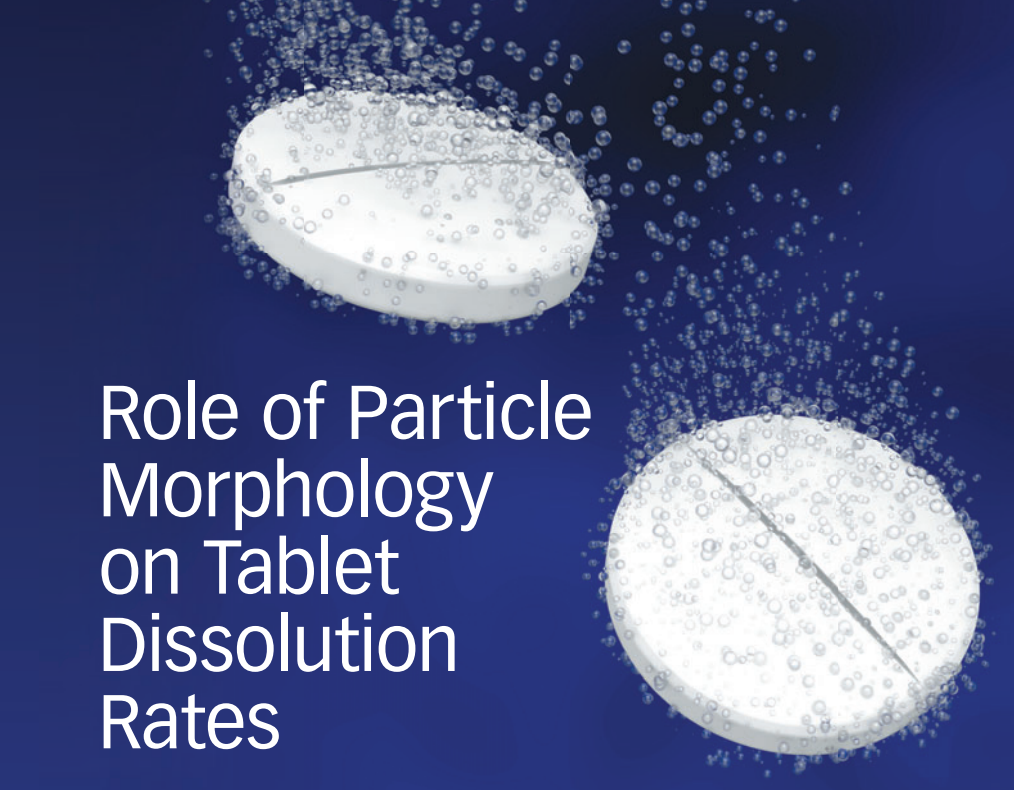
Specialty expertise in highly potent APIs

Identifying a collaboration partner that can meet the aggressive timelines often associated with highly potent drug candidates is critical. At Lonza Pharma & Biotech, we offer the necessary development, upscaling and manufacturing capabilities under full containment that support API handling to exposure levels to 1ng/m^3.

We also offer particle engineering (particle size reduction and spray drying) under isolation as well as specialized dosage forms designed for highly potent, low dose applications. We have more than 20 years' track record in HPAPI manufacturing and compressed scale-up timelines.

A partner that you can count on for all aspects of your drug program – **Lonza**.

Visit pharma.lonza.com
USA +1 201 316 9200
Japan +81 (0)3 6264 0600
Rest of world +41 61 316 81 11
Email pharma@lonza.com



Role of Particle Morphology on Tablet Dissolution Rates

Particle morphology of magnesium stearate, added as an anti-caking agent in a high water-soluble drug substance, has an influence on the dissolution rate of compressed tablets.

Renato BP Pinto* is head of the Global Pharma Tech Lab, renato.bp.pinto@merckgroup.com; **Anderson Albuquerque** is pharma tech lab expert; and **Raphael Lopes** is pharma tech lab expert, all at the Global Pharma Tech Laboratory, Merck SA, Rio de Janeiro, Brazil.

*To whom all correspondence should be addressed.

Magnesium stearate (MgSt) is the most commonly used lubricant in solid dosage formulations to improve the formulation processability. It may be used as an anti-caking agent when blended in lesser amounts with APIs with high caking potential as a pre-mix for further processing. This approach changes the surface properties of powders by dry coating it with hydrophobic materials to modify the surface energy and reduce particle interaction (1). This process uses shear and compression to produce a thin, continuous film of lubricant on the surface of the host avoiding the caking effect. But, this hydrophobic layer prevents water from penetrating into the tablet, thus restraining the disintegration and dissolution of the tablets (2).

MgSt is a naturally sourced excipient, and the excipient suppliers use a variety of processes to manufacture different MgSt grades for pharmaceutical applications. Not surprisingly, several studies have reported the presence of source-to-source, manufacturer-to-manufacturer, and lot-to-lot variability in the physical, chemical, and functional characteristics of MgSt (3).

It is well-known that MgSt with a larger surface area may cause a slowing-down of the dissolution rate of some APIs (4). However, the influence of MgSt particle morphology and the blending shear rates in the preparation of a pre-mix on the dissolution rate of high soluble API are often neglected. This study highlights the influence of particle morphology of MgSt when blended with high water-soluble drug at low and high shear rate on the dissolution rate of immediate-release tablets.

Material and methods

Materials. Metformin hydrochloride (HCl) was selected as a highly water-soluble drug. MgSt samples were purchased from three different suppliers: Supplier 1 (MgSt S1), Supplier 2 (MgSt S2), and Supplier 3 (MgSt S3). Polyvinylpyrrolidone (PVP) was added as the binder.

MgSt characterization. Surface area (SA) was assessed using the Brunauer-Emmett-Teller (BET) method. Samples were accurately weighed into glass tubing (in the range 1–5 g), and predried at 40 °C for 20 h to remove any surface-attached moisture/solvent. Nitrogen sorption measurements were performed on a ASAP 2420 multistage sorption analyser (Micromeritics), using highly purified nitrogen as the probe gas at a measurement temperature of –195.85 °C (liquid nitrogen dewar). Sorption measurements were performed in the partial pressure range p/ps 0.03–0.15, with BET multipoint linear regression analysis being performed on seven sorption points in the partial pressure range p/ps 0.05–0.12.

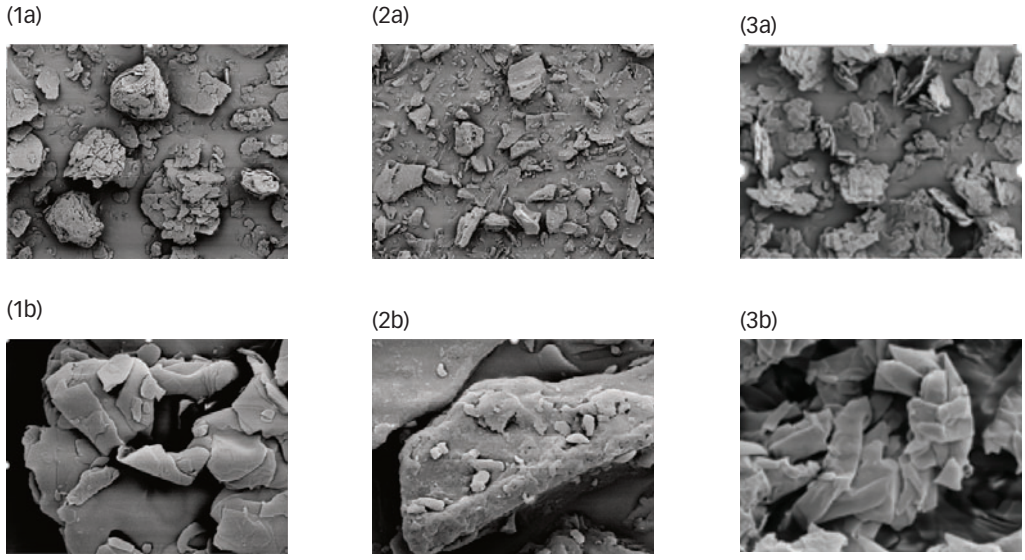
Scanning electron microscopy (SEM) was used to study the agglomeration of the particles. A small amount of powder was prepared on an aluminium sample holder covered by a conductive double-faced adhesive tape. Non-adhered particles were removed from tape by compressed air. To avoid electrostatic charging, the sample was sputtered with platinum (layer thickness: ~10 nm). The prepared sample holder was added into a Leo 1530 scanning electron microscope (ZEISS), and the measurement was performed under high vacuum.

Preparation of pre-mix. About 2 kg of each pre-mix was prepared. 0.5% MgSt was added to Metformin HCl at low shear and high shear mixing rates using a 6-L Laboratory Mixer P 1/6 (Diosna Dierks & Sohne). The low shear mixing rate was run for five minutes with chopper speed at 700 rotations per minute (rpm) and mixer speed at 300 rpm. The high shear mixing rate was run for 10 minutes at chopper speed 2200 rpm and mixer speed at 1000 rpm.

After blending, the pre-mix was allowed to settle for five minutes before unloading the mixer, to reduce material loss due to airborne particles.

Preparation of tablets. All tablets were prepared by the wet granulation

Figure 1: Magnesium stearate scanning electron microscopy pictures at (a) magnification 1000 and (b) magnification 10,000 for three suppliers: (1) MgSt S1, (2) MgSt S2 (3) MgSt S3.



method. The pre-mix was granulated with PVP dissolved in water as a binder agent using the 6 L Laboratory Mixer P 1/6 (Diosna Dierks & Sohne). The wet mass was dried using the fluid bed drier Minilab XP (Diosna Dierks & Sohne). Prior to tabletting, the dried mass was milled using the conical mill Quadro Comil U3 (Quadro Engineering). The milled granules were formed into tablets using a Korsch XL tablet press (Korsch) equipped with 7 mm compression tooling and 10 mm overfill cam.

The machine setting was kept constant. Tabletting speed was set to 10,000 tablets per hour, fill depth was set to obtain a tablet weight of 270 mg, and the main compression was controlled at 15 kN for all experiments.

Dissolution method. The dissolution profile of six tablets of each formulation were tested according to the *European Pharmacopoeia* (*Ph. Eur.*) 2.9.3 (5). Each tablet was placed in a vessel filled with 900 mL of purified water at 37 °C ± 0.5 °C. Apparatus 2, with paddles at 50 rotations per minute, was used for stirring. Aliquots were taken at 5, 10, 15, 35, 45, and 60 min and the API dissolved was quantified by ultraviolet-visible spectrophotometry.

Table I: Pre-mix preparation parameters at high and low shear blending rates.

Parameter	Low shear rate	High shear rate
Chopper speed (rpm)	700	2200
Mixer speed (rpm)	300	1000
Time (min)	5	10

Table II: Surface area (SA) measurements.

Parameter	SA
Supplier 1 (MgSt S1)	7.5 m^2/g
Supplier 2 (MgSt S2)	4.5 m^2/g
Supplier 3 (MgSt S3)	5.5 m^2/g

Evaluating the effect of blending shear rate

To evaluate the effect of shear rate in the preparation of the pre-mix on the dissolution of immediate-release tablets, the Metformin HCl was blended in the mixing equipment with MgSt from different suppliers at high shear and low shear rates. The formulations were then compressed into tablets, and the dissolution profile of six tablets was tested.

Impeller, chopper speed, and mixing time were varied according to **Table I**. All other machine settings were kept constant during the experiment.

Results

Table II depicts the SA measurements obtained by BET determination of MgSt samples. These samples were added in Metformin HCl and blended at high and low shear rate to prepare the free-flowing pre-mix. The pre-mix was used to prepare the immediate-release tablets. The dissolution profiles of the tablets were tested.

Figures courtesy of the authors

Figure 2: Metformin dissolution profile of the tablets prepared with Pre-mix with magnesium stearate (MgSt) S1, MgSt S2 and MgSt S3 blended.

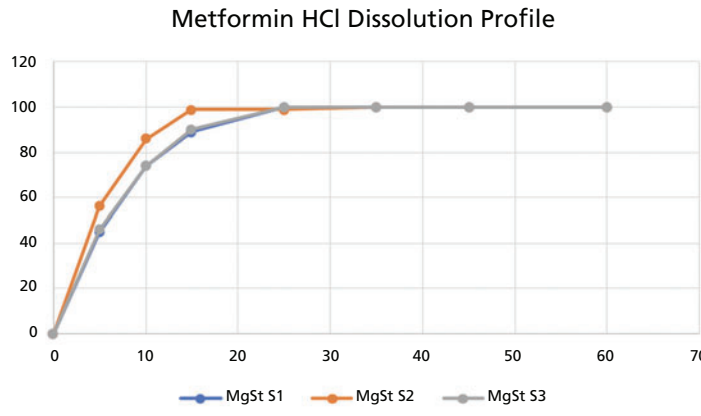


Figure 3: Metformin dissolution profile of the tablets prepared with pre-mix with magnesium stearate (MgSt) S1 at low and high shear rates.

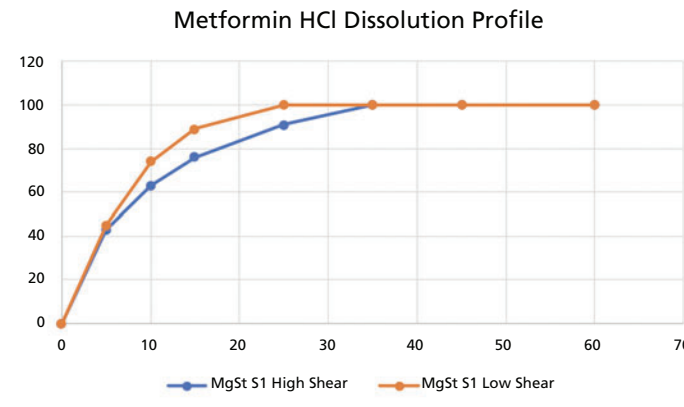


Figure 4: Metformin dissolution profile of the tablets prepared with Pre-mix with MgSt S2 blended at low and high shear rates.

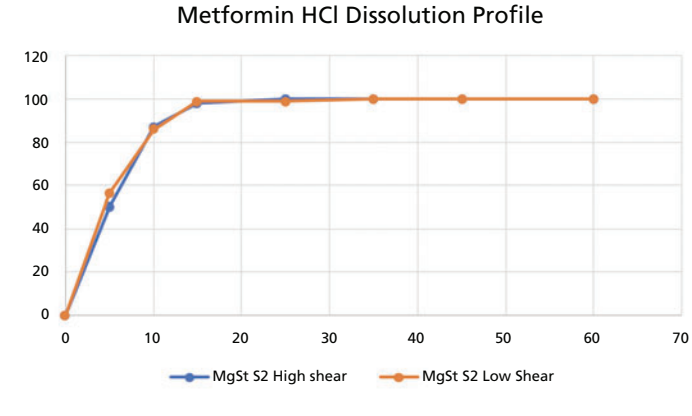


Figure 1 depicts the images obtained by scanning electron microscopy (SEM) of MgSt samples, illustrating the difference in particle morphology. **Figure 2** depicts the Metformin hydrochloride (HCl) dissolution profile of the tablets prepared with the pre-mix, with which the magnesium stearates (MgSt S1, MgSt S2, or MgSt S3) were blended. **Figures 3–5** depict the Metformin HCl dissolution profile comparison of the tablets prepared with the pre-mix blended at high and low shear rates for each of the three MgSt types.

Discussion

The SA plays a key role in the effect of the MgSt on the dissolution rate of some APIs from tablets. This effect is related to the ability of MgSt to cover the particles of the excipients and API during the tablet's manufacturing process. As MgSt is not water soluble, an excessive coating may lead to a slower dissolution rate of the active ingredient from the tablet.

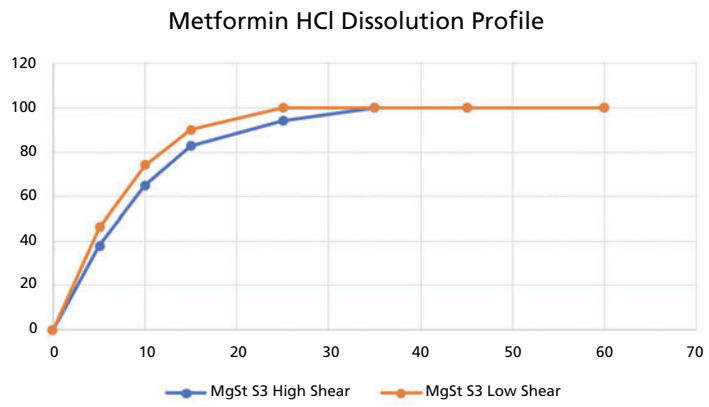
The samples of MgSt obtained from various vendors tested have different particle properties, such as specific surface area and particle morphology, as shown in **Table II** and **Figure 1**. MgSt S1 sample has the highest surface area of all, followed by the MgSt S3 sample. MgSt S2 sample has the lowest (see **Table II**).

The SEM pictures (**Figure 1**) depict differences in particle morphology. MgSt S1 and MgSt S3 samples are agglomerated, flake-like particles, while MgSt S2 particles are more consistent and smoother.

Generally, it is expected that the slow-down of Metformin dissolution rate, due to the MgSt effect, increases on increasing the surface area of MgSt. The increase of surface area can provide more API coverage with the excipient, which is hydrophobic.

Metformin tablets prepared with the pre-mix with MgSt S2, which has the lowest surface area of all, had a faster dissolution rate than tablets prepared with the pre-mix with MgSt S1 and

Figure 5: Metformin dissolution profile of the tablets prepared with Pre-mix with MgSt S3 blended at low and high shear rates.



Mg St S3. Despite MgSt S3 sample having a lower surface area value than MgSt S1 sample, Metformin tablets prepared with the pre-mix with MgSt S3 and MgSt S1 had unexpectedly similar dissolution rates, **Figure 2**.

The specific surface area is not the only driver for the potential coverage of MgSt particles over API and excipients, but particle morphology also plays a key role ...

The dissolution rate of the Metformin tablets was found to be slower when MgSt S3 and MgSt S1 were used in the preparation of the pre-mix blended at higher shear rates, see **Figures 3** and **5**. But no shift was found when the MgSt S2 was used to prepare the pre-mix at both shear rates, see **Figure 4**.

It is suggested, in specific literature, that particle morphology of some MgSt is often pictured as a deck of cards depending on the precipitation process during its preparation (6). During the blending process with active ingredients, carriers, or fillers, the 'plates' of MgSt dismantle from the decks, piece-by-piece, to coat other particles, depending on the particle morphology.

MgSt S2 particles are less susceptible to deagglomeration by shear rates during blending due to the more consistent and smoother morphology. MgSt S1 and MgSt S3 agglomerated flake particles, however, are more susceptible to being dismantled, increasing their coverage potential. The coverage by such a hydrophobic layer prevents water from penetrating into the tablet, leading to a slower dissolution rate when prepared with the pre-mix with MgSt S1 and MgSt S3.

Conclusion

The specific surface area is not the only driver for the potential coverage of MgSt particles over API and excipients, but particle morphology also plays a key role, mainly when MgSt is blended at higher shear rates with an API for further processing as a pre-mix. Agglomerated flake-like particles are more susceptible to being deagglomerated and have higher coverage potential than the more consistent and smoother particles, despite surface area. The increased coverage potential prevents water from penetrating into the tablets prepared with such a pre-mix, leading to a slower dissolution rate.

References

1. R. Pfeffer, et al., *Powder Technology* 158 (1–3) 21–23 (2005).
2. G.K. Bolhuis, A.J. Smallenbroek, and C.F. Lerk, *J. Pharm. Sci.* 70 (12) 1328–1330 (1981).
3. J. Barra, and R. Somma, *Drug Dev. Ind. Pharm.* 22 (11) 1105–1120 (1996).
4. T.A. Miller and P. York, *Int. J. Pharm.* 23 (1) 55–67 (1985).
5. EDQM, *Ph. Eur., General Chapter 2.9.3, Dissolution Test for Solid Dosage Forms* (EDQM, Strasbourg, France, 2014).
6. Peter Greven, "Ligamed Brochure," peter-greven.de. **PTE**

Testing for Water in DMSO: Exploring Alternatives to Volumetric Karl Fischer Analysis

Andrew Johnson and Ashley Jones

Karl Fischer (KF) analysis is a fast and effective way to determine the water content in many excipients and APIs. Dimethyl sulfoxide (DMSO) is a hygroscopic pharmaceutical ingredient. For many years, its water content has been tested using the volumetric KF method, even though the accuracy of results using this method can be affected by reaction between the KF reagent and the DMSO analyte.

In 2018, pharmaceutical companies petitioned the *European Pharmacopoeia* to change the DSMO testing monograph, which prompted the authors to compare different methods and instruments for this application.

Spiking experiments that assessed water recovery were used to evaluate the interference for several reagent and technique combinations. Finally, method linearity, precision, and accuracy were assessed for each reagent and technique. This work resulted in developing a new technique and analytical instrumentation that would produce water standards in DMSO that were suitable for method development.

In Karl Fischer analysis, sulfur trioxide can react with DMSO, invalidating test results. The authors evaluated different instruments and methods, described in this article, to minimize the impact on results.

CITATION: When referring to this article, please cite as A. Johnson and A. Jones, "Testing for Water in DMSO: Exploring Alternatives to Volumetric Karl Fischer Analysis," *Pharmaceutical Technology* 43 (5) 2019.

Submitted: 11 Dec., 2018.
Accepted: 23 Jan., 2019.

The use of *United States Pharmacopeia* and *European Pharmacopoeia* (*USP* and *Ph Eur*)-grade dimethyl sulfoxide (DMSO) has become increasingly common in topical and parenteral drug delivery systems as a way to make APIs more soluble. A wide variety of applications are currently on the market with multiple routes of administration (1,2). Some of its other applications include acting as a reaction solvent for the synthesis of APIs and intermediates as well as use as an API itself.

The US and European compendial methods both specify that volumetric Karl Fischer (KF) be used for water determination in DMSO (3,4). Unfortunately, there are many drawbacks to using volumetric KF with DMSO. For one thing, an intermediate product, sulfur trioxide, reacts with DMSO in the presence of iodide. This redox reaction reduces DMSO to dimethyl sulfide (DMS), generating iodine in the process. This iodine then titrates water in the sample, which results in low recovery. This particular interference has been observed by a number of device manufacturers and has been further discussed in technical papers (5,6). Some manufacturers have also observed the same interference when using coulometric KF (7).

Other issues have also become apparent when analyzing anhydrous DMSO samples. Due to the hygroscopic nature of DMSO, exposure to environmental moisture results in an uptake of water. This interference can lead to skewed results when calculating the recovery factor that is necessary for volumetric KF. The burette for volumetric KF is designed to titrate samples with a water content greater than 1% w/w. Device manufacturers for volumetric KF suggest that 10–90% of the burette volume be used for optimal usage. For anhydrous DMSO samples, the amount of burette volume used can be as low as 0.3%, leading to accuracy and precision errors.

Approach

Each analytical method was evaluated over a wide range of concentrations. Because of the extremely hygroscopic nature of DMSO, special techniques were developed to

prepare and handle DMSO standards that contained less than 50 ppm water.

Septum-lined sample bottles were used to allow for the addition of water spikes and subsequent withdrawal of material without having to remove the container cap. Activated molecular sieves (8) were then used to dry down the DMSO samples to help achieve a lower initial water content. Once dried, the DMSO was transferred to a thoroughly dried sample bottle. To prevent exposure to environmental moisture during transfer, an apparatus was set up to transfer the dry material. It consisted of a stainless-steel cannula and a nitrogen purge, as shown in **Figure 1**. All water and stock spikes were prepared using a gas-tight syringe (9) in the same bottle to control the risk of environmental moisture associated with transferring the dry DMSO into multiple bottles. A 1% w/w water stock solution was also used to control the error inherent to weighing small volumes of water.

To perform recovery calculations, an initial water assay of the DMSO sample was required. This calculation was accomplished using the method of standard addition (10).

The volumetric KF method (11) was then assessed using data from validation exercises that had been performed in 2016 and 2018. Low recovery was exhibited in both validations but could be corrected with the use of a recovery factor. Tests were run using different commercially available Karl Fischer reagents (12) and results were compared. These experiments showed that the use of methanol-based reagents improved both accuracy and precision.

In a pharmaceutical environment wherein accurate water measurements are needed as a means of process control, it is beneficial to be able to make multiple injections without having to change out the solution. An experiment was carried out in which numerous injections of DMSO were made into a titration vessel without emptying the titration cell and filling with fresh solution. When comparing the cumulative volume of DMSO in the titration vessel against water concentration values returned by the instrument, two trends became apparent: A downward trend in the results was seen when using higher concentration material (**Figure 2B**) and an upward trend for lower concentration material (**Figure 2A**).

Figure 1: Sample preparation apparatus.

The method works relatively well for DMSO that contains higher concentrations of water. However, using a recovery factor is not sufficient when using KF analysis on extremely dry product samples. The authors had considered using a Karl Fischer oven module to assess water in DMSO samples, while preventing DMSO from entering the titration cell. Instrument manufacturers suggested, instead, that using an oven would result in the same problems, so the decision was made to consider using a gas chromatograph (GC) equipped with a thermal conductivity detector (GC-TCD) and an ionic liquid-based GC column (13, 14, and 15) as an alternative to volumetric KF.

A GC-based method offered an attractive alternative to a KF titrator for several reasons. First, if it worked, the GC-TCD analysis would avoid the complicated interferences observed between DMSO and components of the KF reagent. In addition, a GC is generally a more robust instrument than a KF titrator. It requires less maintenance and fewer consumables and can be used to analyze for more than one impurity at a time. GC analysis is also less technique dependent, making it ideal for in-process testing.

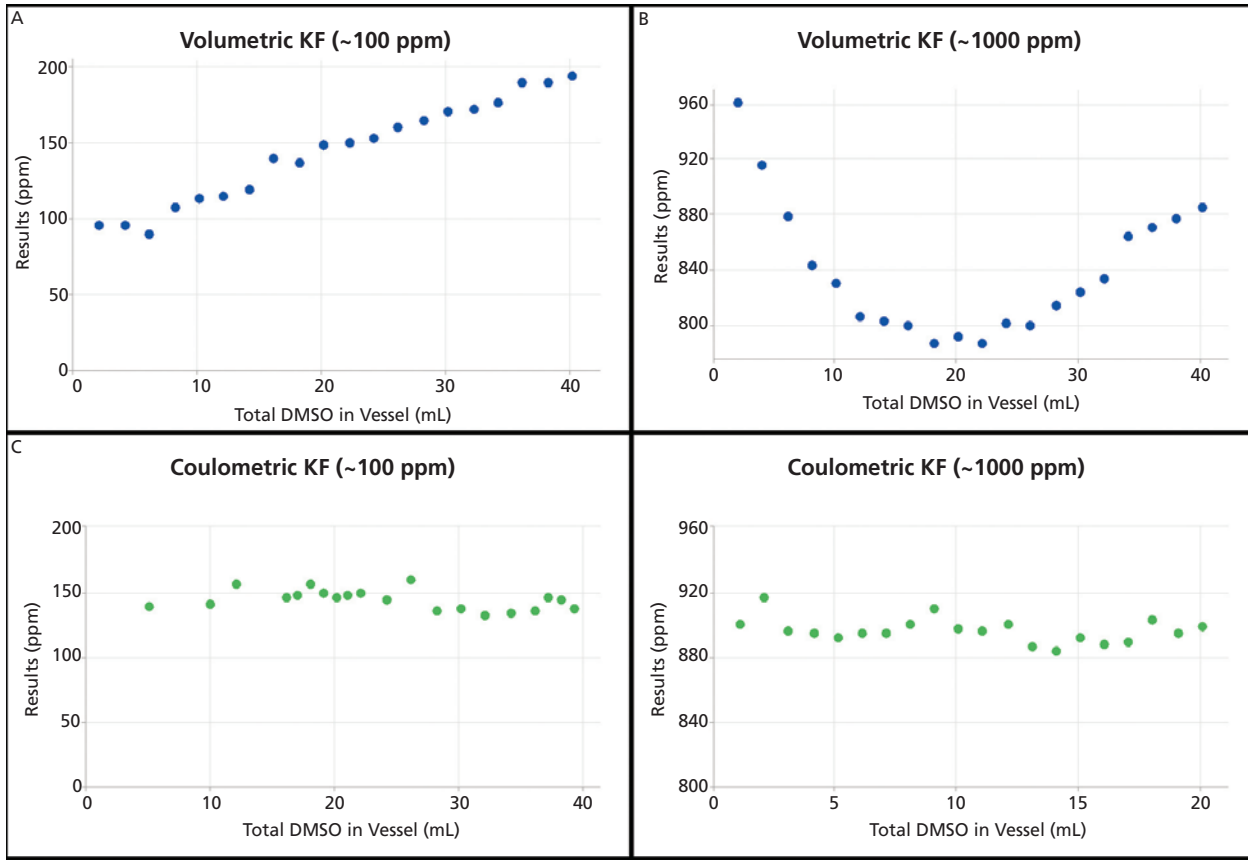
The authors found that the GC-TCD method worked relatively well at higher water concentrations, as shown

Table I. Accuracy and precision data for the gas chromatography-thermal conductivity detector (GC-TCD) method.

Concentration water spiked, ppm	Observed area counts			Average area counts	Standard deviation	% relative standard deviation	Theoretical concentration, ppm	% recovery
	Injection 1	Injection 2	Injection 3					
0.00	4.70	2.74	2.04	3.16	1.38	43.58	83.35	-
198.22	10.34	10.35	10.83	10.51	0.28	2.65	281.57	77.07
299.28	16.04	16.74	14.86	15.88	0.95	5.99	382.63	99.62
400.65	18.24	19.19	18.58	18.67	0.48	2.57	484.00	96.36
497.67	22.23	22.84	22.32	22.47	0.33	1.47	581.02	100.21
615.02	27.14	27.06	27.23	27.14	0.08	0.31	698.38	103.82

FIGURES COURTESY OF THE AUTHORS

Figure 2: Trend in results after multiple injections based on the concentration of water in dimethyl sulfoxide (DMSO) for volumetric and coulometric titrators. ppm is parts per million.



in **Table I**. At concentrations lower than 300 ppm, however, the GC-TCD signal was not intense enough to generate the area counts that were required to reproduce data precisely, which led to linearity problems. However, percent recovery values were deemed suitable across the testing range, based on an assessment of triplicate injections. Using fewer injections resulted in low precision at concentrations less than 300 ppm, causing recovery to vary widely. However, the need for triplicate injections resulted in a significant runtime for each sample analysis.

The authors then considered the coulometric KF (15) method for this application, especially after learning that the approach had been mentioned in a 2018 petition to the *Ph Eur* to change the DMSO testing monograph. Spiking experiments (16) were used to assess the method's capabilities (17).

Excellent recovery and precision were observed, even for concentrations as low as 35 ppm up to around 100 ppm, without the use of a recovery factor. They were also seen for concentrations of up to 1000 ppm with the use of a recovery factor (shown in **Tables II and III**). Manufacturer reviews suggested that a side reaction would occur, but using the recovery factor prevented this problem from taking place. However, coulometric KF does not seem to have the same precision issues that volumetric KF has at lower concentrations.

When numerous injections of DMSO were made into the titration vessel without emptying the titration cell and filling it with fresh solution, there were no significant differences in the results (**Figures 2C–D**). This was observed at both low and high concentrations. It seems that the DMSO/KF reagent interference has no effect on the trend in results after numerous injections for coulometric KF. In fact, the only potential downside of using coulometric KF is that it is not designed to titrate greater than 1 % w/w water. For DMSO samples with a water content greater than 1% w/w, volumetric KF can instead be used with a recovery factor. When a recovery factor is used at a concentration > 1 % w/w, results show a high degree of accuracy and precision.

Conclusion

Of the three methods that were evaluated for water determination in DMSO, the coulometric KF method proved to be the most effective at analyzing samples that contained less than 1% w/w water. Even though the DMSO/KF re-

Table II. Accuracy and precision data for the coulometric Karl Fischer method (~30 ppm to ~100 ppm).

Observed area counts			Average results, ppm	Standard deviation	% relative standard deviation	Theoretical concentration, ppm	% recovery
Injection 1	Injection 2	Injection 3					
38.0	30.7	33.6	34.1	3.7	10.8	30.6	-
37.0	35.9	34.6	35.8	1.2	3.4	35.7	100.3
49.6	43.8	46.1	46.5	2.9	6.3	45.9	101.3
55.6	61.2	61.6	59.5	3.4	5.6	60.9	97.6
81.3	76.9	75.6	77.9	3.0	3.8	80.8	96.4
104.4	113.2	101.0	106.2	6.3	5.9	105.7	100.5

Table III. Accuracy and precision data for the coulometric Karl Fischer method (~40 ppm to ~1000 ppm).

Concentration water spiked, ppm	Observed area counts			Average results, ppm	Standard deviation	% relative standard deviation	Theoretical concentration, ppm	% recovery	% recovery with factor applied
	Injection 1	Injection 2	Injection 3						
0.00	39.2	37.7	42.7	39.9	2.6	6.4	60.7	-	-
48.87	95.7	95.2	105.3	98.7	5.7	5.8	109.6	90.1	99.4
150.35	191.0	196.5	191.4	193.0	3.1	1.6	211.1	91.4	100.8
496.92	502.5	509.6	501.1	504.4	4.6	0.9	557.7	90.5	99.8
1000.32	957.6	959.5	971.1	962.7	7.3	0.8	1061.1	90.7	100.1

agent interference is still present, improved recovery, precision, and a significantly lower limit of quantitation is observed when a recovery factor is applied. Its short run time, as well as the ability to support numerous injections of DMSO without significant differences in results, makes this method ideal for in-process testing.

Volumetric KF and GC-TCD are both suitable methods for DMSO samples that contain a water concentration greater than 1% w/w. A recovery factor should be applied when using volumetric KF due to the DMSO/KF reagent interference. Making numerous DMSO injections into a volumetric KF titration vessel is not recommended due to a decrease in recovery at high concentrations and an increase at low concentrations. In addition, the need for triplicate injections when using the GC-TCD method causes an increase in run time and makes it less ideal for in-process testing.

References

1. A.S. McKim and R.T. Strub, *Pharm. Tech.* 2016 Supplement (3), 30-35 (2016).
2. A.S. McKim and R.T. Strub, *Pharm. Tech.* 32 (5) 74-85 (2008).
3. USP, *USP 40-NF 35,* p. 3792 (US Pharmacopeial Convention, Rockville, MD, 2017).
4. EDQM, *EurPh, 9.0* Volume 2 (EDQM, Strasbourg, France, 2017), p. 2280.
5. W. Fischer, S. Beil, D. Krenn, *Journal für praktische Chemie 337* (1), 266-268 (1995).
6. Metrohm, Application Work AW KF DE5-0377-072012: Dimethyl Sulfoxide as Solubilizer in KF Titration (2011).
7. Hydranal, Laboratory Report L 141: Water Determination in Dimethyl Sulfoxide (2017).
8. 3Å molecular sieves were used (Catalog # 208574-5KG). The DMSO stood over the molecular sieves for >72 hours.
9. Gas-Tight Syringe: 2.5 mL Hamilton #1002 PTFE Luer Lock
10. J. M. Miller and J. B. Crowther, *Analytical Chemistry in a GMP Environment: A Practical Guide,* pp.390-391 (Wiley, New York, NY, 2000).
11. E. Scholz, "Titration Techniques," in *Karl Fischer Titration: Determination of Water* (Springer-Verlag, New York, NY, 1984), pp. 15-19.
12. Comparison of KF reagents: Hydranal KetoSolver (Catalog # 34738) and Hydranal Composite 2 (Catalog # 34806); Aquastar Solvent KN (Catalog # AX-1699EN-6) and Aquastar Composite 2 (Catalog # AX1698B-5); Aquastar CombiMethanol (Catalog # M1880092545) and Aquastar CombiTitrant 2 (Catalog # M1880022545)
13. Y. Zhang, et al., *LCGC Europe* 24 (10), 516-529 (2011).
14. J. M. Miller and J. B. Crowther, *Analytical Chemistry in a GMP Environment: A Practical Guide* (Wiley, New York, NY, 2000), pp.236-240.
15. Watercol 1900 Capillary Column 30m x 0.25mm x 0.2µm film thickness (Catalog # C21615010)
16. E. Scholz, "Coulometric Determination," in *Karl Fischer Titration: Determination of Water* (Springer-Verlag, New York, NY, 1984), pp. 19-21.
17. Coulometric Titrator: Mettler Toledo C20X (Catalog # 51105512); Coulometric Reagent: Aquastar CombiCoulomat Fritless (Catalog # 1092570500) **PTE**

Andrew Johnson is analytical specialist, ajohnson@gaylord.com, and **Ashley Jones** is analytical chemist, ajones@gaylord.com, both with Gaylord Chemical Co, LLC.

Closed Systems for Aseptic Fill and Finish

Isolators, robotics, and other new technologies are ready to modernize aseptic filling and packaging.

Jennifer Markarian

Aseptic processing is as important as ever, and new aseptic product areas, such as personalized medicine and combination products, are growing, noted James Agalloco, president of Agalloco & Associates and member of the editorial advisory board of *Pharmaceutical Technology,* in a presentation at INTERPHEX 2019 (1). Technology is changing rapidly, and equipment manufacturers have introduced new technologies for closed systems, including isolators and single-use disposable systems for product transfer and fill/finish.

Despite the advantages of systems that remove operator intervention, such as gloveless isolators with robotic handling of ready-to-fill components, not all users are ready to adopt these new technologies, said Agalloco. Concerns about costs, regulatory response, and potential project delays are reasons for hesitation. "Like it or not, however, closed systems are the future of aseptic processing," concluded Agalloco.

Closed processing equipment

One option for closed processing is restricted access barrier systems (RABS). RABS are a relatively easy upgrade to implement in existing cleanroom facilities and may have a lower capital expense than isolators, but are more expensive to operate. "RABS are most useful as an upgrade of an existing facility, because the investment can be staged over a period of years, and a portion of the existing infrastructure and utility systems can be reused without modification. Long term, however, I don't think RABS have much of a future," says Agalloco.

Isolators are an increasingly popular solution, agreed equipment vendors at INTERPHEX, where several new systems were on display. According to Randy Fraatz, vice-president of North American Operations at Steriline North America, the increase in use of isolators is driven by the need to reduce contamination risk and increase worker safety, and by encouragement from regulatory bodies to use technology such as isolators. While 25 years ago there may have been only a few isolator installations, today 80% or more of Steriline's projects are isolator based, with only a few RABS or traditional cleanroom installations, says Fraatz.

Another trend is the increasing use of robotics, rather than traditional automation, especially for material handling within a closed system but also for handling components at the front-end and at the discharge, adds Fraatz. Robotics are more efficient and flexible, and they reduce the number of parts needed inside a closed system, which increases cleanliness. While traditional automation is still best for high-speed applications (e.g., greater than 300 vials/minute), robotics are beneficial for the flexibility in handling multiple container sizes and for reducing reject rates, which is more crucial in high-cost goods such as personalized medicines, comments Fraatz.

Olivier Cremoux, business development manager for North America, Robotics at Stäubli, agrees that there is growing demand from machine makers for robotics because robots allow a reduced footprint and lower particle generation with increased flexibility. Stäubli's Stericlean robots, including the TX2 collaborative six-axis robots and the four-axis TS2 SCARA robots, are designed to be compatible with hydrogen peroxide sterilization so that they can be used inside a closed system, explains Cremoux.

Steriline's Robotic Vial Filling Machine (RVFM), designed for filling inside an isolator using bulk primary packaging, uses one or two robotic arms made by Stäubli to move the vials within the machine. The machine is designed to detect missing stoppers or caps and to allow repeated operations to correct the missing piece within the process so that the problem container can be fixed rather than rejected (2). While the RVFM handles bulk containers, the company's robotic nest filling machine is designed for filling ready-to-use nested containers inside a RABS or isolator.

Fraatz sees interest in the industry in continuing to go further in removing possible contamination sources, such as designing isolators

with fewer glove ports, and eventually gloveless isolators.

Vanrx Pharmasystems' SA25 Aseptic Filling Workcell is a gloveless isolator technology in use today. In 2018, for example, Fujifilm Diosynth Biotechnologies reported that it had invested in the workcell to expand its gene therapy and viral vaccine fill/finish capabilities in support of late-phase candidates and commercial supply at Fujifilm's Flexible Biomanufacturing Facility in College Station, Texas (3). The systems from Vanrx use robotic arms for repeatable filling that is also flexible for producing smaller batches and using different container formats (4).

Fedegari displayed a prototype of its multi-process system that contains sterilization, washing, and fill/finish, all within an isolator. The system uses a seven-axis robot, constructed completely from stainless steel, for handling containers inside the isolator. Fedegari's proprietary Thema4 software, used for the robotic control system, provides complete audit trails and data integrity.

Other closed fill/finish systems at INTERPHEX included AST's GENiSYS R robotic filling and closing machine; NJM's Dara NFL/2-RDL aseptic filling and closing machine for ready-to-use, nested vials; and groninger's Integra aseptic filling machine with an integrated isolator using SKANFOG decontamination (5). SKAN's SKANFOG Spectra Modular Aseptic Processing and Sterility Testing Isolator System was awarded "Best in Show" at INTERPHEX 2019 (6). The system allows faster transfer into an isolator and faster isolator decontamination cycles, says the company.

Single-use components

Watson-Marlow Fluid Technology Group displayed its new Flexicon FPC60 peristaltic fill/finish modules that are built to fit a small footprint. The modules—which include vial infeed, filling, stoppering, capping, auto-reject, gas purging, and product outfeed—are designed for users to create their own filling system for small-batch applications. Machine guarding is standard, and integration of laminar airflow, restricted-access barrier systems, or isolators is also available. According to the company, the entire FPC60 fluid path has been developed for single-use, which simplifies cleaning validation and facilitates changeover between liquid types (7).

Meissner's single-use fill/finish assemblies are engineered for precise, isolator-based filling of final drug product. The single-use, all-polymer filling needles are composed of a rigid polyether ether ketone (PEEK) tube with a polypropylene hub (which is the same resin used in Meissner's filters) that is permanently bonded via an overmolding process, eliminating the need for chemical bonding or glues. "The well-characterized materials of construction and our highly controlled, cleanroom manufacturing processes make the needles easy to support via a sterilization validation," notes Karisa Koenig, director of marketing at Meissner.

Decontamination systems

Several systems for decontamination of closed aseptic systems or cleanrooms were on display at INTERPHEX. The DECOpulse Biodecontamination System from Optima Pharma/Metall+Plastic received an INTERPHEX Exhibitor Award for its system that uses atomization to produce vapour-phase hydrogen peroxide. The approach provides faster decontamination, improved safety because of reduced outgassing, and shorter decontamination cycles, says Dena Flamm, business development manager at Optima Pharma. The patented system's atomization-driven evaporation creates droplets of a defined size that evaporate quickly, which results in a more homogeneous and faster distribution of hydrogen peroxide, says Flamm. Another benefit is that the technique, which doesn't require additional heating to evaporate the liquid, prevents unintended decomposition of hydrogen peroxide. Optima offers the DECOpulse system for all its isolators as a turnkey filling solution.

TOMI Environmental Solutions displayed its SteraMist binary ionization technology (BIT), a patented two-step process that creates ionized hydrogen peroxide (iHP). The process, originally developed in a programme with the US Defense Advanced Research Projects Agency, uses a lower percentage hydrogen peroxide compared to other systems. The company installed SteraMist systems in four cleanroom cGMP suites in a new Pfizer facility in Chesterfield, Missouri, TOMI announced in an 10 April 2019 press release. The Chesterfield facility, at approximately 295,000 ft^2, houses Pfizer's BioTherapeutics Pharmaceutical Sciences R&D group. This SteraMist iHP Custom Build-In System uses 20 ceiling-mounted SteraMist applicators connected to dual-generator control cabinets, programmed to run one or all applicators simultaneously, which will be used on a daily basis to ensure total disinfection and decontamination, reported TOMI (8).

References

1. J. Agalloco, "Aseptic Processing 2019: Trends and Challenges," Presentation at INTERPHEX (NYC, 2019).
2. Steriline, "New Technologies and Customization, Steriline is Following the Innovation Path to Meet Pharma Customers' Needs," Press Release, 2 April 2019.
3. Fujifilm, "Fujifilm Announces the Expansion of Its Fill Finish Services to Include Late Phase And Commercial Production Of Gene Therapies And Viral Vaccines to Become an End-to-End Solutions Provider," Press Release, 23 May 2018.
4. J. Markarian, "Robotics Solve Aseptic Filling Challenges," *PharmTech.com*, 10 June 2018.
5. H. Forcinio, "Packaging Innovations at INTERPHEX 2019," *PharmTech.com*, 20 March 2019.
6. SKAN, "Award Winner at INTERPHEX New York," Press Release, 5 April 2019.
7. Watson Marlow Fluid Technology Group, "Uniquely Configurable Flexicon FPC60 Fill/Finish System Offers Production Flexibility," Press Release, 10 Jan. 2019.
8. Tomi Environmental Systems, "TOMI Environmental Solutions, Inc. Implements SteraMist Into Pfizer, Chesterfield, MO," Press Release, 10 April 2019. **PTE**

Single-Use in Downstream Chromatography: Benefit or Hindrance?

Single-use technology is gaining ground in downstream bioprocessing, but challenges stall further adoption.

Feliza Mirasol

Biopharmaceutical manufacturers have embraced the use of single-use technology upstream, but are now increasing its use in downstream processing (DSP) as well. "There are very few DSP unit operations that are not using single-use systems or components," notes Donald Young, senior global product manager, BioProcess Containers, Thermo Scientific BioProduction. "Clarification via depth filtration or tangential flow membrane filtration (TFF) is just one example."

As this trend continues, the concept of an end-to-end single-use manufacturing facility has moved from the world of theory squarely into reality. However, downstream single-use systems are still evolving, as vendors work to improve performance in critical areas. This article summarizes some of the benefits and the challenges of employing single-use technology downstream.

Reduction in bioprocessing time is one advantage that single-use systems offer. As Young points out, re-usable systems can typically require more than 12 hours from set-up to tear-down, while single-use TFF systems require half that time.

Another area where single-use is gaining ground downstream is in buffer preparation, storage, and dispense. "Single-use mixers, coupled with single-use bioprocess containers (BPC), can increase a DSP suite's annual throughput, because they offer turnaround times of around a day or less without the need for clean- or steam-in-place operations. Reusable systems can require three or more days to clean and sterilize," Young explains.

Prefilled BPCs have only made the single-use option more popular, he says, noting that BPCs prefilled with water for injection or purification buffers can be delivered to customers, eliminating the need for them to perform these functions inhouse. These systems can be supplied in volumes ranging from pre-clinical and clinical scale to volumes large enough to satisfy current good manufacturing practice (cGMP)-scale production, he says.

"These large-volume-liquid BPCs are used as the primary source of sterile process liquids or as a second source/back-up supply to reduce demand on the customer's in-house capabilities and capacities," Young states.

Using pre-sanitized single-use columns and flow kits is one way to minimize the risk of bioburden.

Hindrance or help?

Many disposable chromatography columns meet cGMP and industry standards, and also offer reproducibility, scalability, speed, ease-of-use, and operational safety. However, chromatography has been the last purification stage to move into disposable equipment. Although its use is growing downstream, it is still limited. In addition, the industry's adoption of pre-packed, limited-use chromatography has been slow, even though the technology's benefits have been demonstrated in the early stages of clinical manufacturing (1).

Among the common problems that single-use technology can help address is column packing. Column packing requires a stable bed with good flow properties, and, today, automatic packing solutions make packing the columns much more reliable than in the past. Bioburden can still result, however, and its source can vary—usually it is introduced before or during packing. Thus, good sanitation methods and familiarity with the most likely microbial contaminant species present in the immediate environment are needed to address bioburden. Using pre-sanitized single-use columns and flow kits is one way to minimize the risk of bioburden (2).

Cycle-time reduction

Single-use technology implementation in chromatography can greatly reduce cycle times, lower operating costs and energy consumption, and generate less waste, according to Young, who points out that DSP can be a process bottleneck because of a lack of single-use chromatography options or because of the expense, time, and labour of using existing

PDA
Parenteral Drug Association

pda.org/EU/PM2019

2019 PDA EUROPE

Project Management in the Pharmaceutical Industry

5 SEPTEMBER 2019
MUNICH, GERMANY

CONNECTING PEOPLE SCIENCE AND REGULATION®

MARK YOUR CALENDAR

chromatography components as single-use components.

With a facility set up for single-use system operations, facility design can be simplified and can be executed in about half the time needed to build a traditional facility with reusable systems, Young emphasizes. "Start-up/licensure times can be cut compared to traditional facilities using stainless steel-only equipment and systems," he states. In addition, construction costs are lower mostly due to reduced need for clean steam systems that can account for much of a production facility's water needs, he adds.

Column packing requires a stable bed with good flow properties, and, today, automatic packing solutions make packing the columns much more reliable than in the past.

"Single-use systems are an attractive option for emerging markets, not only in chromatography but all along the production workflow," says Young, who sees this as the technology's most important contribution today.

Further needs

Despite wider adoption of single-use technologies, downstream bioprocessing, particularly chromatography, continues to a pose challenges. Available technology may not always be adequate to meeting a specific facility's needs. For example, not all downstream bioprocessing steps are available with single-use technology, and those that are available may be limited by performance, scalability, and cost (1).

For example, one unmet user need is the lack of affinity and ion-exchange chromatography beads that are sufficiently cost-effective to be classified as single-use. These process steps continue to be the biggest process bottleneck in the DSP workflow, and represent a huge opportunity for suppliers, Young remarks.

Another area where single-use technology might be improved downstream is in combining it with process chromatography columns, according to Dr. Nandu Deorkar, vice-president of research and development at Avantor, a manufacturer and distributor of products, services, and solutions to the life-sciences and advanced technologies industries.

"[Adopting] single-use systems gives manufacturers the potential to move from a batch-based approach to something approaching a connected continuous process. It will be possible to minimize the [number of] large storage tanks required, and incorporate single-use systems to streamline sample collection and loading, and other operations. There are single-use systems that make it much more of a continuous process, and remove the time required to clean, dry, qualify, and validate sampling and storage systems between chromatographic steps," Deorkar states.

Resin fouling

Another unmet need for biopharmaceutical manufacturers is technology that reduces the cost of resins (3), to allow for greater use of single-use systems to address the resin fouling that occurs from repeated use of resin during chromatography. Manufacturers are unlikely to dispose of costly resins after one pass, unless costs are significantly reduced to make this practical.

Because chromatography resins make up a large portion of the costs in downstream bioprocessing, switching a polishing step from resin chromatography to a single-use membrane column can significantly reduce expenses and is one alternative when looking to improve DSP. In a study (4) that used modelling software to evaluate commercial monoclonal antibody (mAb) production, it was shown that the unit operation cost was 19% to 33% less for a membrane process used on 1000-L and 5000-L scales bioreactor volumes and various mAb titres. In addition, buffer volume was decreased by up to 55%.

Single-use in overall bioprocessing

Suppliers of single-use downstream chromatography systems continue to improve the options available to manufacturers, and to examine ways to reduce the number of processing steps required for biomanufacturing, by linking steps to improve process efficiencies. For example, the ability to use concentrated buffer components and mix them in-line under controlled conditions (i.e., in-line conditioning) has simplified chromatographic operations (2).

Because chromatography resins make up a large portion of the costs in downstream bioprocessing, switching a polishing step from resin chromatography to a single-use membrane column can significantly reduce expenses.

"Single-use systems have the potential to improve productivity across the entire mAb production process, especially in terms of sampling," adds Claudia Berrón, vice-president of global commercial development, biopharma, Avantor. "Drug producers have to sample for quality and process control purposes many, many times continuously. Typically, to effectively sample, you sample more than what is needed, and, in some cases, it isn't possible to sample exactly what is needed. Every time you take a sample out, you're taking valuable material out of the process."

For its part, Avantor has been creating single-use systems that incorporate design features that make it easy to customize sampling systems to extract only the amount of material required to perform a test or document process results. "These designs are also much easier for plant personnel to use, helping reduce the time and labor costs associated with sampling," Berrón states.

References

1. C. Challener, *BioPharm International* 27 (6) 34–36 (2014).
2. C. Hroncich, *BioPharm International* 29 (9) 28–33 (2016).
3. R. Jacquemart et al., *Computational and Structural Biotechnology Journal* 14, 309–318 (2016).
4. A. Xenopoulos, *Journal of Biotechnology* 213, 42–53 (2015). **PTE**

Managing Biologic Equipment Cleaning

This article takes a look at current practices for cleaning and sterilizing biomanufacturing equipment used in a multi-product versus single-product setting.

Feliza Mirasol

When it comes to cleaning validation in the biopharmaceutical industry, different biopharmaceutical manufactures face similar challenges. Some common challenges include the ability to have reproducibility when manually cleaning small parts and when using non-clean-in-place (CIP) systems as well as having an effective design in which CIP systems are fully automated.

Other challenges include a physical build-up of protein on equipment walls that have been cleaned by CIP. This build-up is a process that happens over time when there is no periodic scrub-down of the equipment, allowing for a layer of residue to accumulate in the inner surface of the vessel. In addition, failure of CIP systems over time due to blocked steam traps, poor maintenance, or irregular/erroneous replacement of a steam trap will pose problems for cleaning validation operations (1).

Because cleaning validation is an important aspect in current good manufacturing practice (cGMP) manufacturing for monoclonal antibodies (mAbs) as well as other biologics, it is important to consider how current practices ensure that cleaning and sterilizing biomanufacturing equipment is conducted properly, and whether differences exist between cleaning and sterilizing equipment used in multi-mAb product versus single-mAb product manufacture in the same facility.

To start with, no real differences exist between single-mAb and multi-mAb product manufacture in regard to cleaning and sanitation/sterilization, industry experts say. Cleaning protocols would be similar in both circumstances. However, it is important to note that there would be no concern with active carry-over in single-product facility as there would be in a multi-product facility.

In the case of AstraZeneca's Frederick Manufacturing Center in Frederick, Maryland, US, for example, the acceptance criteria for sterilization in place (SIP) is based on the European standard EN285 and is non-product specific, according to an AstraZeneca company official. "The acceptance criteria for cleaning are non-product specific because sampling assays and each [n]ew [p]roduct [i]ntroduction (NPI) are challenged on a small-scale (i.e., recovery/cleanability), and protein denaturation (i.e., degradation of proteins using inhouse chemicals) needs to be demonstrated to verify that the facility is fit. Each programme (cleaning/SIP) has on-going monitoring/maintenance programme executed annually to verify systems remain in a validated state," the AstraZeneca official states.

"Each programme (cleaning/SIP) has on-going monitoring/ maintenance programme executed annually to verify systems remain in a validated state."
—an AstraZeneca official

"Cleaning protocols between a single-mAb and a multi-mAb manufacturing facility would assess the degraded product as an organic impurity in the drug substance of the next batch," notes Paul Lopolito, senior manager, STERIS Technical Services. "In a multi-mAb product facility, the main difference is having to assess the cross-contamination risk of mAb product process contaminants with the quality attributes of a subsequent, different mAb drug product," adds Beth Kroeger, manager, STERIS Technical Services.

"A risk assessment should include an assessment of active degradation rinsability, toxicity, host cell proteins, media, cleaning agent residues, cleaning process capability, and bioburden and bacterial endotoxin," notes Kroeger.

Necessary protocols

In a biomanufacturing facility where multiple mAb therapeutics are produced, it is important to note what types of cleaning validation are necessary, and how often validation must be performed. The AstraZeneca official notes that cleaning validation maintenance is performed annually at the company's Frederick facility using a matrix approach. "For each NPI, small-scale cleanability/recovery,

protein denaturation, and large-scale cleaning verification (matrix approach) are required," the official states. In addition, establishing if the product is more challenging to clean compared with previous products will determine the requirements for cleaning validation/verification.

"In a multi-mAb product facility, the main difference is having to assess the cross-contamination risk of mAb product process contaminants with the quality attributes of a subsequent, different mAb drug product."

—Beth Kroeger, STERIS Technical Services

Lopolito points out that a risk assessment should be performed for incoming mAb drug-product toxicity, solubility, degradation product rinsability, media, and buffer constituents compared to the existing validated cleaning procedures for the entire process for the current products.

"If this new mAb is not considered worst case, then at least one production run under normal process conditions for cleaning validation or verification should be executed. Provided no significant changes are made to the process, re-validation is generally not required. Continued process verification should be in place to trend quality attributes to establish cleaning process capability and performance control," he explains.

Systems must be in place that help maintain a sterile environment for manufacturing. In terms of cleaning and SIP validation, all equipment, systems, and production parts used for manufacture should be cleaned with a validated cycle prior to use, the AstraZeneca official says. "Cleaning cycles demonstrate that equipment surfaces are clean and free of residues and ensure any leftover product is cleared," the official states.

Kroeger notes, however, that no additional systems are required in a multi-mAb facility compared to a single-mAb facility "unless the facility is manufacturing products such as antibody-drug-conjugates (ADCs), due to the potential increased toxicity from the small-molecule portion of the ADC, or products other than mAbs/large molecule."

Procedural segregation should exist with separate area clearance between products and batches in a multi-mAb facility, Lopolito adds. "Obviously, packed columns and ultrafiltration membranes would be product dedicated, but equipment need not be dedicated once the resin or membranes are removed. Equipment changeover between products is recommended where elastomeric parts are discarded but is not necessary if cleaning validation testing verifies residue removal from the various materials of construction, or they are not considered to have a significant surface area to exceed the maximum allowed carry over limits," he explains.

In addition, other procedures, components, and systems that are important to have in place for cleaning validation include automation control, gowning, aseptic practices, changeover requirements, high-efficiency particulate air (HEPA) filtered air, closed systems used for manufacture, positive pressure, isolation valves, external equipment cleaning, room classifications/cleaning, and on-going quality control monitoring, the AstraZeneca official emphasizes.

Meanwhile, the selection of cleaning agents requires certain criteria. Lopolito points out that cleaning agents should be selected based on performance, rinsability, analytical methods availability, low toxicity, lot traceability, and compatibility with materials of construction.

Safety is the most important consideration because of toxicity risks, adds the AstraZeneca official. "Do not select cleaning agents that have significant cytotoxicity, allergenicity, or reproductive hazards," the official asserts.

In a multi-mAb manufacturing scenario, residue type is also a key consideration when selecting a cleaning agent because it is necessary to ensure that the cleaning agent degrades the residue of each product, product-by-product, the AstraZeneca official says.

"Continued process verification should be in place to trend quality attributes to establish cleaning process capability and performance control."

—Paul Lopolito, STERIS Technical Services

"Typically, alkaline cleaning agents are used as they are bactericides and emulsifiers [microbial control and dissolving proteins]. Acidic cleaning agents may be used to remove salt deposits. Cleaning chemicals with surfactants and builders, that are compatible and safe, are preferred," the official says.

Need for innovation

Innovations in cleaning/sterilization materials are also important to the process. According to Kroeger, there is at least one cleaning agent that is registered as a biocidal agent with disinfectant, biocidal, and biofilm remediation claims. "Detergent performance enhancements including maintenance derouging, antimicrobial effectiveness, and biodegradability are a few of those being developed to support manufacturers' process optimization and sustainability goals," she states.

In addition, a risk-based approach to acknowledge potential failure modes and provide justification on current controls (detection) is in place. It is important to implement this risk-based approach while maintaining the validated state and regulatory requirements, the AstraZeneca official says. Biostatistical analysis may also be used to establish control limits (within pre-determined acceptance criteria) used for continuous monitoring/trending.

Reference

1. C. Hroncich, *BioPharm International* 30 (8) 22–26 (2017). PTE

Objective and reliable expert editorial coverage in the bio/pharmaceutical industry *since 1989!*

Process Development • Manufacturing Trends • Formulation
Analytical Technology • Regulatory Compliance • Quality Assurance
API synthesis • Packaging and Outsourcing • Industry Best Practices

Sign up for a FREE print or digital subscription today
www.pharmtech.com/subscribe-pharmtech

Contract Packaging Grows

Contract packagers expand operations and services to accommodate growing need.

Hallie Forcinio is *Pharmaceutical Technology Europe's* packaging editor.

Demand for contract packaging is strong. Driving forces for outsourcing include the growing number of virtual pharmaceutical companies, plant consolidation, global emerging markets, the need to maximize internal resources, and the rise in biopharmaceutical products, which prompts more companies to turn to contract packagers to label and kit products. Another influence on growth is the expanding number of rare and orphan drug indications. These often high-value products can be difficult to manufacture and frequently require customized packaging and temperature-controlled handling.

Viewpoint

"From a high-level perspective, outsourcing to contract packagers allows pharma companies to do what they do best: develop and market drugs," says Joe Luke, vice-president of sales and marketing for Reed-Lane, which offers blister packaging, bottling, pouching, and vial filling as well as secondary labelling, cartoning, card sealing, and kitting of vials and syringes. He explains, "A contract packager is usually more nimble and quicker to react than most pharma companies when it comes to packaging launches or changes."

With ever-evolving and increasing regulatory requirements, "outsourcing to a specialist contract packaging organization is often seen as the safest and most reliable, as well as cost- and time-efficient, way to proceed," adds Phil DiGiacomo, senior vice-president of sales and marketing at PCI Pharma Services, a global provider of packaging services for commercial medicines as well as drug development, scalable drug manufacture, clinical trial packaging, and labelling, storage, and distribution.

"Brand owners are increasingly looking for full-service suppliers that are able to support them throughout the entire product lifecycle—from formulation development to compounding and filling through to packaging and delivery," reports Shaun Gaus, president and CEO of Precise Packaging, a specialist in over-the-counter liquids and aerosols. He predicts this contract packaging market trend will continue into the foreseeable future "as it provides a variety of benefits including operational advantages and cost savings."

Brand owner focus on core competencies prompts demand for collaborative partnerships and a range of turnkey services potentially starting with product development and continuing through testing, clinical production/samples, pilot production, sourcing of material/components, and full-scale production. "Sonic Packaging has continued to add expertise to its production management team and develop stronger ties with materials suppliers to co-develop new technologies that will add value and give brand owners a competitive edge," says Howard Thau, president of Sonic Packaging, a cGMP-compliant supplier of turnkey packaging solutions in product development, package design, sourcing, manufacturing, and sampling, specializing in single-use, metered-dose, and applicator devices.

Outsourcing gives brand owners access to the expertise and know-how of seasoned product manufacturing and packaging experts. Gaus says, "Contract manufacturing also reduces the costs of products by providing brand owners with access to flexible skilled labour, bulk purchasing costs, etc. while reducing errors. The result is a lower-priced finished product, which can ultimately increase sales and improve margins."

Luke agrees, noting, "Based on the size of the package, volumes ordered, and packaging configuration, contract packagers can find cost and production efficiencies that in-house packaging may not have been able to find."

Outsourcing not only can lower costs, increase sales, and improve margins, but also streamline the entire production process, by providing "one main contact point for manufacturing, sourcing of all components, scheduling, testing, and shipping of finishing goods," concludes Thau.

Capacity expansions

With demand increasing for a broader range of services, contract packagers are expanding capabilities and infrastructure. For example, Pharma Tech Industries has boosted capacity and speed with the startup of a Mediseal line capable of producing

more than 300 sachets/min. "The Mediseal line supports both client growth within the market category as well as recent and projected business [demand]," reports Tu T. Tran, vice-president of sales and marketing for Pharma Tech Industries. "Such assets are an extension of our customers, facilitating turnkey, high-speed efficiency, which fulfills cost-of-goods-sold metrics without the need to incur millions of dollars in capital expense."

Aphena Pharma Solutions has expanded United States Drug Enforcement Administration (DEA) operations and storage and added powder filling and inhaler capacity. "We've invested millions of dollars in order to provide our customer base with one of the broadest ranges of packaging formats in the industry," said Eric Allen, vice-president of sales and marketing at Aphena, in a press release. Since 2016, the company has expanded both the CII vault capacity and the DEA-licensed CIII-CV cage at its liquid and semisolids division in Easton, Maryland, to hold more than 85 pallets of active products. The Easton liquid and semisolid plant now includes more than 12 custom packaging lines with additional blending equipment and capacity already on the drawing board for 2019 (1).

Aphena's solid-dose division in Cookeville, Tennessee, has almost doubled in size to more than 135,000 ft^2, adding packaging lines and increasing CII capacity to more than 110 pallets for blisters, bottles, carding, or kit packaging. Finally, Aphena has invested millions of dollars in serialization capabilities and to prepare for serialization data exchange (1).

"Investments at PCI Pharma Services have included the acquisition of new sites to support clients both globally and at a more local level, expansions of existing sites in terms of size and scale of overall physical footprint, and general line capacity extensions, as well as innovative technologies plus highly specialized cold chain, ultra-cold chain, and controlled substance capabilities," reports DiGiacomo. In addition, he says, "We have also undertaken selective strategic alliances including an exclusive collaboration agreement with CSP Technologies for US clinical trials and stability testing utilizing Activ-Blister packaging solutions, which help protect and promote speed-to-market for pharmaceutical and medical device products with heightened susceptibility to moisture and gases, especially oxygen."

Serialization and special services

Contract packagers are well-prepared for serialization requirements. With at least 80 serialization lines across its global network of facilities, PCI Pharma Services delivers serialized medicines with integrated overt and covert anticounterfeiting protection features and can meet current and upcoming requirements internationally. "It's been a long journey," noted Brad Payne, PCI's senior vice-president of Global Operations. "The industry still has a ways to go in coalescing around a truly common standard, but PCI has been able to leverage an adaptable solution that allows us to meet the requirements of established markets as well as those countries which are still in flux with shifting or developing standards" (2).

Serialization is just one of the upgrades at Reed-Lane, which recently equipped several bottling lines for full aggregation. "We knew that in order to continue servicing existing customers and to grow our business, we would need to make the necessary investment in serialization," says Luke. "From our conversations with our customers and serialization partners, we decided to install aggregation capabilities right away, instead of waiting until 2023, when it will be required."

Reed-Lane also has installed a new secondary vial and syringe labeling and kitting suite and a fully validated cold-chain storage unit. "With the growth of the biologic market, we've seen a continued rise in the demand for cold-chain storage," reports Luke.

Many contract packaging organizations specialize in certain product or packaging formats. At Precise Packaging, a specialist in over-the-counter liquids and aerosols, a new aerosol production line has boosted capacity. The company also recently opened an 18,000-ft^2 contract manufacturing facility with a high-speed liquid filling line and automated shrink bundler. Plans for 2019 include improvements to bulk storage and compounding areas to improve batching capabilities and capacities.

Halo Pharma specializes in topical products. With topical centers of excellence at its Whippany, New Jersey, and Mirabel, Quebec, Canada, facilities, Halo Pharma helps pharmaceutical companies develop and manufacture compliant, high-quality gels, creams, lotions, and sterile and non-sterile ointments. "Halo covers the full breadth of equipment, technologies, skills, and expertise when it comes to taking a topical drug product from formulation to market," said Lee Karras, CEO of Halo Pharma, in a press release. "Our manufacturing and packaging facilities are co-located for a seamless transition to commercial supply; we handle the bioequivalence (IVRT [*in-vitro* release testing]), chemistry, and microbiology testing that are essential for today's dermatological markets" (3). The company offers packaging that includes tubes, jars, and bottles in various sizes, including trial or sample sizes.

Thermo Fisher Scientific is investing US $150 million (€134 million) in its Pharma Services business to increase capacity for sterile liquid and lyophilized product development and commercial manufacturing. New aseptic filling lines and isolator technology will be installed in Monza and Ferentino, Italy, and Greenville, North Carolina. Projects are expected to be completed before mid-2021 (4).

References

1. Aphena Pharma Solutions, "Aphena Continues on a Path of Growth," Press Release, 25 Sept. 2018.
2. PCI Pharma Services, "PCI Pharma Services Celebrates Significant Milestone–80 Serialization Installations across Global Supply Network," Press Release, 29 Oct. 2018.
3. Halo Pharma, "Halo Pharma Simplifies Topical Drug Product Development and Manufacturing," Press Release, 12 April 2018.
4. Thermo Fisher Scientific, "Thermo Fisher Scientific to Invest $150 Million to Expand Pharma Services Capabilities," Press Release, 18 March 2019. **PTE**

A Meeting of Minds

A new conference is set to provide a platform for European regulatory professionals to come together to discuss relevant issues and share expertise.

Felicity Thomas

As the safety and efficacy of pharmaceutical products is of paramount importance, it is unsurprising that the industry is subject to strict regulations. Within Europe alone, the regulatory system for medicines comprises a network of approximately 50 regulatory authorities, which are based throughout the 31 countries of the European Economic Area (EEA), as well as within the European Commission, and the European Medicines Agency (EMA).

Cooperation between scientific experts across Europe is, therefore, an integral part of the European regulatory system. Through sharing knowledge, information, and expertise across the region, assessment of new medicines and new safety information can be performed to the highest possible quality.

However, the European regulatory landscape is currently undergoing a raft of changes, not least of all because of Brexit but also as a result of pending regulations, set to come into force in the near future. To tackle the issues facing the European regulatory community, the Regulatory Affairs Professionals Society (RAPS) has launched a conference in Brussels, Belgium, 13–14 May. *Pharmaceutical Technology Europe* spoke with Paul Brooks, executive director of the society, to learn more about the conference.

Specifically for Europe

PTE: Could you provide a brief overview of the conference, highlighting the main reasons for its launch?

Brooks (RAPS): The inaugural RAPS Regulatory Conference Europe 2019 will bring together pharmaceutical, medical device, and *in-vitro* diagnostic (IVD) device industry experts, thought leaders, practitioners, and prominent health authority representatives to examine the most critical regulatory challenges and opportunities in Europe at the moment. Speakers and attendees will share the latest available information, ideas, and best practices.

Our European members and others in the European regulatory community have been calling for RAPS to host a conference in Europe, something focused specifically on their major needs and concerns. And with so much of Europe's regulatory system in flux right now, the need is more urgent than ever. This conference has been purposely designed and developed by European regulatory professionals specifically to address the tough issues regulatory professionals working in Europe are currently contending with.

A varied conference agenda

PTE: What topics will the inaugural conference agenda cover?

Brooks (RAPS): The conference agenda will cover a wide range of current issues facing pharma, medical device, and IVD regulatory professionals, as well as some overarching areas that impact all professionals in the healthcare products space.

Clearly, the potential impact of Brexit on regulatory systems, processes, and the supply and availability of critical medicines and medical technology is paramount on the minds of everyone working in health and medicine. The pending EU Medical Device Regulation (MDR) and *In Vitro* Diagnostic Regulation (IVDR) will bring sweeping changes to the medtech world. MDR's effect on drug-device combination products also will be discussed.

Other sessions of particular interest to those working in pharma will cover EMA's priority medicines (PRIME) scheme, paediatric studies, non-biological complex drug follow-on products, and regulator expectations for quality risk management of medicines throughout the product lifecycle, among other topics.

This conference will cover all of that and more, so attendees will find sessions relevant to their main focus, whatever area they may work in. The sessions are grouped into specific topic tracks covering pharma, medical devices, and general regulatory issues, along with tracks specifically devoted to MDR and IVDR. Therefore, attendees can focus on the sessions within a particular topic area or attend

sessions on multiple tracks to suit their individual needs.

Being a part of something

PTE: In your opinion, how important is it for regulatory professionals to come together in forums such as the RAPS conference and how will it be beneficial to those attending?

Brooks (RAPS): Not only does this conference provide access to regulatory experts and leaders, it is an opportunity for the European regulatory community to come together, connect with one another and build relationships. One of the key benefits of a conference like this one and of being involved with an organization like RAPS is the chance to be part of a mutually supportive professional community.

Brexit: A major discussion point

PTE: Will Brexit be an overwhelming part of discussions during the conference?

Brooks (RAPS): There is no doubt Brexit will be among the most discussed topics, both formally in conference sessions and informally between sessions, during receptions, and over meals. Right now, nothing about Brexit is certain. We don't know whether or not a deal will be struck. We don't know what a potential deal may look like or what the relationship will be between UK and EU authorities. We don't know how UK's need to now participate in EU parliamentary elections might introduce new political pressures regarding Brexit negotiations. We are even starting to hear more speculation that there could be a second referendum, offering the possibility that the UK changes course and remains part of the EU.

While this lack of certainty can be unsettling, the regulatory profession is partly about planning for contingencies and being ready for multiple possible scenarios. Regulatory leaders can't wait until they have all the answers; they must work to address challenges as they go, based on their best judgement, experience, and informed interpretations.

Future conferences

PTE: Will the conference take place annually and if so, which topics do you believe will be prominent in future conferences?

Brooks (RAPS): We are already planning for a 2020 conference, which will again be in Brussels. The critical regulatory issues mentioned earlier are likely to be high on the list of priorities in the pharma, device, and IVD sectors for some time. They will develop and evolve, but they are not going away as major concerns.

The RAPS Regulatory Europe Conference agenda will continue to be driven by the needs of the regulatory community in Europe and also will evolve to meet those needs. PTE

Bioprocessing Facilities and FDA Inspection Problems

USFDA inspections can create uncertainty. Supervision of the contract manufacturer is crucial in ensuring compliance.

Ronald A. Rader
is senior director, Technical Research, BioPlan Associates, www.bioplanassociates.com.

The US Food and Drug Administration (FDA) is often considered the 'gold standard' global regulator by many and the most rigorous and respected regulator of pharmaceutical products. Besides evaluating applications for new drugs, generics, and biologics, FDA regularly inspects manufacturing facilities for deficiencies. Because a great majority of drug substances (active agents), particularly generic drugs, are manufactured in foreign countries, primarily China and India, FDA inspections of pharmaceutical facilities manufacturing products for the US market are performed worldwide for both internal drug company manufacturing and outsourced contract manufacturing facilities.

When evaluating the source of inspection problems, most pharmaceutical industry reports suggest that facilities in India, China, and other emerging regions are receiving a greater percentage of Form 483s and warning letters from FDA compared with US-based facilities. The problems noted in these inspections, such as data fraud or inadequate sanitation, are often more dramatic, and get more press coverage than most inspection-related problems noted in the United States, Europe, and other developed regions. But regardless of geography, any problems noted may constitute violations of the US Food Drug and Cosmetic (FD&C) Act. FDA has less authority outside the United States, such as limited ability to force halt of manufacturing, but it can halt imports into the US. The worst-case situations (e.g., Form 483s, warning letters, facility inspection-related recalls, and product withdrawals) happen in all geographies and with all types of companies, including the largest and sophisticated facilities.

FDA inspections can create fear and uncertainty for pharmaceutical companies when FDA finds and seeks correction of manufacturing-related problems. Also, warning letters are published on FDA's website, and Form 483s are available through freedom of information (FOI) requests, both of which may have an adverse impact on a company's stock prices. Negative regulatory actions may halt mergers, acquisitions, licensing, and other business deals, and in the worst case, could result in company financial failure.

Form 483s and warning letters

FDA inspectors are primarily concerned that in-house quality systems are fully documented and followed. Categories of quality systems that are inspected include:

- Production
- Quality
- Materials
- Facilities and equipment
- Laboratory controls
- Packaging and labeling.

For bioprocessing facilities, typical violations are a lack of/or altered documentation, or violations of set procedures, or products not meeting quality specifications.

Deficiencies noted in any area can trigger a Form 483; however, often, a problem can be discussed onsite with inspectors and resolved, avoiding the issuance of a Form 483. Each problem noted by inspections should be responded to specifically, including plans for remediation, generally within 15 days of Form 483 issuance.

Inspectional observations are cited by facility inspectors in the context violating a specific FDA regulation and generally are listed in presumed order of seriousness. FDA welcomes rapid, informal resolution of problems to avoid issuing a Form 483. After receiving a Form 483, the facility/company can use a formal two-step dispute resolution process within 30 days (1). If facility responses are found to be adequate, generally no further action is taken by the agency. If deficiencies noted are not rapidly or sufficiently fixed, a formal warning letter may be issued.

Warning letters are issued after significant compliance problems noted in one or more prior inspections or Form 483s have not been properly addressed and resolved. Warning letters can lead to closure of manufacturing operations; criminal charges; consent decrees potentially involving third parties assuming

responsibilities for manufacturing; product recalls and seizures of products; withdrawal of approvals; or an "Import Alert" letter halting import of products into the US.

By issuing a warning letter, FDA is serving notice that major compliance violations must be corrected, and actions taken to prevent reoccurrence of the same problems.

By issuing a warning letter, FDA is serving notice that major compliance violations must be corrected, and actions taken to prevent reoccurrence of the same problems. Warning letters identify specific problems and the related regulations violated. Generally, the problems noted in warning letters are considered more severe than noted in Form 483s.

Once the facility addresses problems cited in a warning letter, FDA will conduct another facility inspection. If unresolved problems noted are serious and affect product quality and/or safety, FDA may withdraw or recall related products, and even withdraw approvals.

Common problems reported

The top 10 manufacturing facility-related problems reported in Form 483s in FY2018 were, in decreasing order of frequency:

- No written stability programme, improper methods, lack of testing methods, products not testing within schedule, etc.
- Calibration and testing of equipment not following pre-set written operational plans. For example, equipment that is working correctly (enough), as shown by quality-related testing, may not be tested according to schedule.
- Procedures to maintain sterility lacking or not being followed.
- Control systems for computers and automated systems are inadequate to assure persons lacking full permission can modify manufacturing-related records; or proper systems are not in place, such as audit trails tracking by lab equipment erased or not recorded.
- Final release testing did not include full laboratory confirmation of meeting full formal specifications, or related testing data and testing are missing or inadequate.
- Set procedures for facility and equipment cleaning and maintenance not followed, or procedures are inadequate.
- Lack of standard operating procedures (SOPs) for manufacturing and process control to assure product quality, including instructions for what to do when products and procedures do not meet specs or SOPs.
- Failure to investigate and correct deficiencies/problems noted during manufacturing.
- Laboratory testing controls not scientifically sound, not appropriate, not well designed, etc.
- Quality assurance responsibilities and procedures not fully documented or followed, such as for handling of complaints, process deviations, change control, supplier qualification, and batch release.

In general, most problems noted involve:

- Procedures not being documented or are not fully followed
- Investigations and internal resolution of problems not sufficiently followed-up
- Documentation or written procedures missing or not existing
- Lack of sufficiently sound lab controls and methods.

Other common problems involve computer and data systems:

- Computer/data systems not 'locked down,' with persons who should not be allowed to view and modify records
- Critical data files manually rather than automatically saved such that they cannot be modified
- Too many or the wrong people having administrator rights to modify files and computer behaviour
- Not having computer audit trails active all the time, with users potentially able to modify, delete, move, etc. key data without record of the change
- Equipment audit trails, such as from chromatography systems, not being examined and evaluated.

These computer/data-related problems can be expected to increase as ever more data are generated and many facilities/companies move data storage and management to third-party cloud facilities.

If facility responses are found to be adequate, generally no further action is taken by the agency. If deficiencies noted are not rapidly or sufficiently fixed, a formal warning letter may be issued.

Avoiding inspection problems

Regulatory inspections frequently occur without warning; manufacturing facilities should be ready for a formal FDA inspection at all times. Conducting internal audits of quality systems for compliance with US 21 *Code of Federal Regulations* Part 820 (Quality System Regulation) and hiring consultants for mock FDA facility inspections can better prepare facilities for the real thing.

Relevant facility staff should be familiar with Form 483s and warning letters. Most large companies have implemented rigorous internal auditing of facilities and procedures, and maintain internal groups to monitor internal issues and trends in FDA inspections. Reviewing Form 483s and warning letters can provide insight on typical infractions.

contin. on page 41

Capsugel® | Lonza Pharma & Biotech

Building on a history of innovation in polymer science and capsule engineering, the Capsugel® brand, now part of Lonza, offers a suite of HPMC and alternate polymer capsules for the pharmaceutical world. Polymer science and engineering have opened a new era of functional development, which offers the potential for selecting the right capsule for different APIs.

Capsugel® Vcaps® Plus capsules represent a unique and valuable contribution: they perform like gelatin but offer additional advantages, particularly a lower moisture content, which makes them excellent for hygroscopic and moisture-sensitive drugs and manufacturing processes. HPMC capsules are inert and robust against cross-linking or the effects of extreme storage conditions. Furthermore, Vcaps® Plus capsules have equivalent performance and appearance to that of gelatin capsules, offering new possibilities to product developers around the world.

Capsugel® Vcaps® Plus

www.capsugel.com/biopharmaceutical-products/vcaps-plus-capsules

solutions.emea@lonza.com

Capsugel® | Lonza Pharma & Biotech

Integrated Biologics Development

Catalent Biologics provides advanced technologies and tailored solutions for biologic and biosimilar development, from DNA to commercial supply, through its extensive Biologics network.

Its comprehensive end-to-end offering for customers includes cell line development, analytical testing, clinical and commercial biomanufacturing, antibody-drug conjugate development, fill/finish, and clinical supply services.

In January 2019, Catalent commenced a $200 million strategic investment programme to expand drug substance and drug product manufacturing capacity at its sites in Madison, Wisconsin and Bloomington, Indiana. At Madison, the investment will see the construction of two new manufacturing suites, each with a 2 x 200 litre single-use bioreactor system, while new high speed flexible vial and syringe/cartridge lines will be installed in a 79,000 sq. ft. expansion of fill/finish capacity at Bloomington.

The expansions were in response to increasing demand from existing and future customers following the company's 30th commercial product approval.

Catalent

www.catalent.com

solutions@catalent.com

Catalent®

Nexera Series LC-40

Shimadzu has released its Nexera Ultra High-Performance Liquid Chromatograph series, incorporating artificial intelligence as Analytical Intelligence, allowing systems to detect and resolve issues automatically. The Nexera series makes lab management simple by integrating IoT and device networking, enabling users to easily review instrument status, optimize resource allocation, and achieve higher throughput. The Nexera UHPLC series maximizes reliability and uptime with fully unattended workflows that span from startup to shut-down. Operators can set the Nexera to start up at a specified time, so that it can complete auto-purge, equilibration, baseline checks, and system suitability in advance, and be ready for analysis before they arrive at the lab. In addition, FlowPilot ramps up the flow rate gradually, reducing the possibility of damage to columns. The Nexera also has auto-diagnostics and auto-recovery capabilities that allow it to monitor pressure fluctuations to check for anomalies.

Shimadzu Europa GmbH

www.shimadzu.eu

shimadzu@shimadzu.eu

SHIMADZU
Excellence in Science

SMA MicroParticle ICS™

VAI is pleased to announce the addition of the SMA MicroParticle ICS line of non-viable particle counters to our contamination control portfolio. The units utilize the latest innovation in particle counting technology and have several features not found in other Particle Counters.

- *Multi-Processing*—can simultaneously process, perform tasks, and log data without interrupting sampling
- *Real-Time Meter*—displays particles counted per second, per channel, for pinpointing sources of contamination
- *Annotations*—allows users to add notes to data records during sampling
- *Advanced Power Management*—have advanced power management features, including the industry's first sleep mode, and over 10 hours of battery life
- *Sampling*—can store up to 45,000 comprehensive data records for each sample
- *Reporting*—produces reports that comply to ISO 14644-1, EU GMP Annex 1, and Federal Standard 209E

Available in three models: HandHeld, Table Top, and Wall Mount. Remote models are also available for integration into facility monitoring systems.

Veltek Associates, Inc.

www.sterile.com

vai@sterile.com

VELTEK ASSOCIATES, INC.

OUTSOURCING — *contin. from page 39*

Inspections are relatively informal in the sense that facility managers can and should discuss disagreements, offer explanations, and challenge inspectors as needed while they are in the facility. The facility may prudently later seek meet with inspectors to make sure all issues are resolved, giving the facility more certainty that it is properly addressing problems.

When contract manufacturing facilities are used, the drug company passes control … to another company, while maintaining responsibility for the quality and efficacy of the drug product.

Most employees, including process operators, manufacturing-, quality-, and safety-associated staff should ideally be briefed on how to respond to FDA inspectors, who may ask questions during inspections.

Managing contract manufacturers

Drug companies have control over activities in their facilities and can respond to regulatory inspections. When contract manufacturing facilities are used, however, the drug company passes control of manufacturing to another company, while maintaining responsibility for the quality and efficacy of the drug product. Therefore, supervision of the contract manufacturer is crucial.

Quality oversight of CMOs. CMOs currently commercially manufacture 30–33% of commercially manufactured biopharmaceutical products. The CMO is contracted to fully comply with GMP bioprocessing standards, SOPs, and everything else specified in biologic license applications (BLAs)/ new drug applications (NDAs), with this including CMO-internal critical review and oversight. But it is ultimately the product developer, the 'manufacturer' in the eyes of FDA, that needs to take responsibility for control and oversight of its CMO's manufacturing activities. It has been reported that the typical bioprocessing described in a BLA involves approximately 1200 distinct steps. Add in variability in materials, equipment performance, environmental control, sterility, staff doing tasks different ways, and other normal variables, and a lot can go wrong at the off-site CMO. Many aspects of bioprocessing execution and the supply chain are controlled by the CMO, not the sponsor. Obviously, this increases risks for problems in bioprocessing, and the client needs to devote a good amount of relevant staff time, effort, and expertise in oversight of its CMO. Generally, the more time, effort, and higher-level staff assigned to these tasks, the less risk of major regulatory inspection problems and failures.

Many more established manufacturer companies have over time learned that investing in onsite CMO quality oversight is both necessary and cost-effective, including preventing or lessening the extent of problems that may arise. Some 'manufacturers have 'man-in-plant,' with one or more staff on the factory floor and in the labs, providing oversight of the CMO's bioprocessing and testing of its product(s). It is also prudent for relevant client staff or hired consultants to regularly review the CMO's documentation related to its products, conduct audits, and debrief CMO staff, including on the factory floor, to ideally spot problems before they develop. But most manufacturers rely mostly on periodic visits and increasingly on teleconferences and E-mail to keep up with project progress and problems. No matter what, the CMO client should seek to maximize the ease and amount of communications back-and-forth with the CMO and should seek a low barrier for the CMO to report problems and ask questions.

Reference

1. FDA, *Guidance for Industry Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP* (HHS, January 2006). **PTE**

The Auditor Vs. Inspector Issue

We need to understand both sides when it comes to audits, says Siegfried Schmitt, PhD, vice-president, technical, PAREXEL Consulting.

Q. During a recent audit of our company, the auditor found some non-conformance issues that we disagreed with. Do we have to make the changes the auditor suggested?

A. Those of you who have been audited will likely have come across the following situation: the auditor has identified a non-conformance with the applicable regulations. Purely for illustrative purposes, let us say that the auditor identified missing documents that should have been prepared as part of a laboratory information management system (LIMS) validation. Now the auditor informs the auditee about this finding.

The auditee shows surprise and retorts that this site/company/laboratory has a long history of successful inspections by regulatory authorities from three continents and that they never had an observation like this. In fact, during the last inspection by an agency, the LIMS validation package had been reviewed and found perfectly acceptable. Therefore, the auditee refutes the validity of the auditor's observation.

So, how do we resolve this? Shouting match? Exchange of heated arguments? Certainly not! After all, we are professionals. And as such, we need to understand both sides.

Questioning the validity of an audit

No matter what conclusions the auditor comes to, the auditee should review the validity of the results. Obviously, the auditees will accept a positive inspection outcome with no or few or only minor observations as confirmation of the validity and acceptability of their quality systems, modes of operation, facilities and equipment, and organizational structures. However, any such result should be carefully analyzed, and the following questions (not all-inclusive) should be asked by the auditee:

- Was the inspector an expert in the field? Of note, very few people are an expert in everything.
- Did the inspector look at the documentation and the system in detail? Or was the focus of the inspection on other aspects or areas?
- Are we aware of any issues regarding the validation of that system (i.e., something we know about, but the inspector may have missed)?

If the answers to the first two questions are a yes and no to the third, then we can be quite confident that indeed the system documentation is fully supportive of our claim to validation.

The auditor should also question their own results

Auditors should always challenge their decisions and statements, as their audit findings can have as much impact on the audited company as a regulatory inspection. Questions an auditor should ask themself include, but are not limited to:

- Am I sufficiently proficient and experienced in the specific field to make an informed decision?
- Have I referenced the correct and the latest regulations, guidance documents, industry best practices, or other sources of pertinent information?
- Have I been able to collect a sufficient and/or representative sample of evidence to support my statements?
- Did I take the auditee's challenge seriously, and have I managed to refute it based on science, regulatory evidence, and/or other unbiased basis?

We should bear in mind that inspectors and auditors alike are humans. As such, auditors make mistakes, have preferences, and to some extent, may be biased. Furthermore, an audit or inspection can only ever be looking at a snapshot in time. For example, unlike the people working in the company under scrutiny, auditors will not see all the behaviours, all the operations, etc. As a result, all statements made are based on a limited amount of information and observations.

Audits provide needed information

And we must not forget that the focus of an inspection (or audit) can change over time, be it for developments in the regulatory field (e.g., the increase in data integrity-related inspections in recent years) or changes to the circumstances in the inspected site (e.g., new ownership, the introduction of new dosage forms, etc.), to name a few possible reasons. Consequently, a site may have been in compliance over many years, but may not have kept up with the changes, which may suddenly find the site in a state of diminished compliance.

It is better to have a non-conformance picked up during an audit than have it recorded during an inspection. So, the next time your auditor tells you about an issue you didn't know about, it may be sensible to accept and investigate it before deciding to reject it. **PTE**

Your opinion matters.

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

DAMIAN PALUS/SHUTTERSTOCK.COM

Capsugel® | Lonza
Pharma & Biotech

Good as gold.

Capsugel®
Vcaps® Plus capsules

The gold standard in HPMC capsules

- *Immediate release capsule*
- *HPMC capsule with no gelling agents*
- *Perfect for hygroscopic APIs*
- *Non-animal; vegan friendly, cultural and religious acceptance globally*

Made better. By science.™

Want to know more?
Visit www.capsugel.com

Catalent®
BIOLOGICS

Your one comprehensive biologics partner.

We have the passion to help you accelerate, simplify and de-risk your next biologic from development and manufacturing, to fill/finish, clinical supply and commercial launch.

NEW $200M INVESTMENT IN INTEGRATED CAPABILITIES

500+
ANTIBODIES & 70+ RECOMBINANT PROTEINS DEVELOPED

20
COMMERCIALLY APPROVED PRODUCTS THROUGH FILL/FINISH

10
MARKETED PRODUCTS USING GPEx® TECHNOLOGY

5000+
CLINICAL TRIALS SUPPLIED

50+
GPEx® CELL LINES IN CLINICAL TRIALS

Development | Analytical | Biomanufacturing | Fill/Finish & Packaging | Clinical & Commercial

DEVELOPMENT DELIVERY SUPPLY

Comprehensive solutions. Advanced technologies. Better biologics.™
US + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 biologics.catalent.com