JULY 2018 Volume 30 Number 7

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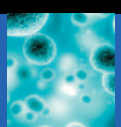

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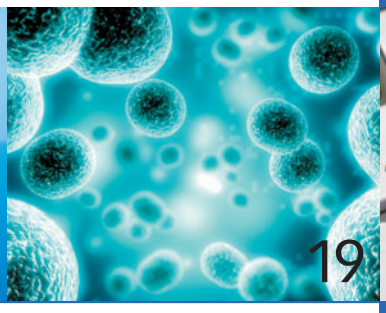

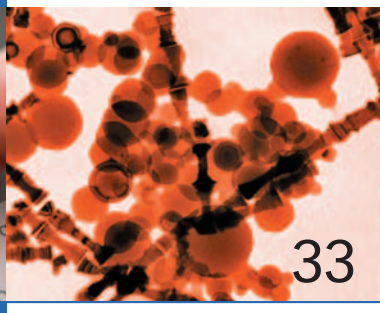

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The 10-gallon model features interchangeable mix vessels and an additional sawtooth blade on each disperser shaft, which doubles the shear input capacity of the mixer, according to the company. A rectangular stirrer orbits the vessel, exposing the entire batch contents to the shearing action of the dispersers.

Patented high viscosity blades are available for more viscous applications prone to climbing up the stirrer. The blades offer a helical curvature that pushes product forward and downward. Fully automated programmable logic controller recipe controls and data acquisition systems are also available for optimal mixing results, as stated by the company.

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Data Loggers with Cloud Storage

T&D's new compact, battery-powered -75wf/nw line of thermocouple data loggers feature a temperature range of -199 to 1760 °C and free cloud storage. The line supports six types of thermocouple sensors (K, J, T, E, S, and R) and comes in two models: TR-75wf for wireless LAN and TR-75nw for an ethernet/wired LAN connection.

The data loggers connect to the company's free cloud-based WebStorage Service where temperature data measured by the thermocouple is automatically uploaded, stored, and viewed from PCs and mobile devices from any location at any time. These data can be simultaneously collected from multiple data loggers from varying locations, enabling real-time reports to off-site users. The service can also send warning emails and text messages to cell phones when measurements stray outside of pre-set limits.

According to the company, these devices can be deployed in almost any quantity to form a unified data reporting network connected to the Internet via Wi-Fi or ethernet.

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Particle Sizer for Dry and Wet Measurement

The Analysette 28 ImageSizer from Fritsch provides analysis of particle shape and size for dry measurement of powders and bulk solids and wet measurement of suspensions and emulsions. The device delivers multiple shape parameters and evaluation possibilities for particle size. According to the company, measurement results are available immediately and measuring time is under five minutes depending on the sample quantity.

For wet measurement, the device is used in combination with a complementary wet dispersion unit. Features include a measuring range of 20 µm–2.8 mm, freely adjustable ultrasonic power for deagglomeration, quiet dispersion with strong pumping power, automatic rinsing cycle, no dead space in measuring and rinsing circulation system, and fast and consistent cleaning. The company states that benzine, alcohol, and various organic solvents can also be used as suspension liquid.

For dry measurement, the particle sizer provides fast analysis of particle shape and size of dry, free-flowing materials. Features include a measuring range of 20 µm–20 mm, three available telecentric lenses, up to 75 images per second, preserved agglomerates, practical clean design of the measuring chamber, and optimal number of particles because of automatic adjustment of the feeder.

The evaluation software used for measuring results displays each recorded particle as a data point in the company's Cloud, which enables each particle to be clicked individually, and the Gallery, which provides an overview of the typical particle shape of the analyzed sample and allows users to view and evaluate all images. Individual particle images can be directly selected for single image analysis.

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The BIOne 1250 bioprocess control station from Distek is a benchtop-scale bioreactor for mammalian and microbial models. The device is available in single-use or traditional glass versions and comes in 2-L, 5-L, and 10-L working volumes (10 L available in glass only).

The company states that the control station can be customized to meet individual laboratory needs. Features include an intuitive touchscreen interface, smart media filling, email and text alerts, trend up to eight parameters, variable speed pumps, up to five gas control modules, rotameters or auto flow control, optical pH or standard, and left- or right-side setup.

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Collaboration on GMP Inspections Has Been Successful but Challenges Exist

EMA, the leading driver behind GMP inspection collaboration schemes, will be cutting back its involvement because of the need to concentrate on its relocation to Amsterdam.

The drive by the European Union, the United States, and other leading developed regions and countries to harmonize standards of good manufacturing practice (GMP) inspections to avoid duplications and gain other efficiencies seems already to be paying dividends. There are, however, at the same time, signs that the rate of progress may soon slow down because of a limited number of agencies capable of participating in mutual recognition schemes.

A decline in GMP inspections

The European Medicines Agency (EMA), the EU organization responsible for the centralized authorization of medicines and a major driving force behind international collaboration in GMP, has also warned it is having to slow down its activities in this area because of its need to concentrate resources on relocating its headquarters from London to Amsterdam due to Brexit. The agency has in fact reported a steep 43% decline (1) in GMP inspections in 2017, carried out on its behalf by inspectors from EU national agencies. Furthermore, it is forecasting an even sharper decrease this year to 100 inspections, equivalent to an annual drop of 68% (1).

In its latest annual report (2) published in May 2018, EMA linked the decrease in inspections mainly to a mutual recognition agreement (MRA) on GMP inspections between the US and the EU's 28 member states, which came into operation in 2017 and is due to be fully implemented in 2019. It also benefits from MRAs on inspections between the EU and seven other non-EU countries and their agencies, the latest of which, in addition to the US and its Food and Drug Administration, includes Canada and its licensing authority Health Canada.

The relative success of the current international collaboration projects has also been highlighted in a report (3), published in April 2018, on the activities in 2011–2016 of the International Active Pharmaceutical Ingredients Inspection Programme. This 10-year-old scheme, in which 12 national and international agencies are participating, aims to make more efficient use of inspection resources through greater international co-operation and information sharing.

The programme's members, the majority of them European, include EMA; the European Directorate for Quality of Medicines (EDQM), run by the Council of Europe, a body separate from the EU; the World Health Organization (WHO); and a number of national agencies including FDA and those of Australia, Japan, Canada, as well as the EU national licensing authorities in France, Italy, and the United Kingdom. Over the past six years, the project has focused mainly on sharing information on inspection plans and outcomes. On specific sites of common or high interest, inspection reports have been exchanged or joint inspections carried out.

The report (3) on the programme's activities in 2011–2016 was based on a review of inspections of 944 API sites in third countries by the participants. The vast majority of the sites were in India or China. Most of the objectives behind the programme were being achieved during the period, according to the report's conclusions. There was an increase in the number of API sites inspected by the participating authorities. As a result of this rise, "more information was shared by participating authorities and, therefore, the programme brought more transparency and efficiency for the planning and realisation of GMP inspections," the report said (3).

The number of duplicated inspections went down, although by exactly how much has been difficult to estimate because of factors such as separate inspections by authorities after a site has been declared non-compliant, according to the report. EDQM, for example, called off 36 planned inspections of sites in 2016 after they were inspected by other authorities in the programme (3).

Overall, 28% of the sites in the review that had been found to be non-compliant were inspected an average of 3.6 times. This figure contrasted with 72% of sites with a history of compliance, which were inspected 2.7 times. The number of sites of common interest has shown the potential for shared information and tools such as joint inspections. At least two participating European authorities, including EDQM, had 350 sites of common interest with FDA, 136 with the Australian agency Therapeutics Goods Administration (TGA), and 41 with WHO.

The report (3) conceded that some aims were not achieved, such as the implementation of recommendations from a 2008–2010 pilot scheme. These aims included a shared database with a comprehensive list of API manufacturers and a common policy framework on the re-inspection of sites in third countries.

"These ambitious undertakings would likely require many years of work beyond what has occurred to date," the report

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warned (3). If the programme is to achieve even bigger objectives, it will have to increase not only the number of participants but also the involvement of existing members. The report said that gaining a more active participation among members of the group remained a challenge.

The relatively limited participation by some members has demonstrated how much collaborative schemes in areas such as GMP inspections relied on the work of well-established and resourced agencies. Ireland's Health Products Regulatory Agency (HPRA) has had to limit its involvement because of other responsibilities. "The HPRA is a participant of the programme, but we have not been in a position to take part in it in an inspection capacity," an agency spokesperson said.

When the programme was set up in 2008, nine agencies and organizations—EMA, EDQM, and the national agencies of the US, Australia, France, Italy, Ireland, UK, and Germany—took part in a pilot project to prove the scheme's long-term viability.

In the years after the pilot trial, comparatively few new participants have been recruited, although one of the new members was WHO, a large player in global GMP inspections. The inspections covered in the 2011–2016 report were also conducted by nine authorities and organizations, but compared to the pilot, excluded the agencies from Germany and Ireland and included Denmark's agency, a new member, and WHO. Japan's Pharmaceuticals and Medical Devices Agency (PDMA), Health Canada, and WHO became full members of the programme in 2016 but they were too late to participate in the 2011–2016 review.

Confidentiality issues

Even for European organizations, it has been a tough task meeting the criteria laid down for membership. ZLG, Germany's co-ordinator of the GMP inspections by the country's Laender states, withdrew from the programme altogether after the end of the pilot trail because of legal issues over the confidentiality of inspection information. In fact, the matter of confidentiality still remains a difficulty with Germany's participation in international GMP collaboration projects. It has become a problem with its participation in the EU–FDA mutual recognition agreement.

"Discussions between Germany and FDA regarding the signing of a confidentiality commitment for the German Laender in the context of the MRA are ongoing," a ZLG spokesperson told *Pharmaceutical Technology Europe*. Among recommendations made by the report (3) were improvements to the generation and sharing of information through the establishment of a central repository with write access or updating capabilities. This is a role that has been taken on by EudraGMDP, the EU database of information on GMP inspections and those for good distribution practice. The database is run by EMA, which further underlines the important position assumed by the agency in international GMP collaboration schemes.

Impact of Brexit

However, work by EMA on international collaboration schemes will be disrupted over the next few years because of pressure on its resources from the relocation of its headquarters from London to Amsterdam in time for the UK's departure from the EU at the end of March 2019. The agency has had to set itself priorities so that some activities such as international collaboration will be given less importance. Some will be reduced or suspended altogether. "While EMA will continue to be an active participant in the programme, its activities will be prioritized as per the agency's business continuity plan [on relocation]," an EMA spokesperson told *Pharmaceutical Technology Europe*.

As many as 20% of the agency's staff are likely to leave the organization because of the move to Amsterdam (1). In addition, the agency will have to operate in temporary offices in the city until a newly built headquarters is completed.

One casualty has been a scheme for the training of existing or potential GMP inspectors in third countries. The project is now being restricting to inspectors in India and China, which accounts for 85% of API inspections by EU inspectorates or their non-EU partners. But even the training support for inspectors in these countries is being reduced this year and in 2019. Other schemes for the training of not only inspectors but also assessors and international regulators in third countries are also being reduced or suspended.

A three-year project, due to end in 2020, to develop guidance on data integrity in collaboration with the Geneva-based Pharmaceutical Inspection Co-operation Scheme, a Geneva-based organization with 52 participating inspectorates, has been suspended (1), even though a draft guidance had already been published.

Data integrity remains a major importance because of the key part it plays in GMP standards. It also fits in with the agency's top priority—the maintenance of uninterrupted supplies of medicines and the assurance that medicines will continue to be authorized and supervised at the same high quality level as previously. Nonetheless, the collaborative development of a consistent approach to data integrity may have to wait, like other matters requiring international co-operation, until the EMA is firmly settled in its new headquarters.

References

1. EMA, *Multi-Annual Work Programme 2018–2020* (London, 3 March 2018).
2. EMA, *Annual Report of European Medicines Agency 2017* (London, 2 May 2018).
3. EMA and 11 other organizations, *Report on International Active Pharmaceutical Ingredients Inspection Programme* (March 2018). **PTE**

Fifteen Years of Progress: Biopharmaceutical Industry Survey Results

This article highlights 15 years of changes in biopharmaceutical manufacturing.

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Since 2003, BioPlan Associates, Inc. has published an extensive annual survey of bioprocessing professionals. Since the first survey, which was started in collaboration with the American Society for Microbiology, critical bioprocessing issues have grown. The annual report has expanded to include 60 questions with nearly 500 pages of analysis and data (1,2). Manufacturing capacity issues have always been at the core of the annual survey, but as the industry has matured, the factors impacting capacity have become more complex.

This article highlights some of the significant changes in biopharmaceutical manufacturing (bioprocessing) that have occurred from 2003 to 2018. Most all of the changes in bioprocessing that have occurred over the past 15 years have generally been for the better. Examples of these changes can be found in **Table I**, which compares 2003 and 2018 survey data, in the online version of this article at *PharmTech.com*.

In retrospect, many of these trends were not always predictable, and some have gone counter to expectations at the time. Predictions of periodic capacity crunches, for example, have not materialized as the industry has matured. The industry has also become fairly effective at addressing production costs by developing efficient, more flexible processes.

Trends in adoption of diverse mammalian expression systems have also not materialized, as Chinese hamster ovary (CHO) cell lines have become the dominant expressions systems. In fact, nearly 80% of respondents now report their organization has mammalian manufacturing capacity, up from 54% in 2003. The percent reporting use of microbial has not increased much in 15 years. As discussed in the current annual report, companies prefer to concentrate on one or a few platforms to be applied to as many products as possible. Most have or are moving to adopt mammalian systems as their primary manufacturing platform. This move toward single-platform manufacturing is continuing, even when alternatives have been shown to be more cost effective.

Also unpredicted 15 years ago was the rate of adoption of single-use devices. While 15 years may seem a long adoption cycle, in the bioprocessing industry, where regulators are involved in most decisions, change comes slowly. At present, pre-commercial bioprocessing is now dominated (approximately 85%) by single-use systems. And much of the current growth in capacity involves single-use adoption at commercial scales.

Geographically, 15 years ago, the industry did not predict the rise in bioprocessing in developing regions such as China and Latin America.

Geographically, 15 years ago, the industry did not predict the rise in bioprocessing in developing regions such as China and Latin America. In a BioPlan survey of 100 participants at the BIO conference 10 years ago, China was noted nearly universally as an unacceptable potential partner in biopharmaceuticals due to the lack of intellectual property protection and the virtual absence of quality management systems. Today, many Chinese companies are expanding through biosimilars, contract manufacturing organization (CMO) partnering, and other means to reach Western markets. For example, China's WuXi Biologics, a contract development and manufacturing organization (CDMO) with global reach, is investing €51.71 million (US$60 million) to build a manufacturing operation in Worcester, MA, in addition to its plans to build a €337.81-million (US$392-million) biologics facility in Dundalk, Ireland (3,4).

(Spotlight image) Stockbyte/GettyImages

BioPlan has also reported data and trends for bioprocessing titers and yields over the past 30 or more years (5). Average commercial-scale titers have increased from estimated 1.1 g/L in 2003 to current 3.2 g/L, a nearly 300% increase. Also, during this period, the number of US Food and Drug Administration (FDA)-approved recombinant therapeutics has increased by approximately 400% (6,7). In 2017, FDA set a record for the number (31 approvals) and percent (93%) of approved biopharmaceuticals being recombinant-based compared with 18 approvals in 2003 and 69% for recombinant products (with 2003 a relative outlier in the early 2000s, with higher number of approvals).

Industry outsourcing views and practices have changed significantly in the past 15 years (8). Outsourcing or the use of CMOs or contract research organizations (CROs) has significantly increased. The percent of respondents citing any current outsourcing of manufacturing task has doubled, from 35% in 2003 to 70% in 2018. Similarly, the percent reporting outsourcing mammalian manufacturing tasks has increased 164%, from 44% in 2003 to 72% in 2018.

Trends in adoption of diverse mammalian expression systems have also not materialized, as Chinese hamster ovary (CHO) cell lines have become the dominant expressions systems.

Capacity issues: Changes in 15 years

Back in the early 2000s, a significant shortage in capacity, a "capacity crunch," was a major concern. With commercial manufacturing capacity then being tight, and in high demand, facilities were generally operating at much higher levels of capacity utilization rates than currently—79% overall in 2003 compared with 2018 rates of less than or equal to 60% overall and 63% for mammalian manufacturing. As discussed in the current report, having a lower—but still greater than 50%—capacity utilization rate is much healthier for the biopharmaceutical industry versus operating at high rates (e.g., the 79% reported in 2003). Process lines and facilities tend to become bottlenecked, and bioprocessing limited, when utilization rates approach and exceed 80%. The percent of respondents currently reporting severe or significant capacity constraints at their facility has fallen dramatically in 15 years, from 44% in 2005 to 20% in 2018. In 2018, lower percentages of severe constraints were projected as expected in five years, with this now falling from 44% in 2003 to 19.6% in 2018. This "future projection" is also an indication of the level of comfort many in the industry now have for managing their facilities, projecting

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operational needs, and dealing with intermittent capacity problems.

Bioprocessing lines/facilities need some downtime, including for switchovers, maintenance, new equipment installation and validation, staff training, and cleaning and sterilization of stainless steel facilities. Current survey data continue to show that downstream operations still are struggling to keep up with improvements in upstream output, so downtime with upstream versus downstream equipment is normal.

Cellular and gene therapies, many of these involving both technologies (genetically-modified cells), are shaping-up as the next big biopharmaceutical manufacturing trend.

Fixing capacity problems then vs. now

The "capacity crunch" perceived in the early to mid 2000s was largely resolved by industry responding with construction of many new facilities, including many for commercial manufacturing, combined with incremental technology improvements. These have included the rather steady increase in titers (5). In 2003, 79% of respondents reported planning for facility expansion in five years. In contrast, less than 30% overall (32% mammalian, 24% microbial) now report planning facility expansions in five years. The percentage of respondents reporting no current capacity constraints at all has increased significantly from 10% in 2003 to 28% in 2018.

The factors cited as the primary causes of facility capacity constraints have changed somewhat over the past 15 years. Lack of experienced production and scientific staff were the top issues in 2003. In 2018, "facility constraints" has become the primary bottleneck factor, suggesting another round of industry capacity expansions may be coming, while inability to hire staff moved to second place.

Survey respondents now report that downstream, compared with upstream, operations are where most bottlenecks in their bioprocesses are continuing to occur. The advances in upstream titers are reflected in survey responses regarding the top areas industry needs to address to avoid future capacity constraints, with developing better continuous and better overall downstream purification technologies now the top two most-cited responses. In contrast, upstream concerns, "optimizing cell-culture systems," was number one in 2003.

Exciting technologies have come and gone over the past 15 years. For example, back in 2003, transgenic animals for *in-vivo* manufacture of recombinant proteins was considered a "hot" topic, with fully 73% of respondents then citing this as likely to become a viable manufacturing alternative in the future. Transgenic animals are now a relatively ignored area of bioprocessing. Today, cellular and gene therapies, many of these involving both technologies (genetically-modified cells), are shaping-up as the next big biopharmaceutical manufacturing trend and also problem area in terms of capacity issues. BioPlan has reported an ongoing 'capacity crunch' in cellular/gene therapy areas (9). This includes a significant shortfall in capacity (e.g., five times the current capacity could be used if available).

References

1. E. S. Langer, et al., *Advances in Large Scale Biopharmaceutical Manufacturing and Scale-Up Production: A Survey of Industry Capacity* (BioPlan Associates (in conjunction with the American Society for Microbiology), Nov. 2003).
2. E.S. Langer, et al., *Fifteenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (BioPlan Associates, 2018).
3. WuXi Biologics, "WuXi Biologics to Invest $60 Million to Establish a Biologics Production Facility in the United States," Press Release, 11 June 2018, www.wuxibiologics.com/wuxi-biologics-invest-60-million-establish-biologics-production-facility-united-states/
4. WuXi Biologics, "WuXi Biologics to Invest €325 Million to Build Largest Biomanufacturing Facility Using Single-Use Bioreactors in Ireland," Press Release, 30 April 2018, www.wuxibiologics.com/wuxi-biologics-invest-e325-million-build-largest-biomanufacturing-facility-using-single-use-bioreactors-ireland/
5. R.A. Rader, E.S. Langer, *BioProcess Intl*., 13 (3), p. 10-14 (February 2015).
6. R.A. Rader, *BIOPHARMA: Biopharmaceutical Products in the U.S. Market*, 2nd edition (Biotech. Info. Inst., June 2003).
7. R.A. Rader, BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets, online database (www.biopharma.com).
8. R.A. Rader, E.S. Langer, *Contract Pharma*, p 46-49 (May 2018).
9. R. A. Rader, *Genetic Engineering & Biotechnology News* (GEN), 37(20) (15 Nov. 2017). **PTE**

Authors' Note: Survey Methodology: *The 2018 Fifteenth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* yields a composite view and trend analysis from 222 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 22 countries. The methodology also included over 130 direct suppliers of materials, services, and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time and assesses differences in the major markets in the United States and Europe.

Maintaining GMPs Requires Continued Vigilance

Maintaining good quality control practices throughout the entire manufacturing process requires robust development, a drive toward product and process understanding, and pre-established, comprehensive written procedures that are consistently reviewed and updated.

Susan Haigney

Good manufacturing practices (GMPs) are established by regulators to ensure that pharmaceuticals are safe and effective for the patients that rely on them. In the United States, requierments governing finished pharmaceutical quality are described in the Current Good Manufacturing Practices (CGMPs) regulations established by the US Food and Drug Administration (FDA) and published in the *Code of Federal Regulations* (Title 21 of the *CFR*, parts 210–211 for most finished pharmaceuticals). FDA also publishes guidance to further describe recommended practices for complying with the CGMP regulations. The agency states that "CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations" (1).

In Europe, GMPs are defined by the European Commission in *EudraLex*–Volume 4–Good Manufacturing Practice (GMP) guidelines (2), which were first published in 1989. *EudraLex* states that quality management is "a system of marketing authorizations [that] ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality, and efficacy" (2).

To harmonize GMPs and other quality requirements worldwide, the International Council for Harmonization (ICH) works with international regulators and industry to develop common guidelines across the industry to ensure consistent quality expectations worldwide.

"At its core, CGMP is a science- and risk-based focus on assuring drug quality. As described in ICH Q10, *Pharmaceutical Quality System,* an overall attitude to drive meaningful and continuous improvements from the quality unit and other manufacturing employees is essential" (3), FDA told *Pharmaceutical Technology Europe*.

The global nature of the pharmaceutical supply chain requires regulatory agencies to inspect and govern GMPs at manufacturing facilities. These inspections sometimes result in actions by regulators (e.g., FDA 483s, warning letters, import bans, and court actions) against companies that fail to follow GMPs. Common CGMP deficiencies cited by FDA in warning letters sent to pharmaceutical companies inspected during the past year include failures to ensure product sterility, ensure data integrity, create quality control units, and develop and follow written procedures (4–7).

"Companies should vigilantly encourage manufacturing practices that reflect the most current and robust methods of processing and control, and with a focus on providing a quality product to US consumers," says FDA. "The approach to successful CGMP is not merely a check-box approach where a single obstacle can be identified, nor is it meant to be unchanged throughout the life of a product or a facility. Using a holistic and quality risk management approach,

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a manufacturer can select and study specific products and processes with the goal of continual improvement of product quality and quality systems and widespread optimization."

So how do companies ensure they are "vigilantly" following GMPs and avoid the wrath of regulators? The answer appears to be found in a company's "quality culture" and in the development, writing, and following of written procedures.

Establishing a quality culture

Performing pharmaceutical manufacturing according to GMPs involves a dedication to quality throughout development and manufacturing processes. "Corporate management plays a vital role in this endeavor by establishing a commitment to quality, which includes providing sufficient resources and oversight for manufacturing operations. There are many elements to successful implementation of CGMPs but measuring and monitoring quality indicators and managing change are key among them," says FDA.

According to Susan Schniepp, executive vice-president of Post-approval Pharmaceuticals and distinguished fellow at Regulatory Compliance Associates, maintaining GMPs throughout all processes and procedures involves a combination of personnel training, keeping tools and equipment updated, having a strong quality unit, and developing a quality culture at all levels of the company. "How the company goes about achieving this objective is what is critical. Traditional training may not be enough. There should be constant on-the-job training and oversight on a continual basis. Upgrading tools and equipment, especially computer-driven programmes, needs to involve IT departments and adhere to the current data integrity concepts," says Schniepp. "No one element will be able to sustain GMPs. All the elements work together to establish a culture where sustaining GMPs is a priority."

Chris Moreton of FinnBrit Consulting agrees. "Too often, in my experience, certain factions in an organization think that quality is someone else's responsibility. There may be an organizational chart that shows where the quality unit sits in an organization, but 'quality' (including GMP) is everyone's responsibility within an organization; from the most senior to the most junior and vice versa." Management is key in creating a quality culture, says Moreton. "If the staff see the managers taking an interest and checking on things on a daily basis, the staff will respond, and they will try harder to get things right."

A commitment to staying current with regulatory expectations is a must, according to Schniepp, and she warns that complacency is the biggest

Responding to US Food and Drug Administration CAPA Requests

Pharmaceutical Technology Europe spoke with Sharon Ayd, executive vice-president of Pre-approval Pharmaceuticals and chief scientific officer at Regulatory Compliance Associates, about developing a corrective action and preventive action (CAPA) plan.

PTE: What are the best practices for developing a detailed CAPA?

Ayd: A CAPA program requires a well-documented system that determines the root cause of nonconformances, system failures, or process problems, corrects them, and prevents them from recurring. A corrective action is a reaction to a situation that has occurred and is intended to fix the problem or modify the quality system so that reoccurrence is prevented. The result is a complete documented investigation/solution that meets regulatory requirements and is the basis for effective continuous improvement. A preventive action is initiated to stop a problem from occurring. It assumes that monitoring and controls are in place to assure problems are identified and eliminated before they happen. If the quality system indicates a problem may develop, a preventive action should be implemented to avert the situation.

PTE: A variety of recent US Food and Drug Administration (FDA) warning letters have cited companies for not providing the agency with 'timely' and/or complete CAPA plans in response to FDA 483s. What does the agency consider 'timely'? Is there a time limit CAPAs should be performed by?

Ayd: Response to a [FDA] warning letter should be done by writing a cover letter, and all observations need to be addressed as separate CAPAs. An appropriate sense of the urgency means your response should be received within 15 business days. It is advised to use the company's CAPA form and cover letter instead of memo. The response should include documentation of the investigation with a concisely stated root cause. Containment measures and corrections for each specific observation and identified corrective actions planned with date(s) for completion also need to be included. In addition, documentation of all containment and corrective actions that are completed at the time you submit the response should be included.

PTE: How should companies develop a CAPA in response to an FDA 483?

Ayd: FDA will look for and review a company's response. The investigator will get a copy of the FDA 483 response and will comment. As to whether the response is adequate or not will require additional review. If you don't hear back from FDA, don't assume the response was adequate. You should also follow-up within four to six months with a letter that includes evidence of the completed corrective actions and verification of effectiveness.

PTE: If the agency feels the CAPA is 'incomplete,' how should a company respond to a CAPA plan request after a warning letter?

Ayd: If FDA requests or proposes additional actions or asks for a more appropriate CAPA, this means FDA is concerned with the company's first response. The proposed actions of the company were insufficient to correct the issues cited. Presumably the company has retained a qualified and experienced third-party firm to provide guidance and if not, it is highly recommended to do so. The role of the third-party is to objectively review a company's response to ensure it addresses all cited issues and can be implemented within an acceptable time to FDA.

PTE: How does a CAPA plan written in response to a request from FDA differ from an internal CAPA plan?

Ayd: A company may consider their existing CAPA plan to be adequate until circumstances demonstrate that it is not. This may occur as the result of different situations that cause the weaknesses of a CAPA plan to rise to FDA's attention. Perhaps there are numerous consumer complaints, recalls, or an FDA inspection that is the impetus that uncovers deficiencies or failures in a company's CAPA plan. Regardless of the reason, it is expected that FDA will request a company to address every issue associated with their CAPA plan and to understand what changes are needed and to implement them.

obstacle to maintaining GMPs. "Once a process or procedure is established and functional, there does not seem to be the impetus to update and revise it as regulatory interpretation and understanding changes. This leaves the process or procedure compliant to outdated standards," Schnieep says.

Companies must also learn from prior mistakes, according to Mark Lynch, vice-president of Strategic Compliance at Parexel. "It's best to take the lessons learned from product experience and apply them to the culture overall so those lessons only need to be learned once. Those experiences should be continuously applied on the product level, and also used to make improvements to standard operating procedures (SOPs), policies, personnel, and technology."

Problem solving is another technique that must be honed, according to Lynch. "Companies must also pay continuous attention to problem identification, solution, and improvement. Refinement of problem-solving techniques contributes to organizational learning."

Enforcing quality procedures through a policy that ties failure to follow procedures with grounds for dismissal and using internal audits to detect improper performance are options to ensuring a quality culture, according to Lynch. "It is also important that tools are a regular topic of discussion with operators to capture improvements and assure consistency. Additionally, sufficient supervisory presence and oversight are key both for monitoring purposes, and to be sure operators can raise questions and get the support they need. Finally, it's best practice to put a reporting mechanism in place that does not require identification, so employees feel comfortable flagging an issue without fear of blame," he says.

Lack of consistent GMPs may lead to repeat offenses

Companies who do not consistently maintain GMPs may find themselves under additional scrutiny by regulators for repeat offenses. A variety of FDA warning letters have pointed out repeat CGMP violations at companies and/or a particular facility (8, 9).

FDA reports that the agency, "… strives to provide clear guidance to companies proactively and in its enforcement actions. Where repeated violations have been found at the same facility or among different facilities of the same firm, we highlight those violations so that they may be addressed adequately. A focus on a commitment to quality is essential to correcting repeated violations, as are adequate corrective actions and procedures. While we generally encourage a focus on overall quality, there are times when we encourage firms to take specific actions, which are included in our warning letters as well as in applicable guidance documents and regulations."

Repeated offenses may be a failure to look at the big picture and apply solutions across all systems and/or products, according to Schniepp. "Companies think in terms of solving the individual citation but fail to take that answer for change to a global look at fixing other processes and procedures that might be susceptible to the same observation. Tunnel vision when responding to warning letters has a great potential to result in repeat observations," says Schniepp.

"Some of these 'repeat mistakes' are found to be violations of the same section of the regulations but stem from a different problem. Investigators tend to use repeat findings as a way to point to simplified trends that make one issue appear to be really bad, rather than the complex combination of issues that it truly is," Lynch says. "Some companies lack the staff, procedures, capability, and time to fully investigate and solve problems, so they pick something (e.g., a personnel error), close the investigation, and move on to release product, and the same issue reappears because it wasn't solved."

Cost can be another factor to repeated offenses, according to Moreton. "Often cost and/or short-term shareholder interests are used as an excuse to avoid some measures [to long-term change] … People complain that quality costs money, but if they really want to see how expensive things can be, they should try a consent decree."

Developing and following written procedures

The lack of written procedures and/or a quality unit is another frequent infraction identified in warning letters. From October 2016 through September 2017, FDA issued more than 400 FDA 483 observations for a lack of written procedures or written procedures that were not fully followed (10).

Written procedures are key to a robust quality programme, according to FDA and industry experts. FDA believes that the "most effective quality assurance (and compliance) strategies begin with robust internal procedures to adequately design and maintain a robust operation, and that can quickly identify and correct manufacturing problems when they occur."

What are best practices for developing written procedures for GMPs? While the agency does not endorse one particular approach to developing written quality procedures, FDA notes that these procedures should "be written to effectively communicate to the users of the procedure. FDA recommends that the style and format of procedures be accessible to users, as well as ensuring adequate coverage of its purpose. We recommend that the effectiveness of a procedural training programme be evaluated to ensure that personnel learn and can follow the procedures as intended."

The trend in a failure to have written procedures is disturbing, according to Schniepp. She suggests that outsourcing quality, especially for start-up companies, may add to this problem. She questions whether outsourcing companies have the processes and procedures in place to handle new products. A robust sharing of information between client and contract manufacturing organization is also key, including product and process understanding. "We need to also remember that new products, particularly in the biotech segment of the industry are novel in nature so the old way of doing business may not be applicable. Whatever the reason the industry must focus effort on making sure there are processes, procedures, and written instructions in place that support the release of product," Schniepp stresses.

Having all parties involved in the development of written quality procedures is necessary. "Including everyone affected by the procedure and writing the procedure with their input will result in streamlined and

efficient procedures, which will be easier to maintain in the long run," says Schniepp.

Standard operating procedures (SOPs) written by people not familiar with the specific operation can cause disconnects, according to Lynch. "The best way to assure adequate SOPs is to sit down with people most familiar with operations and map out the process steps and handoffs. This can be incorporated graphically using [swim lane diagrams] and similar tools like Visio (Microsoft) and include them as part of the document."

"In my opinion, in order to ensure that quality procedures are effective, it is necessary to involve those who know the process or operation being documented," Moreton agrees. "This may mean sitting down with the operator and finding out exactly what is being done and how, not what management thinks should be done and how they think the operation(s) should be carried out."

According to Schniepp, procedures should be mapped out, committed to paper, reviewed periodically, and updated as necessary. "Companies need to remember that their processes and procedures are not carved in stone and need to be changed to stay compliant with the operations being performed and the current interpretation of regulations," says Schniepp. New technologies and new product types may necessitate an update to procedures. Companies should be careful to not try and fit technology or product advances into current procedures but should instead take the time to review their processes and procedures and update them appropriately in responses to these advancements, she says.

Consistent review of procedures is important, especially if a change in equipment, facility, or regulatory requirements has occurred, experts note. "Written procedures should be reviewed and updated as often as needed. However, if a process and procedure is being updated frequently then it probably wasn't very well written in the first place," says Schniepp. "This being said, procedures that are fairly stable should be reviewed at least every two years to make sure they are still current and reflective of regulatory expectations."

When developing written procedures, says Lynch, "each process and procedure should be tailored to its specific purpose, so they don't include unnecessary steps that add time to the process without applicable value to the procedure at hand."

Companies often lack details that will help operators understand the process, says Lynch. "The most important concept to remember when writing procedures is to include the detailed instructions for the operation or processes being defined by that procedure and not include extra explanatory or extraneous information that has no bearing on the operation or process being defined," agrees Schniepp.

It doesn't hurt to ask for help

In warning letters, FDA commonly suggests the hiring of a third-party GMP consultant to help companies address their GMP deficiencies. Schniepp says these consultants can provide a "fresh perspective" when resolving GMP issues. "A new and fresh approach is valuable because the consulting firm has no preconceived ideas and can offer new insight to what may seem to be an old and uncorrectable problem," says Schniepp. These consultants can be helpful even when not suggested by regulators "because they are looking at the quality with eyes not steeped in the corporate culture," according to Moreton.

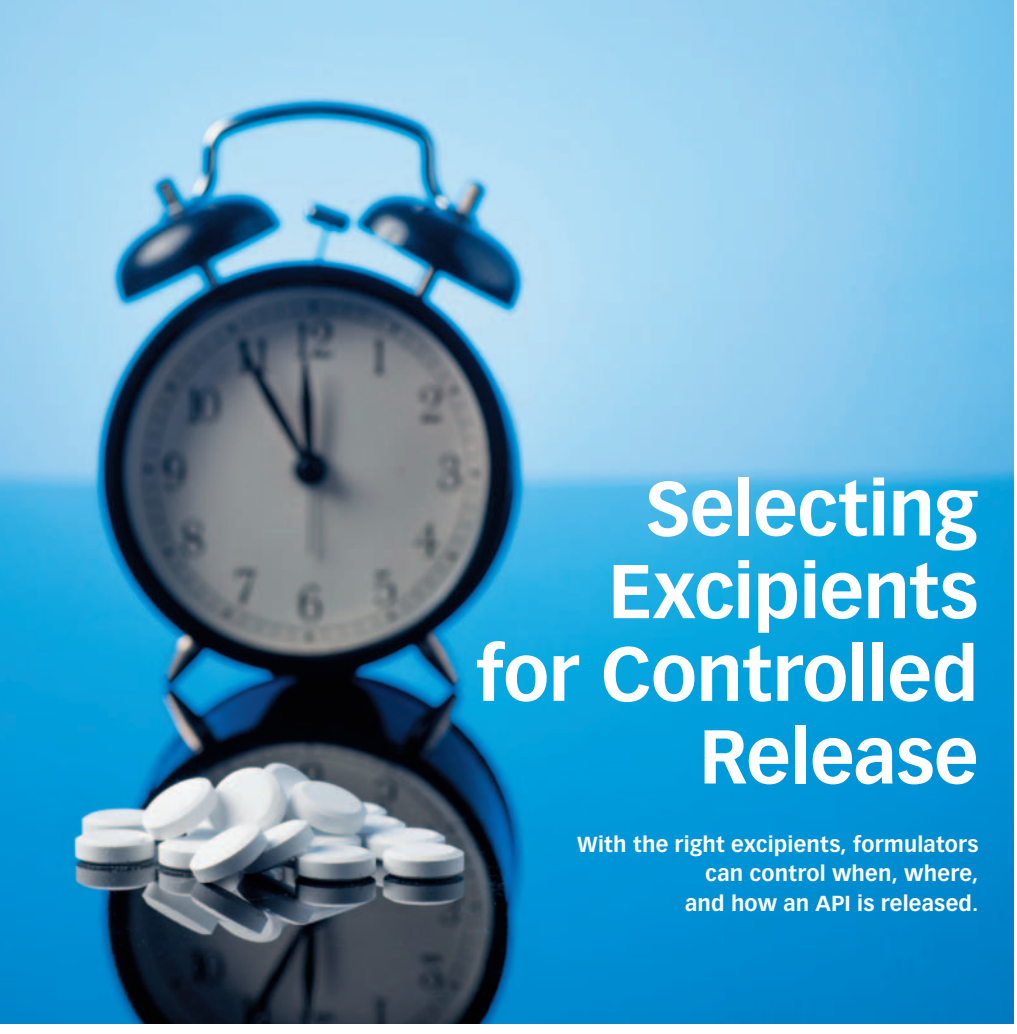
Consultants also have knowledge and expertise the company does not have. "[Consultants] can offer a variety of approaches and suggestions for remediating current problems as well as offering solutions to maintain and improving systems moving forward. One of the most important aspects to consider when hiring a consulting firm is to make sure they not only have the expertise, but they also have the time to devote to fixing the problem," says Schniepp.

When hiring a GMP consultant, Moreton suggests companies look at the experience of the contractor as a whole as well as the qualifications of the individual consultants "to ensure there is a good fit with the contractee's needs."

Lynch warns, however, that pharmaceutical companies should not rely too much on outside help. "Consultants can help companies get back on track if companies lack the resources internally. However, eventually companies have to sustain compliance themselves. Third-parties should provide expertise in the needed area and technology and have demonstrated success. Then, they should be able to teach and mentor personnel for improved behaviours and provide flexible models to fit company operations and culture. Usually, this is more than one-time training, but a program of measurement and support over time."

References

1. FDA, Facts about the Current Good Manufacturing Practices, *FDA.org*, www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm
2. European Commission, *EudraLex, Volume 4, Good Manufacturing Practice Guidelines*, https://ec.europa.eu/health/documents/eudralex/vol-4_en
3. ICH, *Q10 Pharmaceutical Quality System* (ICH, June 2008).
4. FDA, Warning Letter 320-18-17 sent to Deserving Health International Corp., 18 Dec. 2017, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm589455.htm
5. FDA, Warning Letter sent to Ridge Properties, LLC dba Pain Relief Naturally, 13 Oct. 2017, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm581620.htm
6. FDA, Warning Letter sent to Meridian Medical Technologies, Inc., a Pfizer Company, 5 Sept. 2017, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm574981.htm
7. FDA, Warning Letter 320-18-05 sent to Guangzhou Baiyunshan Pharmaceutical Holdings Co. LTD, 1 Nov. 2017, www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm595745.htm
8. FDA, Warning Letter 320-18-47 sent to Lijiang Yinghua Biochemical and Pharmaceutical Co., Ltd., 19 April 2018, www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm605392.htm
9. FDA, Warning Letter sent to Tris Pharma Inc., 26 March 2018, www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm603613.htm
10. FDA, FY 2017 Inspectional Observation Summaries, www.fda.gov/ICECI/Inspections/ucm589892.htm#Drugs, accessed 13 June 2018. **PTE**



Selecting Excipients for Controlled Release

With the right excipients, formulators can control when, where, and how an API is released.

Cynthia A. Challener
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Demand for controlled-release formulations is expanding as patients' expectations for greater convenience are increasing. Extended-release products have reduced dosing frequencies, which are particularly beneficial for paediatric and geriatric patients, but are appreciated by most patients and in general lead to improved medication adherence (1). Reformulation of branded drugs in controlled-release formats is one of the most common methods for extending the product lifecycle. Generic drugs are also often formulated with controlled-release properties (2).

Controlled-release behaviour can be achieved using polymer coatings on solid dosage forms or by the incorporation of various types of polymer matrix systems, enzyme-activated systems, or systems that respond to changes in physical conditions within the formulation. Mechanisms include dissolution, diffusion, osmotic pressure, maintaining a hydrologic or hydrodynamic balance, and ion exchange. Newer approaches are currently being developed based on nanotechnology and novel matrix technologies and include gastro-retentive drug delivery for controlled release, buoyant systems, and mucoadhesive systems for regulated release of anti-viral medications (1,2).

Excipients are key ingredients in controlled-release formulations. They act as matrix formers in matrix delivery systems and as polymeric membranes for drug powders and multi-particulate systems in oral solid dosage (OSD) forms, says Bujar Muça, technical product manager, IMCD. Plasticizers and pore formers impact drug release in coated products, and, often, two-polymer chemistries are used to provide tailored drug release. In oral liquid products, excipients can also provide taste masking and protection for the gastric mucosa, he adds. Excipients can provide abuse deterrence and aid in the avoidance of alcohol-induced dose dumping, says Evonne Brennan, technical marketing manager at IMCD.

"Ultimately," says Shawn Branning, strategic marketing leader for controlled release at DuPont Nutrition & Health, "excipients that provide controlled-release characteristics to oral solid dosage forms allow not only control of the rate of the API release, but also targeting of where that release occurs." He adds that when considering OSD forms, controlled-release formulations can refer to various types of sustained-release or targeted (delayed)-release profiles.

Making the right excipient choice

Several factors must be considered when selecting specific excipients for controlled-release formulations, according to Chhanda Kapadia, technical manager, IMCD. Dosage form type and design need to be considered along with the solubility of the API to ensure that the desired dissolution profile can be achieved with a given excipient, and/or that a good *in vitro-in vivo* correlation is obtainable. Issues that relate to patient compliance and safety should also be considered, according to True Rogers, technologies leader at Dow Pharma Solutions.

Ethylcellulose remains the polymer of choice in multi-particulate drug delivery systems with or without an additional coating platform, the use of which is dependent on the characteristics and dosage form type of the drug, according to Brennan. Methacrylate polymers are broadly used in delayed-release dosage forms and also provide gastro-resistant functionality. In monolithic delivery systems, hydroxypropyl methylcellulose (HPMC) continues to be the excipient of choice, although the use of two-polymer matrix systems is growing. "This approach can provide unique synergies and enable fine-tuning of the drug release pattern via modification of polymer entanglement and matrix texture," Muça explains.

The key for pharmaceutical formulators, concludes Rogers, is to have proven and flexible polymers such as cellulosics along with knowledgeable partners that can help provide solutions to formulation challenges.

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Many APIs with unique formulating challenges

Formulators can, in fact, face many challenges—from achieving desirable dissolution and release profiles for poorly soluble drugs to risk management of dose dumping to the selection of biocompatible materials with the desired controlled-release properties (1). Controlled-release products also require high API dosages, which can in some cases be difficult to formulate into the desired dosage forms with acceptable properties (2).

Newer APIs present some unique formulating difficulties, according to Rogers, such as small therapeutic windows or sensitivity to certain pH environments. On the other hand, formulating controlled-release alternatives to already-marketed products can be challenging if it is necessary to select different polymer chemistries and excipients to avoid patent infringement issues, according to Lies d'Olieslager, technical product manager, IMCD. Consistently matching the drug release profile, the scale-up of controlled-release coating processes (which requires extensive process knowledge), the curing of aqueous coating systems—particularly under dynamic conditions—and resistance to ethanol-induced dose dumping are additional challenges, she adds.

"Controlled-release excipients are excellent solutions to these particular challenges," Rogers asserts. For instance, he notes that some excipients can now offer dual functionality, both controlling the release of the API and providing increased solubility to poorly soluble APIs. Understanding polymer chemistry and exploring synergies are also important to overcoming these difficulties, according to Brennan.

New excipient options

Given that excipients are key ingredients in controlled-release formulations, it may seem surprising that excipient choices are somewhat limited, particularly for certain patient populations, notably children. Suppliers are developing "novel" excipients that may provide solutions and support to move existing formulations into new areas, according to Mary Tanenbaum, technical manager, IMCD, but excipients do not have their own approval pathway. "Pharmaceutical companies are hesitant to take on the responsibility of toxicology and clinical trials with an untested material and run the risk of jeopardizing approval of their new drug applications," Tanenbaum observes.

Most new excipients, therefore, are modifications or combinations of previously approved excipients. For instance, Muça points to granular Carbopol developed by Lubrizol to address flowability issues in direct-compression processing of matrix delivery systems. The Dow Chemical Company has also developed and commercialized Methocel DC2, a more flowable morphology of HPMC for streamlined direct-compression manufacture of modified-release matrix tablets, according to Rogers. In addition, custom grades of Benecel HPMC from Ashland fill a gap in HPMC polymer choice for matrix systems, providing formulators with more predictable release profiles and reducing batch-to-batch variability previously observed due to HPMC blending, according to Brennan.

Meanwhile, FMC Health & Nutrition, now part of DuPont Nutrition & Health, has promoted the use of surfactants for *in-situ* curing while coating with Aquacoat ECD, a 30% by weight aqueous dispersion of ethylcellulose polymer. "This pseudolatex dispersion has advantages over solvent systems because it has a high-solids content with low viscosity, and thus a shorter processing time," notes Engin Sari, technical product manager, IMCD. DuPont has also developed a coating with a robust sustained-release profile in the presence of alcohol that helps formulators create products with resistance to alcohol-induced dose dumping, he adds.

Collaboration is essential to finding solutions

IMCD represents a portfolio of products and continually pursues a training programme covering excipient functionality to ensure ongoing knowledge transfer, according to Brennan. "Engaging with formulators to review any challenges they face is key to successful development of solutions. Continued education is also fundamental; excipient manufacturers regularly provide information on product functionality, product consistency, and product variability, and we need to stay up-to-date," she comments.

As an industry group, the Controlled Release Society provides a forum for networking and the development of connections within other formulation groups. It does not provide an avenue for the discussion of intimate formulation details, however, which remains challenging, according to Brennan. "Using confidentiality agreements is one approach, but these take time. Good relationships with development teams, therefore, continue to be of primary importance," she says.

Excipient manufacturers need to work side-by-side with drug product manufacturers as early as possible in the drug product development process in order to not only identify the issues, but to mitigate the impact of the issues proactively, agrees Rogers. He adds that excipient manufacturers must understand every detail of their processes and polymers in order to achieve the best solutions for their customers.

"Partnering with our customers not only helps us in suggesting the right solutions for their formulations, but also helps drive our development of new excipients to meet the ever-changing needs of the market. We have found this type of partnership to be the best strategy for addressing the challenges faced by the pharmaceutical market today," Branning says.

References

1. Future Market Insights, "Controlled-Release Drug Delivery Technology Market: Global Industry Analysis and Opportunity Assessment 2017–2027," To be published July 2018.
2. Future Market Insights, "Oral Controlled Release Drug Delivery Technology Market: Analysis 2012–2016 and Opportunity Assessment 2017–2027," Press Release, 20 July, 2017. **PTE**

The Search for Next-Gen Expression Systems

Biopharma seeks alternatives that meet the needs for next-gen biologic drug production.

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Mammalian cell lines, particularly Chinese hamster ovary (CHO) cell lines, have become the standard expression systems for the production of biologic drug substances from recombinant proteins to more complex monoclonal antibodies (mAbs). CHO cells have played a significant role in the manufacture of revolutionary drugs for the treatment of many diseases, and their use is still the focus of major investment among biopharma companies worldwide, according to Barry Holtz, president of iBio. Although the standard, they do possess limitations that need to be addressed as the biopharmaceutical industry evolves to meet government, payer, and patient expectations for cost-effective, safe, and efficacious medicines. In addition, conventional mammalian cell lines may be inappropriate for the production of next-generation medicines such as bi/multi-specific antibodies and gene and cell therapies.

Mammalian drawbacks

High cost and long development timelines are two major drawbacks of conventional expression systems, according to Mike Laird, senior director and principal scientist for process development at Genentech. These systems also have the potential for low expression levels for some novel protein structures.

The biggest issue, asserts Holtz, is the time involved in the development of mammalian expression systems. "Traditional mammalian cell-based systems require the development of stable cell lines that perform well, which requires the completion of multiple evaluations in small reactors over several months. While the product is well-characterized at that point, scale up to larger reactors is often needed, and the environmental changes in bigger vessels, whether single use or stainless steel, can impact the post-translational modification of the protein, which can cause problems and delays in the business timeline. At each step, the protein must be extensively characterized to assure efficacy and potency. All of this effort adds significant expense as well."

Therapeutic protein production using CHO is expensive, agrees Mark Emalfarb, founder, CEO, president, and director of Dyadic International. "Mammalian expression systems require costly upfront investments in manufacturing facilities and high material and production costs. In addition, CHO expression entails a relatively low mAb yield (low-single-digit g/L/d) and a long cycle time. Furthermore, CHO cell lines typically require two viral purification steps, which are not necessary for some alternative systems, such as the *Myceliophthora thermophila* (C1) fungal system we are developing. C1 has no viruses and thus the need for those purification steps is eliminated," he observes.

Another important issue relates to the fact that the current generation of mammalian expression systems has not seen the complex, non-natural protein formats currently found in discovery and thus their synthesis, folding, and secretion machinery has not evolved to handle such proteins, according to Andy Racher, associate director of future technologies at Lonza Pharma & Biotech. "These systems have limited ability to produce these new proteins with clinically relevant attributes and in clinically relevant amounts," he notes. In addition, many new proteins contain three or four rather than one or two different polypeptides, and current expression vector formats are challenged by these new protein heteromers.

"It is time to realize the limitations of CHO and look beyond it to explore newer and potentially more efficient drug development and production methods," asserts Emalfarb.

Engineering solutions

As the need to make biologic drugs more accessible and affordable to patients increases, the industry

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is ramping up its investigation of other manufacturing methods. The drawbacks of mammalian expression systems are also driving the exploration of new and alternative technologies to move many next-generation biologic drug candidates through later development stages.

A number of "new" technologies will become more routine as the demands for new "designed" proteins strain the capabilities of conventional CHO cell systems, according to Holtz. One important approach is the engineering of new mammalian cell lines using new genetic editing technologies and the innovative design of gene constructs to optimize yields. He also notes that techniques to evaluate libraries of cell lines will help optimize expression and yield.

Limitations of convention cell lines are prompting exploration of alternative expression systems for current and next-gen medicines.

Lonza, for instance, has developed a suite of multigene vectors where three, four, and possibly more different genes can be easily inserted into a single expression vector. "By putting all the genes into a single vector, all genes are ensured of being inserted into a transcriptionally active locus in the genome and being transcribed at high levels," Racher says.

There are also efforts to develop entirely different expression systems based on plants, baculovirus, bacteria (such as *Pseudomonas* in the Phoenix system), and yeast, many of which have already been demonstrated to get proteins to the clinic and licensure, according to Holtz.

"In the not-too-distant future, it is likely that drug companies will evaluate two or more expression systems simultaneously as a routine best practices approach in early stage development," he comments.

Plant-based option

iBio's plant-based system offers rapid evaluation of protein expression at a very low cost, according to Holtz. Because vectors are used to transfect the plant leaf cells, multiple constructs can be evaluated in parallel. Once infected, the plants produce the required proteins in less than seven days. At that point they are harvested, homogenized, and a clarified protein extract is ready for traditional protein separation and purification. In addition, scale-up is seamless and reproducible; each 10-g plant is an individual bioreactor, so it is only a matter of growing more plants and there are no issues around changes in protein structure or post-translational modification, according to Holtz. He also notes that plant bioreactors are grown with no human or animal-derived materials and are not handled at any time by humans, which eliminates the chance that mammalian adventitious viruses will be present.

"Production of plant-made biologics been scaled-up by several companies in new facilities that can produce hundreds of kilos of mAbs and other therapeutic proteins per year. Successful antibodies (cancer vaccines and others) and other therapeutic proteins such as enzyme replacement therapies have been successfully taken to advanced clinical trials and some to licensure. In all cases, there have been no reports of adverse events associated with production of therapies in plants," Holtz states.

iBio grows 2.2 million plants continuously at its Texas, US facility and has worked with a variety of clients to produce mAbs, fusion proteins, antibody-drug conjugates, and vaccines, including virus-like particles (VLPs). "We have invested in increased product and process facilities and a cGMP-compliant pilot plant that—coupled with our large-scale manufacturing facility—assures clients that they can develop their protein through clinical trials and then be supported for the commercial launch of their products," says Holtz. iBio will also transfer the technology to clients if they want to build and operate their own facilities.

Fungal developments

Emalfarb believes that the C1 fungal expression system may one day be a safe and efficient approach to speeding up the development, lowering the production costs, and improving the performance of vaccines and biologic drugs at flexible commercial scales.

Dyadic's Cl gene expression platform is based on technology originally developed for industrial biotech applications, such as biofuel and enzyme production, and sold to DuPont for $75 million (€64.3 million) in December 2015. The genetically modified strain of *M. thermophila* is designed to produce enzymes and other proteins at a rapid rate. The company retained the rights to apply C1 to human and animal biopharma applications and has been investigating its use for the production of mAbs with humanized glycostructures; non-glycosylated mAbs, antibody fragments, FC fusion proteins, next-generation biologics, and other therapeutic proteins for which glycosylation structures are undesirable; and antigens, vaccines, and VLPs.

"We are applying the power of an industrially proven gene-expression system that has been used by the likes of Abengoa, BASF, Dyadic, DuPont, and Shell Oil, among others, to produce industrial enzymes and proteins at greater than 100 g/L of total protein at up to 80% purity (80 g/L) at commercial scales greater by 25 times (500,000-L scale) or more than some of the largest CHO bioreactors (12,000-L scale) in one-half to one-third the time," Emalfarb explains, noting that there is still room for yield improvement with C1. He adds that Dyadic has to date achieved a productivity for mAbs of 9 g/L in 90 hours or a 2.4 g/L/d production rate, which can be compared to 4 g/L in 336 hours or a 0.30 g/L/d for typical CHO processes, an eight-fold improvement.

Emalfarb notes that the media cost for C1 is a fraction of that for CHO, there is no need for viral inactivation,

and C1-expressed proteins are secreted from the cells in a purer form than those produced by CHO cells so are likely to be quicker and easier to purify.

Dyadic is currently working with pharmaceutical companies that are researching its C1 platform to speed up the development and lower the cost of biologics, enable the development and commercialization of genes that are difficult to express at reasonable yields in CHO and other cell lines, and apply C1 for the production of larger quantities of proteins earlier in discovery and development. The company and its partners are also investigating the possibility of getting difficult-to-express genes that have potential as new and novel cures—but have been shelved due to lack of expression into the clinic—in a commercializable and affordable way, according to Emalfarb.

New yeast platform

In late 2017, Lonza introduced a new yeast-based expression system for the production of next-generation biologics. Its XS Pichia 2.0 Expression and Manufacturing Platform, based on *Pichia pastoris*, was designed to combine the best features of bacterial and mammalian systems in one system: fast and easy strain development and robust and rapid fermentation combined with a highly pure secreted product for a simple downstream processing, according to Christoph Kiziak, research and technology lead for microbial technology at Lonza Pharma & Biotech.

"The driving force was to rethink the whole production strategy for producing proteins to circumvent the main bottlenecks of bacterial systems (e.g., intracellular production, endotoxin), CHO systems (e.g., time-consuming, viral clearance), and yeast systems (e.g., use of methanol, hyperglycosylation), while maintaining the use of *Pichia* due to the general advantages and regulatory acceptance of this yeast cell," Kiziak says.

The "auto-inducible" setup of the new system makes it convenient for high-throughput clone screening, which results in highly pure material for preliminary quality analysis of the product at an early time point.

In addition, fermentation development follows a product-specific model-based approach, which allows yeast fermentations to be performed in two to three days with a high volumetric productivity, according to Kiziak. It can also be expanded by an *in-silico* model for process productivities over a wide production window. "This predictive model allows us to take into account production plant and process-specific limitations at any stage of development and provides high flexibility and quality for later production," he explains.

The methanol-free process also avoids the negative impact on cell viability and product quality of the commonly used AOX1 system, according to Kiziak. There is no need for explosion-proof facilities and the lower oxygen transfer rates compared to the AOX1 system provide additional flexibility regarding production plant requirements. There is also no need for endotoxin or viral clearance testing.

Furthermore, the product is secreted into the culture supernatant, where the minimal medium together with the low host-cell protein background provides an ideal starting point for an efficient downstream process.

To date, Lonza has focused on producing multispecific novel antibody mimetics from various sources using the XS Pichia 2.0 and has achieved productivities of more than 2 g/L per day. The company is working to make the system even more customer friendly and easy to apply and to refine the model-based approach in order to improve the accuracy of the prediction of fermentation processes. Additional promoters with different strengths and induction profiles are also being developed to allow the tuned expression of helper factors, auxiliary proteins, heteromeric products, enzyme cascades, etc., which will expand the applicability of the XS Pichia 2.0 in the future, according to Kiziak.

Mammalian best approach for now

Regardless of the technology, there is a general acceptance that existing mammalian expression technology can no longer meet the needs of the biopharmaceutical industry. "One way to make healthcare more accessible and affordable to patients could be changing the cell lines we use for manufacturing," Emalfarb observes. "Our goal is to bring affordable medicines to more patients, in addition to improving processes to develop new treatments," he adds.

The industry isn't there just yet, however, according to Laird. "At this time, we are not aware of novel expression technologies appropriate for commercialization of next-gen biologics with significantly reduced costs, timelines, or complexity that can also ensure consistent post-translational modifications such as glycosylation. Although some new complex molecules could be harder to express using current or conventional mammalian expression systems, we think these systems are and will be the best approaches to express proteins for therapeutic purposes for the foreseeable future, especially given the vast knowledge from current advances in genome sequencing and CRISPR [clustered regularly interspaced short palindromic repeats] gene-editing technology that can be used to modify these conventional mammalian expression systems," he explains.

"With that said, we are very open to evaluating novel expression systems and will feverishly pursue new technologies as they become available," Laird asserts. "We all have the same goal of delivering medicines to patients as quickly and efficiently as possible," he concludes.

Genentech is currently focused on the development of targeted integration mammalian cell lines to enable faster, more consistent medicine development with higher productivities. To date, engineered host-cell lines to optimize performance, increase productivity, ensure product quality, increase the ability to produce complex formats, and decrease timelines have been achieved, according to Laird. PTE

Oral Delivery of Macromolecular Drugs

Ronak Savla, Olga Hartwig, William Wei Lim Chin, Brigitta Loretz, and Claus-Michael Lehr

Macromolecular drugs are typically injected, but oral dosage forms are being developed to improve the treatment of gastrointestinal conditions such as inflammatory bowel disease.

Small-molecule drugs in oral solid-dosage forms are considered the first line of defense in treating diseases of the gastrointestinal (GI) tract, which affect millions of patients around the world each year. A number of patients, however, either do not respond to these drugs or experience side effects from these drugs.

Macromolecular drugs, such as peptides, proteins, and antibodies, offer a newer class of drugs that can treat diseases of the GI tract, such as inflammatory bowel disease (IBD). These drugs have demonstrated improved efficacy and represent a new paradigm of treatments for IBD.

Macromolecular drugs are usually injected subcutaneously or intravenously, and only a fraction of the administered dose reaches the disease sites in the GI tract. There has been tremendous amount of research to capitalize on the potential benefits of oral delivery macromolecular drugs, which include:

- Better patient acceptance and adherence
- More convenient dosing, including patient self-dosing
- An improved therapeutic profile.

This article reviews current treatment options, analyzes the knowledge and technology gaps that have prevented development of more oral macromolecule dosage forms so far, and discusses some approaches that are being tried and could be used in the future to overcome these gaps.

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal (GI) tract that is mediated by the host immune system and is prevalent in Western countries (1, 2). In Europe alone, approximately three million individuals are estimated to have IBD (3).

IBD can be subdivided into two types: Crohn's disease and ulcerative colitis. Inflammation seen in Crohn's disease spreads deep into tissues and involves the small intestine, large intestine, or both. Patients with Crohn's disease may have multiple, non-continuous areas of inflammation. Therefore, the drugs must be available at different points in the GI tract.

Ulcerative colitis causes inflammation in the innermost lining of the large intestine and rectum. Treating patients with ulcerative colitis requires drugs that are protected and released in the distal portion of the GI track. IBD patients

Submitted: 15 Jan. 2018
Accepted: 16 April 2018

CITATION: When referring to this article, please cite it as R. Savla *et al.*, "Oral Delivery of Macromolecular Drugs," *Pharmaceutical Technology* 42 (7) 2018.

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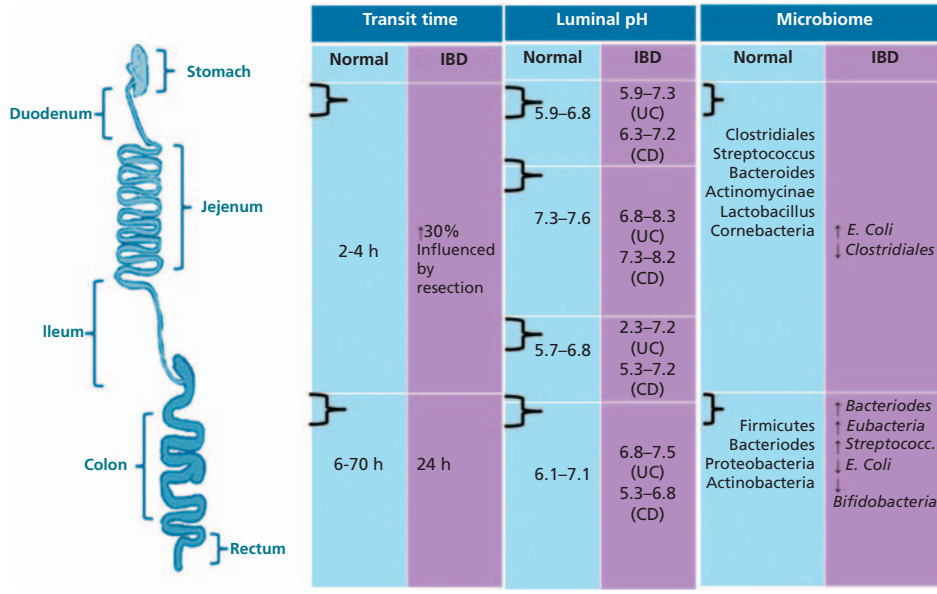
Figure 1: Physiological differences between gastrointestinal (GI) tracts of healthy and inflammatory bowel disease (IBD) patients. CD stands for Crohn's Disease.



suffer from mild to severe symptoms comprising diarrhea, abdominal pain, and malnutrition, as well as an increased risk of developing colorectal cancer.

In-vitro and *in-vivo* IBD models

IBD pathogenesis is multi-factorial; therefore, current *in-vitro* as well as *in-vivo* experimental models attempt to address each of the critical elements associated with IBD. Various *in-vitro* cell-based models are available to mimic the human intestinal mucosa by simplifying the physiological complexity and, thus, allowing the controlled analysis of discrete cell-to-cell or cell-to-molecule interactions.

Static cultures of intestinal epithelial cells (IECs) are made of one or more cell lines that originate from human colon carcinoma (e.g., enterocyte-like Caco-2 or goblet-like HT29). A more complex 3D co-culture model mimics the intestinal barrier through a co-culture of IECs with immune cells such as macrophages and dendritic cells (4). The addition of pro-inflammatory mediators results in an inflammatory microphysiological environment that includes impaired epithelial barrier function and immune cell activation.

3D modelling of stem cell culture

Another approach to study IBD conditions is the near-physiological 3D model of epithelial organoid cell (EpOC) culture derived from isolated human intestinal stem cells. As an important bridge between the traditional 2D cell cultures and *in-vivo* animal models, EpOCs could serve as a platform with which to screen various therapies for a personalized medical application.

Because the gut microbiota of IBD patients is altered regarding composition and metabolic activity, the newer model has been developed to analyze the interaction of potential therapeutics with gut bacteria. The simulator of human intestinal microbial ecosystem (SHIME) is a dynamic *in-vitro* model used to study of the entire GI tract comprising diverse microbial communities.

The pathogenesis and etiology of human IBD have been studied in various animal models that reflect the complexity of the whole organism (5,6). The most widely used animal model, dextran sodium sulfate (DSS) colitis model, is characterized by a loss of epithelial barrier function and the subsequent entry of luminal bacteria into the mucosa.

Factors that affect drug targeting of the colon can be generalized into pre- and post-absorption challenges (5). Typical pre-absorption challenges include the avoidance of drug absorption and/or degradation in the upper gastrointestinal tract, absorption surface area, mucosa permeability, bile contents, presence of food, and specialized structures such as the Peyer's patches and lacteal ducts. Post-absorption factors to be considered include potential enzymatic degradation existing in the gut wall and the hepatic first-pass effect.

Inter-population differences in gastric functioning and physicochemical characteristics of gastric fluids also impacts drug disposition further down the GI tract (6). Physiological variations such as differences in the transit time,

Table I: Target sites of enteric coated marketed drugs to treat irritable bowel disease.

		Target site release			
Drug	**Enteric coating polymer**	**Duodenum**	**Ileum**	**Colon**	**Rectum**
Mesalazine (Asacol®)	Eudragit S				
Mesalazine (Asacol® HD)	Eudragit S, Eudragit L				
Mesalazine (Salofalk®)	Eudragit L, Eudragit E				
Mesalazine (Salofalk Granu-Stix®)	Eudragit L100, Eudragit NE40D				
Mesalazine (Claversal®)	Eudragit S				
Mesalazine (Pentasa®)	Ethylcellulose microgranule				
Beclomethasone (Clipper®)	Eudragit L 100-55				
Budesonide (Entocort® EC)	Eudragit L				

luminal pH, and microbiome in healthy populations versus IBD patients also influence oral drug absorption (**Figure 1**) (6, 7).

IBD and unmet medical need

To date, no cure for IBD exists, and, in severe cases, surgical intervention is inevitable. There is an unmet medical need for novel drugs, and more specific anti-inflammatory approaches, to treat refractory or intolerant IBD patients.

Currently, several therapeutic strategies are currently available to reduce the intestinal inflammation, each one targeting a different site in the GI tract (**Table I**) (8-10). Classical treatments for IBD include the use of anti-inflammatory and immunomodulatory drugs such as mesalazine, aminosalicylates, corticosteroids, antibiotics, probiotics, and immunosuppressants such as cyclosporines (8, 9, 11).

Biological therapies have also been developed to target specific IBD pathways. Monoclonal antibodies may be used, for example, to block, selectively, such pro-inflammatory cytokines as tumor necrosis factor-α (TNFα). In addition, anti-cell-adhesion antibodies such as integrin blockers may be used to help inhibit lymphocyte migration to the gut. However, these biological agents are not effective for all patients with IBD and may increase the risk of infection and the potential for immunogenicity.

A newer strategy focuses on inhibiting signaling by using small molecules to transport Janus kinase (Jak) inhibitors, which can block numerous key cytokines associated with IBD, simultaneously. Unfortunately, these new treatments pose safety questions. Clinical trials are currently exploring more selective targeting of single Jak inhibitors, for example, using RNA interference (RNAi) via synthetic siRNA, to downregulate Jak expression in a specific manner. Advanced drug-delivery strategies are indispensable to successfully deliver siRNA to the target tissue or cells.

So far, the US Food and Drug Administration (FDA) has approved two anti TNFα antibodies, Infliximab and adalimumab, to treat moderate-to-severe active Crohn's disease or ulcerative colitis. Because they are biologics, both drugs are administered by injection. Infliximab requires intravenous infusion on weeks zero, two, and six, and then every eight weeks. Adalimumab is administered as a subcutaneous injection on Days 1, 15, and 29, then every other week. Both treatments pose the risk of adverse effects (12). Ustekinumab is another monoclonal antibody indicated for the treatment of moderate to severe Crohn's disease, which targets IL-12 and IL-23 cytokines. The initial dose is administered as an intravenous infusion followed by maintenance therapy of a subcutaneous injection every eight weeks.

Oral delivery of macromolecule drugs

Being able to deliver macromolecular IBD treatments orally would improve patient experience, avoid systemic exposure, and increase drug presence at disease sites. However, maintaining stability and activity in the GI is a significant challenge. So far, in studies that have evaluated the potential for oral delivery (13–16), considerable variability has been seen in the recovery, stability, and activity of orally administered macromolecules.

Clinical trials of target oral therapies for IBD have also shown insufficient results. One case in point is Mongersen (GED0301), a 21-base single-strand antisense oligonucleotide that complexes to Smad7 mRNA to cause degradation via the classical antisense pathway (17) to restore the function of TGF-β1's anti-inflammatory actions. The compound was tested in modified-release film-coated tablets using methacrylic acid-ethyl acrylate copolymers as a pH-dependent coating. The target treatment areas were the lumen of the terminal ileum and right colon. However, results were inconclusive, and clinical trials were discontinued in October 2017.

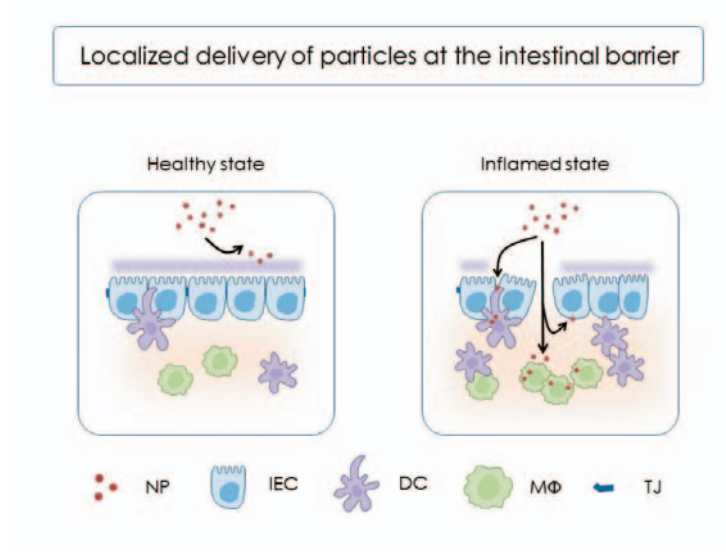
Another compound undergoing clinical trials is AVX-470, a novel polyclonal anti-TNF antibody candidate isolated from bovine colostrum, whose in-vitro activity is similar to that of infliximab (13). Disease severity was reduced when the murine version (AVX-470m) was orally administered in mouse models of IBD. Minimal systemic exposure was seen in mouse models. A Phase I placebo-controlled study

in 36 ulcerative colitis patients assessed the safety, pharmacokinetics, immunogenicity, and efficacy of four weeks of treatment (18). Clinical response was seen in 25.9% of patients and only treated with the candidate therapy, compared to 11.1% of the patients who received the placebo.

Formulation and dosage-form considerations

In addition to addressing stability, to ensure that the drug remains in the GI tract long enough to be effective, targeted delivery to the colon is the greatest challenge for developing oral therapies for IBD. Most current approaches use an enteric coating system to protect the drug and only release it at target sites. However, each IBD patient has a different disease profile, so a formulation that, for example, releases in the colon will not help a patient whose IBD affects the small intestine.

Figure 2: Pathophysiological changes during intestinal inflammation facilitate particle accumulation inside the inflamed tissue. Abbreviations: nanoparticles (NP), intestinal epithelial cells (IEC), dendritic cell (DC), macrophage (MΦ), tight junction (YJ).



Technology toolkit

Ensuring sufficient residence time in the GI tract will require use of a toolbox of technologies and approaches that are designed to enhance the predictability and reproducibility of targeting of the drug in the colon.

Use of pH-sensitive polymers. Once the macromolecule is exposed to the environments of the small and large intestines, proper formulation and dosage form design can help ensure that it retains activity. One formidable challenge is to protect the macromolecule from the acids secreted by the stomach until the dosage unit reaches IBD sites in the intestines.

Use of a coating system. A coating system can help control the release the macromolecule at specific pH points. One of the approved therapies for IBD, the small molecule, mesalazine, use different grades of Eudragit polymers to achieve specific release profiles. Even though this example is a small-molecule, the principle of using coatings for controlled release could also, in theory, work for larger molecules, as was shown in clinical trials (e.g., for mongersen).

Biodegradable polymers. Biodegradable polymers, known for their low toxicity and biodegradability, have been extensively used to formulate GI tract treatments that target the lower GI tract. Within the colonic environment, these mostly hydrophilic polymers can be broken down by various bacteria (19) for a controlled release of the drug within the colon. These polymers can be combined or used individually to modulate the rate of drug release and absorption (19). Options include guar gum, pectin, chitosan, chondroitin sulfate, galactomannan, and amylose, all of which are categorized as "generally regarded as safe" (GRAS).

Mucoadhesive systems. Mucoadhesive systems have been designed to increase the time that the formulation is retained within the GI wall in order to increase absorption of poorly absorbable drugs or improve their topical application (20). Some of the better-known mucoadhesive polymers include polycarbophils, polyurethanes, and polyethylene oxide.

Multiparticulate systems. Although most efforts to develop oral dosage forms for GI therapies focus on capsules or tablets, this approach may not allow the drug to be adequately released at all disease sites throughout the small and large intestines. Using multiparticulates, formulating dosage units with different coating systems may be more efficient.

The size of the pylorus is known to be around 7–8 mm when a patient is fasting, decreasing to 2–3 mm after a patient has eaten. Multiparticulate dosage units smaller than 2–3 mm in diameter would be able to leave the stomach, whether the patient was in a fasting or fed state.

Nanoparticles. Micro- and nano-particles represent novel approaches to localized delivery. Taking advantage of the GI tract's leaky epithelial barrier, these particles tend to accumulate in inflamed portions of the GI tract, optimizing drug delivery. In murine models and first-in-human clinical trials, nanoscale particles were found to accumulate in inflamed areas (21).

Smart delivery of nano-scale systems takes advantage of the physiological homing mechanisms to the site of injury

Table II: Review of conventional and novel approaches for localized delivery.

Technology	Pros	Cons
Coated drug delivery systems	• Simple and inexpensive • Protects against intestinal environment	• Altered colonic pH in some patients with Crohn's Disease
Delayed Release (time dependent drug release systems)	• Unaffected by individual differences in pH or intestinal bacteria	• Variation in gastrointestinal transit time may alter site of drug release
Prodrug design (microbial triggered)	• May reduce drug intolerance	• Dependent on intestinal enzymes for activation
Embedding in matrix	• Degradation of polysaccharide matrix by colonic flora • Independent of pH, pressure • Possible higher release rate	• Altered flora in irritable bowel disease may affect degradation rate and controlled release of active
Osmotic controlled	• Zero order kinetics • Increased intestinal resorption	• No commercially available products • Altered motility and water absorption in IBD
Lipid/ self micro-emulsifying drug delivery systems	• Improved oral absorption if systemic therapy is needed • May protect drug from degradation	• Altered bile secretion and metabolism
Multiparticulates	• Better spatial coverage of the intestinal lumen • Multiple release rates in single unit	

and inflammation (**Figure 2**), and nanotechnology is an area of intense research and development for GI-tract therapies that target the colon (22).

Other options for controlled and targeted release include prodrugs, embedding the drug in a matrix, and using osmotic control for delivery. Ultimately, the choice of delivery system depends on many factors, including target product profile. **Table II** lists the pros and cons of a number of available technologies.

Conclusion

Small-molecule drugs have been the treatment of choice for IBD, but a large percent of patient eventually don't respond the therapy. Macromolecular drugs are a newer class of drugs that have improved efficacy and require injection. Researchers are studying oral delivery approaches for macromolecular drugs that have better patient acceptance and adherence, more convenient dosing, and an improved therapeutic profile. Before patients can benefit, researchers must address the technology gaps that have prevented development of more oral macromolecule dosage forms.

References

1. Magro F., et al. *J Crohns Colitis*, 7(10):827-51 (2013).
2. Coward S, Kaplan GG. *IBD in the New World, Old World, and Your World. Inflammatory Bowel Disease*, p. 13-27 (Springer; 2017).
3. Molodecky NA, et al. *Gastroenterology*, 142(1):46-54 e42; quiz e30 (2012).
4. Susewind J, et al. *Nanotoxicology*,10(1):53-62, (2016).
5. *Non-invasive Macromolecule Drug Delivery Guide*, Catalent Applied Drug Delivery Institute (2015);www.drugdeliveryinstitute.com/nmdd-guide/
6. Van Den Abeele J, et al. *Eur J Pharm Sci.* 96:207-31 (2017).
7. Nalle SC, Turner JR. *Mucosal Immunol.* 8(4):720-30 (2015).
8. Asacol® HD [package insert], Proctor & Gamble Pharmaceuticals, Inc., Cincinnati, OH; April 2009, www.accessdata.fda.gov/drugsatfda_docs/label/2009/021830s002lbl.pdf.
9. Asacol® [package insert]. Warner Chilcott (US), LLC, Rockaway, NJ; May 2015, www.accessdata.fda.gov/drugsatfda_docs/label/2015/019651s025lbl.pdf.
10. Lautenschlager C, et al. *Adv Drug Deliv Rev.* 71:58-76 (2014).
11. Triantafillidis JK, Merikas E, Georgopoulos F. *Drug Des Devel Ther.* 5:185-210 (2011).
12. Maurer JM, et al. *Int J Pharm* 505(1-2):175-86 (2016).
13. Bhol KC, et al. *Inflamm Bowel Dis.*19(11):2273-81 (2013).
14. Jasion VS, Burnett BP. *Nutr J.* 14:22 (2015).
15. Tonelli F, Giudici F, Asteria CR. *Dis Colon Rectum* 55(8):870-5 (2012).
16. Brod SA. *J Neurol Sci.*361:19-25 (2016).
17. Monteleone G, et al. *N Engl J Med.* 372(12):1104-13 (2015).
18. Harris MS, et al. *J Crohns Colitis.* 10(6):631-40 (2016).
19. Rajpurohit H, Sharma P, Sharma S, Bhandari A. *Indian Journal of Pharmaceutical Sciences* 72(6):689-96 (2010).
20. Varum FJ, et al. *Critical Reviews in Therapeutic Drug Carrier Systems* 25(3):207-58 (2008).
21. Schmidt C, et al. *J Control Release* 165(2):139-45 (2013).
22. Amidon S, Brown JE, Dave VS, *AAPS PharmSciTech.* 16(4):731-41 (2015). **PTE**

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Aseptic Transfer Technology: Weighing Up the Advantages of Varying Approaches for Sterile Drug Manufacturing

The author reviews current approaches to sterile containment and compares several sealed transfer and barrier techniques, including isolators, restricted access barrier systems, and split butterfly valve technology.

Christian Dunne is global product manager for ChargePoint AseptiSafe.

The manufacture of sterile drug forms must be subjected to strict controls to minimize the risk of contamination by micro-organisms, endotoxins, and particles. Because the presence of something unwanted in a dosage form can pose serious risks, legislation demands that steps be taken to reduce these risks that threaten product quality and ultimately patient safety.

Pharmaceutical manufacturing environments are open to multiple sources of contamination from the air filtration systems to the process of materials transfer and the fact that a fully gowned operator can create more than 10,000 colony forming units an hour. As a result, measures need to be taken to ensure the safe and sterile transfer of APIs and formulation ingredients during aseptic processes. This article reviews current approaches to sterile containment and compares several sealed transfer and barrier techniques, including isolators, restricted access barrier systems (RABS), and split butterfly valve (SBV) technology.

Sterile containment techniques

Sealed transfers and barrier technologies have been designed to contain aseptic manufacturing processes. They provide a robust alternative to conventional "cleanroom only" methods of handling sterile products, ensuring that pharmaceuticals are not exposed to viable organisms or particulate contamination, while also protecting operators from potent compounds.

RABS

RABS have been designed to enhance the aseptic processes carried out in conventional cleanrooms. These systems put a physical barrier between operators and processing lines, while still offering the flexibility to interact with the process. To enable the use of a less restrictive barrier, RABS are required to be set up in class ISO 7 cleanrooms, which means they do not require their own bio-decontamination system.

Two different types of RABS are commonly used in today's manufacturing facilities. The first are active RABs, which actively pull air from outside the cleanroom environment, filtering and extracting it so that the RABS is completely isolated. The second type are standard passive RABS that use a cleanroom's heating, ventilation, and air conditioning (HVAC) system.

RABS bring their own unique advantages by enabling operators to maintain a distance from the process, while allowing the cabinet to be opened if further intervention is required. Processes can also be quickly turned around to suit different batch sizes and requirements.

Sealed transfers and barrier technologies have been designed to contain aseptic manufacturing processes.

Isolators

Isolators create an airtight barrier or enclosure around an aseptic processing line, hence, providing complete separation between the product and the operator/cleanroom environment. Operators perform tasks through half-suits or glove ports, enabling manipulation to be undertaken within the space from outside the enclosure without compromising integrity.

The clean environment is maintained through a combination of techniques, including the use of positively pressurized chambers with closed loop control. High-efficiency particulate air (HEPA) is supplied to the chamber in a laminar flow and ensures that particulate generation is suppressed and removed efficiently, while integrated bio-decontamination systems provide a validated sterility assurance level (SAL) of 10-6 on the chamber surfaces.

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Due to the high-performance requirements for these enclosures, integrated pressure decay tests have become the norm during start-up and prior to any bio-decontamination phase, with the leak of the chamber being a key factor in the classification of the device. More information can be found via ISO14644 (1) on leak rates for separative devices.

Pharmaceutical manufacturing environments are open to multiple sources of contamination from the air filtration systems to the process of materials transfer.

Weighing up the advantages of isolators and RABS

Isolators and RABS both offer rigid wall environments that provide a physical and aerodynamic barrier between the operator and the sterile drug manufacturing process. While both provide an ISO 5 cleanroom environment, they each have their own unique advantages and limitations.

One of the major benefits that isolators have over most RABS is that the interior can be decontaminated through an automated process. This allows for repeatable and consistent high-level bio-decontamination providing increased SALs over conventional cleanroom manufacturing. Comparably, most RABS rely on the use of manual cleaning processes.

A limitation of isolators is that they can create difficulties in transferring materials in and out of the cabinet. This system can require a docking isolator to be connected and its interior sanitized before materials can be transferred. The qualification of hydrogen peroxide vapour systems in isolators can also be difficult. As a result, there is a need to suspend everything within the cabinet to remove any hidden surfaces.

In comparison to isolators, RABS can ensure faster start-up times, while also improving the ease of changeover. They can also bring increased operational flexibility and reduced validation expenditure. Isolators, however, offer the advantage of higher integrity chambers for a more robust closed solution.

As an alternative handling technique to these more traditional barrier techniques, many manufacturers are finding that an SBV approach can provide a more practical option in achieving assurance of product sterility.

Isolators and RABS both offer rigid wall environments that provide a physical and aerodynamic barrier between the operator and the sterile drug manufacturing process.

SBV technology

SBV technology enables a product to be transferred from one container, process vessel, isolator, or RABS to another without compromising sterility. The valve consists of two parts: the active half and the passive half. Generally, the active half will be attached to the receiving vessel, with the passive half attached to the discharging drum or container, such as an intermediate bulk container (IBC) or flexible bag. When the two halves of the "butterfly" disc are brought together, a single disc is created, which allows product to flow on the internal surface of each half. When the passive and active halves are detached, the external face remains clean and can be safely exposed to the process environment.

Decontamination is able to take place in a closed environment using SBV. A gap is created between the discs when the two halves are connected, which enables hydrogen peroxide gas to be flushed through. Chemical indicators are used to validate the process and ensure that full coverage of the enclosure is obtained. Biological indicators also ensure a six-log reduction in microbiological contamination has been achieved.

The SBV approach offers manufacturers a closed handling method that reduces the resource associated with cleaning and validating large areas and minimizes the need for manual intervention, all while achieving the necessary SAL. By reducing cleaning requirements, the technique results in less downtime.

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Depending on the gassing system used, processing times when employing SBV technology can range between four and 30 minutes, which represents a significant time-saving in comparison to conventional airlock systems or isolators that generally require four to six hours. The aseptic SBV also makes it possible to downgrade the surrounding cleanroom environment because of the integrity of the approach, again generating further time and cost savings.

Conclusion

The key to advanced aseptic processing is the elimination and absolute control of all sources of contaminants, including human-generated contaminants. The selection of an appropriate barrier containment technique will be dependent on several factors, including the requirements of individual manufacturing facilities and the types of products being processed. Choosing the right contamination control platform requires considerable research into what a product needs for an effective process design.

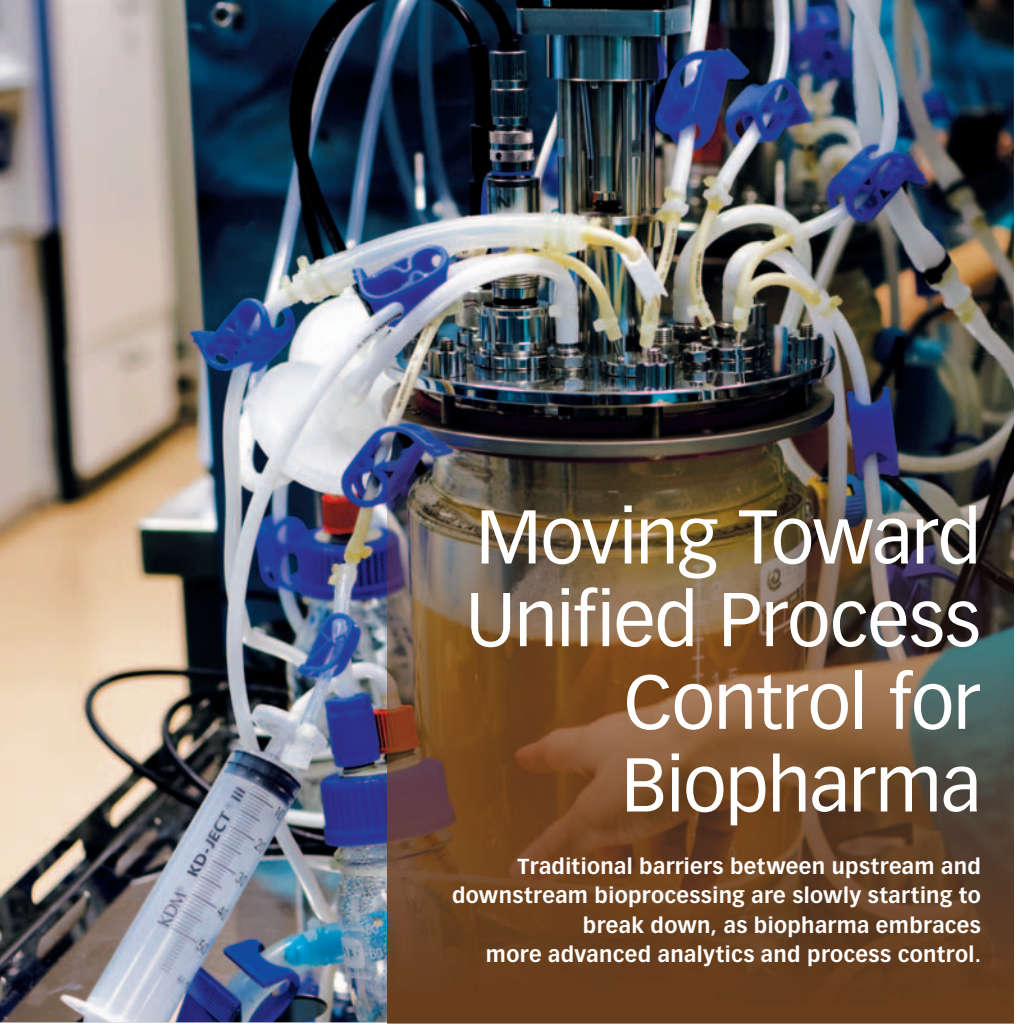
The split butterfly valve approach offers manufacturers a closed handling method that reduces the resource associated with cleaning and validating large areas and minimizes the need for manual intervention, all while achieving the necessary sterility assurance level.

While ease of decontamination and a high degree of sterility assurance can be readily achieved using isolators, RABS bring increased operational flexibility and speed of changeover which appeals to manufacturers that need to adapt to varying requirements from different customers. Aseptic SBV technology not only complements and works in harmony with these solutions, but can, in many circumstances, eliminate the need for other methods.

For manufacturers who require high-speed commercial manufacture, barrier isolation technologies may make business sense. For smaller batch sizes, a more flexible RABS solution may be more suited to the process.

Reference

1. ISO 14644-7: Cleanrooms and Associated Controlled Environments—Part 7: Separative Devices (Clean Air Hoods, Gloveboxes, Isolators, and Mini-Environments) (2004), www.iso.org/obp/ui/#iso:std:iso:14644:-7:ed-1:v1:en. PTE



Moving Toward Unified Process Control for Biopharma

Traditional barriers between upstream and downstream bioprocessing are slowly starting to break down, as biopharma embraces more advanced analytics and process control.

Agnes Shanley

Since the early days of biopharmaceutical manufacturing, upstream and downstream primary processing have been considered separate worlds. There was no profound reason for this separation, explains Charles Cooney, professor emeritus of chemical engineering at the Massachusetts Institute of Technology (MIT). "It goes back to the pre-biotech days of industrial bioprocessing, when the people involved upstream were mainly biologists, microbiologists, biochemists, and chemists, and the downstream people were usually chemical engineers, because they were engineering unit processes for product recovery," he says.

Still, these historic disciplinary roots have continued to organize and define the industry for decades, and the result has often been isolation, rather than integration, Cooney says. More recently, however, as financial pressures intensify and interest in continuous biopharmaceutical processing increases, distinctions between up- and downstream are starting to disappear. "The conversation is no longer split by differences in vocabulary and has become much more integrated," he says.

Greater integration is also seen, he says, in the move to fed batch processes (now standard for monoclonal antibodies [MAbs]), perfusion processes (standard for therapeutic enzymes and more unstable products), and continuous chromatography, enabling, for instance, a continuous capture step using a perfusion culture.

The industry may still be years away from adopting integrated, end-to-end biopharmaceutical process control, but it is getting closer. Enabling this move has been greater acceptance of approaches that had already been in use for years in other industries.

The US Food and Drug Administration's (FDA's) support of process analytical technologies (PAT) helped drive this change, says Bob Lenich, life-science business director at Emerson Automation Solutions, but economic pressures also play a role. "In the past, pharmaceutical manufacturers didn't have to optimize manufacturing, but now they do, and they are applying more advanced analytics and control to help reduce costs," Lenich says.

Now that automation standards such as the International Society of Automation (ISA's) S-88 and S-95 (1) have been adopted by the pharmaceutical industry, the current focus is on "plug-and-play" solutions that will reduce the cost of automation, says Christie Deitz, engineering manager at Emerson Automation Solutions. "Equipment vendors are looking at unit operations that can run continuously, and skids on wheels, whether for chromatography, filtration, or bioreactors, that they can reconfigure to get to the next run," says Deitz. Emerson, meanwhile, is extending use of its flagship DeltaV product, through the Discovery platform, into the R&D lab, secondary manufacturing, and packaging, and automation standards are moving from the plant floor to the lab and to secondary manufacturing.

PAT foundations

Enabling this change has been greater adoption of PAT, the use of which is now widespread in biopharmaceutical manufacturing, both upstream and downstream. "Even though downstream processing is still practiced as individual batch processes, use of PAT with those batches is standard," Cooney says.

Initially, use of PAT was limited to monitoring specific culture attributes upstream with near-infrared (NIR) spectroscopy, or performing transition analysis and performance studies with ultraviolet (UV) and NIR spectroscopies downstream, but there were challenges with sensitivity and specificity (2), says José Menezes, CEO of 4Tune Engineering, Ltd.

An important evolutionary step for PAT in biopharma came when companies moved from simply monitoring parameters to using PAT for process state estimation and to explore control opportunities.

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As Menezes explains, multivariate analysis was used to provide a complete estimation of the bioprocess state over time (e.g., a process trajectory during upstream cultivation, creating the opportunity to define guided sampling and endpoint determination strategies). NIR, mid-infrared (MIR), and Raman spectroscopy are all being used in this type of approach (2,3).

Recently, Menezes says, some manufacturers have begun to use *in-situ* mass spectrometry in multiple attribute methods (MAM), a term coined by FDA's Emerging Technologies Team to describe a method that aims to connect process condition-monitoring to accurate product quality-control during processing. "The ability to use mass spectrometry MS as a PAT [tool], and to aggregate the multiple attributes that it can very specifically measure, is a real breakthrough," he says.

Using new approaches such as MAM to monitor product quality attributes, end-to-end, both upstream and downstream, will open up new uses for PAT in biopharma, Menezes predicts. "Not only will it be used earlier in biopharmaceutical development to build very fast process and product understanding, but to support process performance qualification (PPQ, Stage 2) and the entire commercial lifecycle (Stage 3)," he says.

Many biopharmaceutical manufacturers are now at a stage where they are integrating quality measurements (typically spectral measurements) inline, so that they know they're producing what they expected to produce, and connecting those measurements to closed-loop control, says Lenich. "That approach is everywhere," he says, "but the question has now become: Where can you take a new measurement that you didn't have inline before, and how can you apply that measurement in a model to show that the process is working better?"

Biopharma is also relying more on model predictive control (MPC), says Deitz, and a number of presentations at the International Forum on Process Analytical Chemistry (IFPAC) 2018 focused on this area, which is still relatively new for biopharma.

"Today, many of our biotech customers are using MPC to look at an individual unit operation (e.g., a chromatography column or a bioreactor process)," says Deitz, "and many are also using it to synch connected operations downstream, for example, when a chromatography column and a filter skid are connected to several other operations inline, and a specific liquid level must be maintained in a feed tank to tangential flow filtration (TFF) skid. MPC can help prevent disturbances (e.g., a tank overflow or insufficient liquid level) from impacting unit ops down the line," she says.

At this point, MPC is being used more widely in secondary than in primary biopharmaceutical manufacturing to control more straightforward processes such as filling and powder management, says Lenich. On a broader level, he says, modelling is also being applied to optimize facility operations. Rather than focusing on yield, companies are using MPC to examine throughput more closely and improve manufacturing.

Modelling downstream biopharmaceutical processes remains challenging, however. "It's not an easy thing to do. You need to know what's going on in the process and you need a good understanding of the technology. You have to have the right people involved, and they need to be taking the right kinds of measurements," says Lenich.

At this point, he says, some crucial measurements exist offline in the lab, and it may take hours or days to get this information. "These data need to be moved inline or at line so that things can be done in real time," he says, noting that Emerson is collaborating in a BioPhorum Operations Group study that is determining what kinds of measurements are needed to optimize manufacturing and improve quality in biologics.

Analytics and digital strategy

Having a digital strategy is the key to fast, successful biopharmaceutical process development, says Cooney, who notes that analytics and good data are fundamental. "Analytics is the vocabulary with which process development people communicate with each other and regulators, and the chemistry, manufacturing, and control (CMC) filing is all about this," he says. "What is new is the ability to use those analytics more effectively to learn what is important and to improve the quality of control. We are beginning to see the use of machine control techniques that will be the hallmark of process development strategies in the future."

The final obstacle to increased use of MPC is regulatory. "Everyone appreciates that these approaches work. But FDA and industry are not sure how to validate what is essentially a black box approach," says Lenich. "Guidance is starting to come but no definitive ruling, so, for many, the question is: When you are using MPC, how can you be sure that you're using the best approach and that it can be validated?"

Increased uptake of PAT has also led to more use of soft sensors in bioprocessing, not only within unit operations, to provide real-time estimates of hard-to-measure parameters or end-point predictions, but across operations, says Menezes. "As data-management becomes sophisticated at most companies, the possibility to retrieve and aggregate data from critical process parameters (CPPs) and critical quality attributes (CQAs) in real-time will allow CQA estimates during processing for subsequent operations. That opens many possibilities for end-to-end optimization and feedforward control that will make pharmaceutical quality by design a reality in bioprocessing," he says. Examples already exist in areas such as media, relating quality attributes to upstream yields or stability (4).

Continuous manufacturing

Although the use of continuous manufacturing is much more evident in small-molecule oral solid dosage form manufacturing, all major biopharmaceutical companies are evaluating continuous, at least at the unit operations level. Some companies, such as Merck, Bayer, and Sanofi, have begun to explore

the potential for continuous end-to-end primary biopharmaceutical manufacturing. This approach will require global integrated control. At this point in biopharmaceutical manufacturing, control is typically handled locally, says Cooney.

However, growing interest in end-to-end continuous manufacturing is stimulating development of global control strategies. One prototype employing this approach has been developed by Chris Love, associate professor of chemical engineering at MIT. It involves a fully-integrated biologics process done at a very small scale, in an installation roughly the size of a refrigerator (5), says Cooney.

Love's project, part of MIT's Biomanufacturing Research Programme (BioMan), was originally sponsored by the US Defense Advanced Research Projects Agency (DARPA), with the goal of developing a process to make biologics on demand to manufacture small lots of material in response to emergencies. It uses a continuous, highly integrated process that can deliver doses of biologics, says Cooney, and a group of biopharmaceutical companies have been involved in the development of the concept, which would enable highly distributed biopharmaceutical manufacturing strategies. All of the major biopharmaceutical manufacturers with continuous manufacturing research in progress are paying very close attention to the control strategy, says Cooney. "If you're going to run an integrated process, you have to have an integrated control strategy in place. The systems control industry is prepared to deliver the technologies (e.g., DeltaV) that are needed for this approach."

"Bottlenecks often come when a biopharmaceutical manufacturer tries to put a business case together for moving to continuous or integrated processes," says Cooney. "The right business case must be in place, and that case is typically based on one or more of four metrics: cost, quality, speed, and flexibility," he says.

"If you own a big stainless-steel manufacturing plant and are making a good product, you'd be hard pressed to throw that all away and start over again with continuous, but if you're expanding capacity and you want to be able to respond with greater agility to market trends and forecasts, then continuous becomes a very attractive option," he explains.

Batch processes do pretty well, Cooney says, but if one or more of the four business-case criteria are of concern, then continuous processing can offer an effective solution. Improved quality can be one incentive, he notes. "Research suggests that a continuous process can result in reduced variance in critical quality attributes. You have more integrated control, as seen in the food and chemical industries," says Cooney. Reduced capital expenditure and even operating costs can be another, he notes.

Obstacles to integration

Not only effective business case development, but other issues make the move to continuous manufacturing and integrated process control more challenging. For example, Cooney says, continuous process requires adaption and use of different unit operations, and different integration and interfaces are required between those unit processes. "The biopharmaceutical industry is just starting to learn how to handle these interfaces," he says.

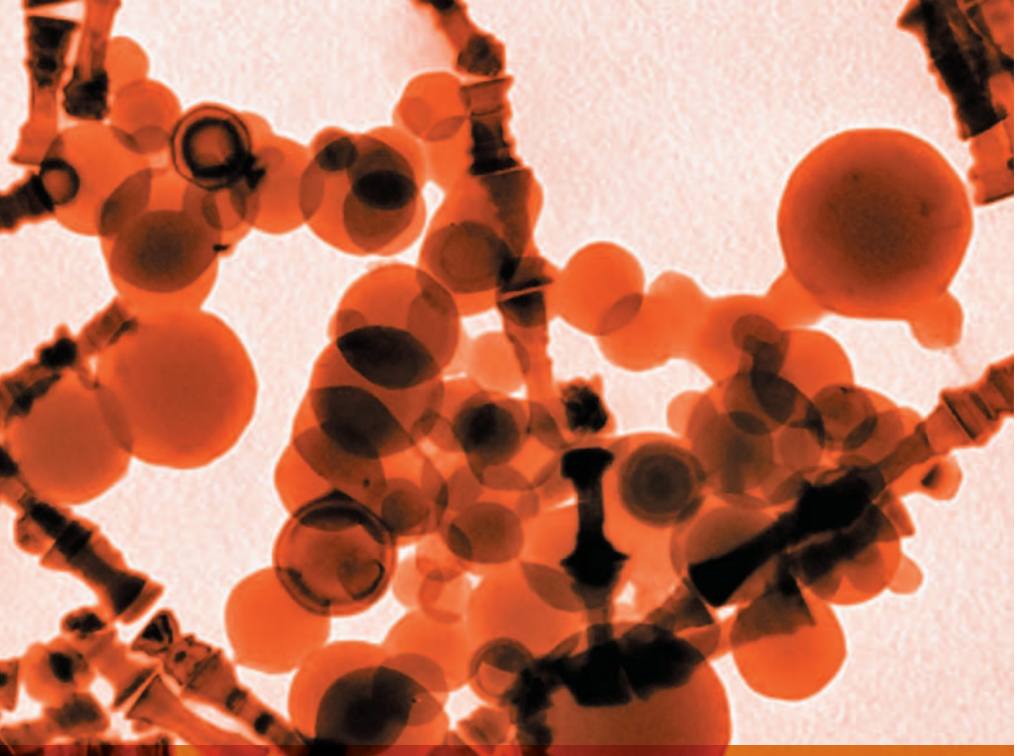
The third challenge is operating existing, successful batch processes if the batch unit operation is different from what would be done continuously. Cooney points to membrane tangential flow filtration (TFF) as an example. "TFF is historically a continuous operation, but we choose to operate it in batch mode. However, if you want an integrated batch process, it is more difficult to use the traditional mode of operation for TFF where you have recycle across the membrane," he says. The emergence of single-pass TFF has been somewhat enabling to the adoption of membrane filtration to continuous manufacturing, says Cooney, as has the use of multicolumn or continuous chromatography, or replacing batch acidification for viral inactivation with a continuous reactor. "You are accomplishing the same things, but with very different unit processes," he says. Integrated bioprocessing presents challenges that include:

- Operations stability over long periods of time, due to the biologic component and aspects of current process designs
- The integration of upstream and downstream processes with very different unit operations, in terms of dynamics and duration
- Insufficient data aggregation capabilities and a dearth of IT platforms that can extract, automatically, the information needed to support effective decisions and control actions
- Insufficient end-to-end lifecycle risk and knowledge management capabilities
- Limited ability to aggregate and provide regulatory reviewers and inspectors with the evidence and rationale required for risk-based change-management.

Menezes predicts that plant modularization and new designs will be a major driver to reshaping the industry, and enabling Industry 4.0 in biopharmaceutical manufacturing.

References

1. B. Scholter, "Integrating ISA-88 and ISA-95," *isa.org*, www.isa.org/pdfs/integrating-isa-88-and-isa-95/
2. J. Menezes, "Process Analytical Technology and Quality by Design in Bioprocess Development and Manufacturing," Industrial Biotechnology, Volume 3, Ed. A Moreira, in *Comprehensive Biotechnology* (2nd Edition), Moo-Young Ed., Elsevier, pp 501-509 (2011).
3. "Near-Infrared Spectroscopy in Laboratory and Process Analysis," *Encyclopedia of Analytical Chemistry* (Wiley, 2012), DOI:10.1002/9780470027318.a9361
4. "Method and System for Preparing Synthetic Multicomponent Biotechnological and Chemical Process Samples," Hoffmann-La Roche AG, WO/2015/097217
5. MIT, "MIT Team Receives $10.4 Million Grant," 18 Sept., 2013, *mit.edu*, www.news.mit.edu/2013/biomanufacturing-research-programme-grant-0918 **PTE**



Testing Foreign Particulate Matter in Inhaled Products

The delivery device and drug form should be considered when choosing a test method.

Jennifer Markarian

Orally inhaled and nasal drug products (OINDPs) are formulated as either solutions, suspensions, or dry powders that are delivered using devices such as nebulizers, metered dose inhalers (MDIs), or dry powder inhalers (DPIs). One of the critical quality attributes of an inhaled drug product is the amount and size of foreign particles in the product. "Foreign particles—including glass, stainless steel, or different types of polymers—can come from any step in the manufacturing process or from the source materials," notes John Bak, PhD, principal scientist at PPD Laboratories' GMP Lab. Manufacturers must develop appropriate tests to identify and measure these particles so that they can be eliminated or maintained below a certain level. *Pharmaceutical Technology Europe* spoke with Bak to learn best practices for developing these tests.

Guidance documents

PTE: What US Food and Drug Administration (FDA) or *United States Pharmacopeia (USP)* guidance documents are used to develop appropriate tests for foreign particulate matter in inhaled products?

Bak (PPD): Current guidance documents that are available include:

- *USP <5>* Inhalation and Nasal Drug Products—General Information and Product Quality Tests (1)
- FDA, *Guidance for Industry—Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products—Chemistry, Manufacturing and Controls Documentation (2002)* (2)
- FDA, *Draft Guidance for Industry—Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (1998) (3).

Although the requirement to do particulate matter testing is included in these documents, no techniques or guidelines for specifications are given. It is up to the applicant to develop and justify the choices made.

USP <788> Particulate Matter in Injections (4) and its specifications are specifically for parenteral products and are not appropriate for OINDPs. The testing procedures can be used to help develop an appropriate test, but not the specifications.

While FDA and USP provide little guidance, there have been some position papers published to fill the gap. Two papers by Blanchard et al., 'Foreign Particles Testing in Orally Inhaled and Nasal Drug Products' (5) and 'Best Practices for Managing Quality and Safety of Foreign Particles in Orally Inhaled and Nasal Drug Products, and an Evaluation of Clinical Relevance' (6), describe the types of tests that can be done and a rational means of setting product specifications specifically for OINDPs.

The means of setting specifications proposed in the paper (5) is to use the US Environmental Protection Agency National Ambient Air Quality Standards (NAAQS) for particles with < 10 µm aerodynamic diameters. A small percentage (1–5%) of the allowable exposure is suggested for the maximum daily exposure due to the use of the product.

The first article (5) also has a survey of the commonly used techniques for testing for particulate contamination along with each technique's strengths and weaknesses.

Testing strategy

PTE: What factors should be considered when deciding upon a testing strategy?

Bak (PPD): Based upon the recommendations of these two articles (5,6) and our experience, when looking at a strategy to test a product under development, the device used for delivery (e.g., nebulizer, MDI, or DPI), the location of action (e.g., nasal or pulmonary), the state of the formulated drug (e.g., solution, suspension, or dry powder), and the testing strategy (e.g., delivered dose or extracted formulated drug product procedures), all impact choices that are made as far as the technologies used, the test method validation strategies applied, the robustness of the resulting procedure, and the cost of the ongoing testing for stability and release.

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The first step in putting together the strategy is to harvest the particles from the drug product, drug substance, excipients, and delivery devices and analyze them using microscopic techniques that allow chemical identification, such as Fourier Transform infrared (FTIR) microscopy, Raman microscopy, and scanning electron microscopy with energy dispersive X-ray probe (SEM/EDX), to elucidate what the common contaminants are and identify their sources so they can be eliminated or reduced in the manufacturing process. In addition, a toxicological assessment can be performed to ensure that no particularly harmful materials are present. Special consideration is given to the < 10 µm particles because they are respirable and therefore present the highest risk from exposure.

Understanding the particulate profile and having it be reasonably stable from lot-to-lot demonstrates control of the manufacturing process with respect to particulate contamination in the drug product. When this level of understanding is established, the use of faster and less-expensive techniques to monitor the level of particulate contamination is warranted. Light obscuration is the most common technique used for monitoring.

PTE: What are the considerations for choosing to collect and analyze particles using the delivered-dose technique or analyzing the drug product extracted from the device or container?

Bak (PPD): The delivered-dose technique sounds better because it simulates the actual exposure the patient receives. These techniques, however, tend to be difficult to implement because of their poor precision, which requires higher-skilled analysts and thereby increases the cost of testing. In addition, the incidence of atypical and out-of-specification result investigations is increased with the associated delays. If a justification can be made to use material extracted from the device or container, the routine testing for stability and release is typically more robust and trouble-free.

Delivered-dose techniques for particulates often can be created by modifying methodology used in delivered-dose uniformity testing. A sufficient amount of material is collected, and then any solid drug substance or solid excipients are dissolved using an appropriate particle-free solvent. If no other solids are present, a compatible suspending solvent is added instead. The solvent is then well mixed to suspend the captured particulate contamination and tested by light obscuration or other techniques. This approach allows the use of the same or similar devices that analytical teams are used to working with, for instance, those described in *USP* <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests (7) and *USP* <1601> Products for Nebulization—Characterization Tests (8).

When extraction techniques are used, the testing is usually simplified. For nebulizers, the blow-filled vials are opened and the liquid pooled. The pool is then tested by light obscuration or another technique. For DPIs, the powder is extracted as appropriate. For instance, blister strips are cut open and the powder pooled. The powder is then dissolved in an appropriate solvent. The remaining particulate matter is then suspended in the solution, and it is tested. For MDIs, the material is extracted by cutting open the frozen can or by dispensing into a container that catches the drug product. If needed, any solid excipients or drug substance are then dissolved in a particle-free solvent. The resulting solution has the particulates suspended and is then tested.

Light obscuration typically is preferred for analyzing the resulting test solutions. If visible light microscopy is used, the solutions are filtered, and the remaining particulate contamination is counted. The magnification should be set high enough that the < 10 µm particles are clearly visible. Techniques based on *USP* <788> often undercount particles in the 2–5 µm range because at 100x magnification specified in *USP* <788> (4), these particles are difficult to see against the background of a filter membrane. Light obscuration testing, on the other hand, has good sensitivity to particles in the 2–5 µm range.

PTE: What are the most significant challenges in developing appropriate tests for foreign particulate matter?

Bak (PPD): Typically, the most challenging part of developing the testing is to find a solvent that dissolves the drug substance and the excipients at the same time, while minimizing interfering artifacts like microbubbles. The second most significant challenge is cleaning the equipment in a particle-free environment to control laboratory contamination of the samples.

PTE: What is typically required for validating these analytical methods?

Bak (PPD): We typically recommend that the < 10 µm particles be validated as a quantitative impurity test, since they present the highest risk because they are respirable. The range of analysis is demonstrated from the limit of quantitation to 120% of the product specification along with any demonstrations of method robustness indicated from the method development. The ≥ 10 µm and ≥ 25 µm particles also can be validated in the same manner, or be shown to have impurity-limits compliance, because they present less risk and are monitored more from a product quality standpoint than a safety risk.

References

1. USP, *USP* 40 Supplement 2 <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests (2017).
2. FDA, *Guidance for Industry—Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products—Chemistry, Manufacturing and Controls Documentation* (CDER, 2002).
3. FDA, *Draft Guidance for Industry—Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* (CDER, 1998).
4. USP, *USP* 40 Supplement 2 <788> Particulate Matter in Injections (2017).
5. J. Blanchard, et al. *Pharm. Res.* 21 (12) 2137-2147 (2004).
6. J. Blanchard, et al. *Pharm. Res.* 24 (3) 471-479 (2007).
7. USP, *USP* <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests (2014).
8. USP, *USP* 40 Supplement 2 <1601> Products for Nebulization—Characterization Tests (2017). **PTE**

Selecting Primary Packaging for Parenterals

Traditional glass and polymeric materials compete for market share.

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Despite the proliferation of new drug delivery systems for parenteral products, glass vials remain the most widely used primary containers worldwide. This trend is expected to continue for several years, with global demand for glass vials projected to rise to nearly €5 billion in 2024 (1).

In fact, borosilicate glass has been the primary packaging choice for parenteral products since its development more than 100 years ago due to its excellent barrier properties, chemical resistance, regulatory acceptance, and broad range of applications served.

But glass is not the only choice, especially for sensitive biotech products, and polymeric materials have captured market share in recent years. Polymeric materials offer light weight, shatter resistance, greater formability, tighter tolerances, strong barrier, and chemical compatibility. As a result, plastic packaging is gaining ground with global demand for plastic parenteral vials forecast to grow 7.7% per year to more than €1.3 billion (13.1 billion units) in 2021 (2).

One popular polymeric option, cyclic olefin copolymer (COC), combines formability, break resistance, and light weight with a glass-like transparency. Other polymers such as cyclo-olefin polymer (COP) and polyethylene naphthalate (PEN) offer similar attributes.

"The physical stability as well as the diverse design options make COC an attractive alternative for some drugs," explains Tom Van Ginneken, global product manager SCHOTT TopPac at SCHOTT Pharmaceutical Systems, a supplier of glass and plastic packaging for parenteral products. Anna Malori, business development manager at Bormioli Pharma, a producer of pharmaceutical primary packaging both in glass and plastic, agrees and predicts, "Some fields of application for COC will be highly sensitive drugs, biotech drugs and vaccines, and high-value drugs such as oncology treatments."

Glass or plastic?

With glass and polymers offering advantages and limitations in different scenarios, many factors must be considered to determine the better choice. Some pros and cons are listed in **Table I**. Commercializing new primary packaging for parenteral products tends to be time-consuming due to the complex regulatory approval procedures that must be followed to adopt a new packaging material. "The regulatory approval process can take years, and that is why each single change in the glass vial configuration may be seen as an obstacle toward the final drug product approval," explains Malori.

As a result, many producers of glass packaging for parenteral products are leaving glass chemistry unchanged, but they are fine-tuning processes and quality control practices and increasing inspection capabilities to ensure shipment of flawless finished containers.

Malori says: "Each packaging choice should be strictly related to the specific needs and characteristics of the formulation that will be contained inside." Working in close collaboration, the packaging supplier and drug maker identify the best packaging material and container-closure system for the formulation. Once that decision is finalized, suppliers provide support during the validation process.

Ginneken details the holistic approach: "We consider what we call the three Ps—product, process, and patient. For example, we examine specific requirements for the drug. Does it need a particularly inert packaging? We also look at the process requirements to consider how the product will be integrated into existing manufacturing lines or how to create a low-waste filling process, among others. Lastly, we focus on the patient as we aim to continuously meet the patient's comfort and needs. Therefore, we study if drug delivery in a home setting is required. If so, the primary packaging must be easy to handle for the patient and work with self-administration devices."

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Table I: Parenteral packaging pros and cons.

Glass pros	Glass cons	Plastic pros	Plastic cons
High barrier properties	More susceptible to breakage if not handled properly	Break-resistant	Semi-permeable (oxygen, gases)
Known material and commonly used	Potential risk of drug/container interaction	Heavy metal and tungsten free, low or no siliconization	Must be handled carefully to prevent scratches
Compatible with multiple filling machine vendors	May not be compatible with certain needleless Luer access devices	Light weight	Sterilization process can cause haze formation, discoloration
Regulatory acceptance		Greater design flexibility	
Multiple sources		Tight tolerances	

Reference: SCHOTT Pharmaceutical Systems, "A Tale of Two Materials: What the Glass vs. Polymer Debate Really Means" and "Glass or Polymer: What's the Right Choice for Prefillable Syringes?" http://blog.us.SCHOTT.com/a-tale-of-two-materials-what-the-glass-vs-polymer-debate-really-means/, accessed 11 May 2018.

Expanding applications

The need for stability and design flexibility have increased market share for polymeric materials, especially in the prefilled syringe segments. Applications include a variety of therapeutic areas within clinical settings, home care, or hospital-care environment.

"Benefits such as break resistance and reduced risk of syringe clogging make prefillable polymer syringes ideal for emergency drugs and diluents," says Ginneken. "Moreover," he adds, "polymer syringes are also suitable for highly viscous drugs, such as hyaluronic acid, which is used in the cosmetic field. In addition, large-format polymer syringes of 10, 20, or 50 mL are especially suited for infusion therapy in conjunction with syringe pumps, which allow continuous administration of a drug, such as anesthetics or cardiovascular medications, for a longer period of time. To ensure a seamless integration of the syringe and pump, packaging suppliers and device manufacturers must work closely together."

The more complex molecular structure of biotech drugs requires packaging with properties that ensure stability. SCHOTT offers polymer as well as glass containers for the pharmaceutical market. Polymeric packaging can offer a lower extractables and leachables profile as well as tighter dimensional tolerances. As a result, polymeric primary packaging, such as the SCHOTT TopPac SD COC syringe, is gaining ground for highly sensitive products.

Optimized glass containers, however, also address the need for stability. A new option for glass containers, Valor Glass from Corning, is a coated aluminosilicate glass that became commercially available in 2017. Eliminating boron from the formula and altering the ratios of other ingredients results in glass with a high degree of chemical durability and surface homogeneity and virtually eliminates delamination problems. An ion-exchange process helps minimize breakage, cracks, and particulate contamination, while the coating lowers coefficient of friction and eliminates cosmetic flaws. Despite the difference in chemistry, Valor Glass meets the current *United States Pharmacopeia (USP)* Type I hydrolytic criteria and has low extractable concentrations (3).

Another optimized glass option, Gx Elite Type I borosilicate glass vials from Gerresheimer, relies on proprietary technology to produce an extremely durable, delamination-resistant vial that is free of cosmetic defects. Compression and side-wall impact tests show the Gx Elite vials are substantially stronger than standard Type I glass vials (4).

Gerresheimer also supplies polymeric vials. Its Gx MultiShell vial features a multilayer COP and nylon structure, which offers clarity, shatter resistance, and barrier protection. Sizes include 2-, 5-, 10-, 15-, 50-, and 100-mL vials, which can be supplied ready-to-use (including validated gamma sterilization). Gerresheimer also offers monolayer COP packaging for parenterals (5).

A press-blow process gives Clareo Type 2 glass vials a more uniform wall distribution, flatter bottoms, and enhanced strength. "The vials perform better with less breakage and uniform heat transfer," reports Kevin McClean, quality and technical manager, Americas for SGD Pharma Packaging. The Type 2 glass containers cost less than Type I and are an acceptable alternative to regulatory authorities for some molecules. Clareo vials currently may be ordered in 20-, 50-, and 100-mL sizes (6).

Syringes also feature optimized glass. To maximize the quality of Ompi Nexa syringes from Stevanato Group, the production process eliminates glass-to-glass contact and minimizes glass-to-metal contact. Automated inspection checks each container. Options include a 1-mL long design and a 2.25-mL design with staked needle (7).

Whether glass or plastic, the highest levels of activity are being observed in the development of cartridges for pen and infusion pump systems and a transition from vials to prefilled syringes. In addition, "There's a lot of activity in auto-injectors for insulin," says Dave Dugan, account manager for Stevenato Group's Ompi of America.

One of the major forces driving interest in auto-injectors is

the growth in home care. Self-administration "lessens the burden on the healthcare system," says Uzzo Calderaro, business development manager at Duoject Medical Systems. "When a patient can stay at home, there's cost savings and a better quality of life for the patient," he explained. Well-designed auto injectors also reduce the chance of sharps injuries, prevent loss of product, and deliver accurate doses.

With auto-injectors, easy, consistent operation is essential, because the devices are intended for patient use. Uniform silicone levels are needed to ensure consistent movement of the plunger and help keep injection duration at no more than 10 seconds. These features do not come without challenges. "When injection time needs to be reduced, the drug needs to be concentrated, which increases its viscosity, necessitating more pressure on the syringe and increasing the chances of breakage," says Dr. Nicolas Eon, SCHOTT's global product manager, syriQ.

Made of highly inert FIOLAX borosilicate glass, the recently launched syriQ BioPure staked-needle syringes offer low tungsten and adhesive residuals for a superior extractables and leachables profile, plus accurate dimensions for optimal device compatibility. To maximize mechanical resistance and minimize the chance of breakage, the syringes are produced under strict cosmetic defect specifications in a process that eliminates glass-to-glass contact. A multi-camera quality control system provides 100% inspection of the complex shape from tip to flange. To accelerate speed to market, SCHOTT offers more than 40 validated configurations combining different flange designs, 27-g or 29-g needles, and elastomer components along with full documentation. "The availability of full documentation reduces the risk profile for the drug maker and ensures the syringe and device work together," notes Eon.

Some auto-injectors, especially those integrated into wearable devices, rely on cartridges. "Cartridges occupy less space and cost less than prefilled syringes," explains Duoject's Calderaro. Duoject has developed a multi-dose auto injector with a diluent-filled cartridge. The modular, integrated Penprep Evo system simplifies reconstitution and ensures dose accuracy via patented vacuum transfer technology, which also minimizes drug hold-up in the vial and air transfer back to the cartridge. Configurations include 13- or 20-mm drug vials with various diluent fill volumes (8).

Another recent auto-injector development, the SelfDose patient-controlled injector from West Pharmaceutical Services, departs from the traditional spring-loaded design and is larger than most pen systems. "The SelfDose injector restores control to the user, particularly for the arthritic population who may find standard injectors difficult to use," reports Carl Dabruzzi, director, Self-Injection Systems at West Pharmaceutical Services. The golf-ball size top of the larger-than-usual injector features a 1-mL long syringe. To use, the patient simply removes the cover and pushes down to dispense. Injection speed is user controlled and may even be paused. A visual indicator ensures proper administration. Needle depth can be customized to optimize drug absorption, and the needle is not visible before or after injection (9).

For wearable devices, West Pharmaceutical Services offers its SmartDose drug delivery platform. "We're seeing a lot of IV [intravenous] products being developed for subcutaneous administration via wearable devices," explains Dabruzzi. Driving forces for the transition include cost containment and patient convenience. A wearable device, he notes, reduces the need for trips to an infusion clinic. "With one or more visits per week at $300 to $1200 [€260–1030] per visit, costs for infusions can easily add up to thousands of [US] dollars per year, plus the cost of the drug product. Instead, the wearable device is applied and activated, and audible and visual indicators guide the patient through the administration process."

The SmartDose drug delivery system is based on a user-loaded, custom COP cartridge with septum/cap and FluroTec piston. Pre-programmed delivery times and duration can give the patient a more comfortable injection experience, particularly when delivering high-volume or high-viscosity drugs (10). Dabruzzi adds, "A patient who experiences pain or feels intimidated about self-injection is less likely to be compliant. So increased patient comfort is likely to improve patient compliance, which leads to better outcomes."

References

1. Freedonia, "World Pharmaceutical Packaging Industry Study #3269," July 2015, p. 73-75.
2. Freedonia, "World Pharmaceutical Packaging Industry Study #3591," January 2018, p. 66-67.
3. H. Forcinio, *Pharm. Tech. Europe* 29 (9) 18-19 (2017).
4. Gerresheimer, "Gx Elite Glass Vials Setting New Standards Regarding Quality Requirements," www.gerresheimer.com/en/services/innovations/elite-glass-vials.html, accessed 24 May 2018.
5. Gerresheimer, "Gerresheimer to Unveil Innovative Vials Made from Glass and Plastic at the PDA in Orlando," Press Release, 15 March 2018.
6. SGD Pharma Packaging, "SGD Pharma Introduces Its New Clareo Range," www.sgd-pharma.com/company-news/sgd-pharma-introduces-its-new-clareo-range, accessed 24 May 2018.
7. Stevenato Group, "Prefillable Syringes," https://pharma.stevanatogroup.com/glass-primary-packaging/products-platforms/prefillable-syringes/#nexa-syringes, accessed 24 May 2018.
8. Duoject Medical Systems, "Penprep EVO," http://duoject.com/realisations/penprepevo/, accessed 24 May 2018.
9. West Pharmaceutical Services, "SelfDose Patient-Controlled Injector," www.westpharma.com/products/self-injection-platforms/selfdose, accessed 24 May 2018.
10. West Pharmaceutical Services, "SmartDose Gen. I 3.5 mL Drug Delivery Platform," www.westpharma.com/en/products/self-injection-platforms/smartdose/smartdose-gen-I, accessed 24 May 2018. **PTE**

Serialization: Scaling Down for the Final Stretch

Vendors are offering template-based models and direct data-filing to help smaller companies meet imminent deadlines.

Agnes Shanley

For the past few years, it has been no secret that many small to mid-sized pharmaceutical companies in the United States, the European Union, and beyond, have not yet begun to prepare for serialization deadlines set by the US Drug Supply Chain Security Act (DSCSA), the EU False Medications Directive (FMD), and other traceability directives around the world (1).

In the US, this compliance gap led the US Food and Drug Administration (FDA) to postpone by one year the implementation deadline, moving it to November 2018 (2). The FMD's deadline still stands at February 2019.

However, in the second quarter of 2018, Tracelink's 2018 Drug Supply, Safety, and Traceability Report found that only one-third of 660 pharmaceutical manufacturers, contract manufacturing organizations (CMOs), wholesale distributors, hospitals, and pharmacies were confident that they were ready to meet requirements, and only half of the companies had prepared their internal packaging lines for serialization or projected the number of units that would need to be serialized each year.

The survey found that, at that time, only 8% of pharmaceutical manufacturers had integrated serialization processes with their CMOs and only 11% said their CMOs were ready to ship serialized product (3). Where executives from half of CMOs in the US felt ready, only a third of their counterparts in Europe did.

EU behind schedule

Manufacturers and CMOs in Europe are well behind schedule, according to recent reports (4). Second quarter 2018 data from the European Medicines Verification Organization (EMVO) suggested that 50% of countries whose manufacturers sell pharmaceuticals in the EU will be too late to meet the FMD deadline. Even for all European suppliers to comply would require equipping some 10,000 packaging lines at 1500 pharmaceutical sites in a matter of months (5).

Getting EMVO approval is itself a process that can take several weeks. First, a series of transactions must be submitted and reviewed before the company is allowed to submit relevant production and other data to the EU Hub.

At the Serialization Innovation Summit, held on June 20, 2018 in Philadelphia, US, and sponsored by the serialization IT supplier Adents, Maarten Van Baelen, market access director for Medicines for Europe, a generic-drug trade association, revealed the scope of the challenge.

As of May 2018, he said, out of the 2200 pharmaceutical companies that are required to submit serialization data to EMVO in order to comply with FMD, only 749 had done so. Meanwhile, further along the supply chain, only 10% of wholesalers were connected to the EMVO system, although they were working very hard to solve the "considerable technical challenges" involved, he told attendees at the June Summit.

Faster data submission

Solution providers have responded to these issues with a number of "quick compliance" tools—modular, template-driven approaches designed to help companies meet serialization requirements quickly. In May 2018, TraceLink, a cloud-based IT serialization solutions provider, introduced the EU FMD Express platform, designed to help smaller manufacturers and CMOs in Europe to meet requirements and send serialization data to EMVO (6).

As of June 2018, TraceLink reported that 34 companies had completed conformance testing using TraceLink's kit. Of these, 11 companies received EMVO approval to submit data to the EU Hub and 14 companies were awaiting review. Biosyn is one company that reported good results from the programme, while, in June,

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IBI Lorenizini, an Italian CMO and supplier, signed up.

Adents, another cloud-based IT vendor, is approaching the serialization readiness gap with programmes of its own. Started up in 2007 in France by specialists with experience handling provenance and serialization issues in the fine perfumes and champagne markets, the company introduced Serisa, a line-level serialization solution supported by Siemens, in 2010. In 2014, Adents released Prodigi, a cloud-based system designed to facilitate serialization data exchange.

In 2017, the company established a collaboration with Microsoft, and the two partners introduced NovaTrack to the US market in June 2018 (7). The approach, utilizing Microsoft's Azure Cloud technology, is designed to incorporate blockchain and artificial intelligence, and to bring Internet of Things (IoT) technology to bear on cold-chain and other supply chain issues. Julien Faury, vice-president of operations for Adents Americas, says that the programme features open architecture and works both at the centralized IT level and at the line level. It uses a "top down" approach, and is vendor agnostic, and is cloud-native, or designed for a distributed platform, Faury says.

The company offers users a certified gateway to enable faster transmission of data to EMVS. It has integrated with the Origin database in the US, operated by the Healthcare Distributors Association, and is developing a gateway to Russia's serialization database.

Adents is also working with Microsoft to develop and optimize blockchain solutions using Microsoft's Coco Framework, which offers faster transaction speeds than found in existing solutions, according to Tianna Umann, cross-domain solution architect with Microsoft, who spoke at the June summit.

Both partners have assembled an industry workgroup lead by the Healthcare Distributors Association to evaluate different approaches to blockchain. In addition, Adents and Microsoft are working on systems that would use Microsoft's Hololens technology to train operators on serialization and to make relevant documents accessible to them in their workspace via a wearable device (8). Hololens is based on the concept of Mixed Reality, which incorporates some of the elements of virtual reality, but operates in real space.

Adents' operations manager, William Minaeff, senior project director, shared some insights into pharmaceutical serialization efforts in the US and Europe with *Pharmaceutical Technology Europe*.

Compliance outlook for 2018

PTE: What changes have you seen in the industry's approach to serialization in 2018, as the DSCSA and FMD compliance deadlines draw near?

Minaeff: We have seen several changes since FDA offered a year-long extension in 2017. FDA recognized that solution providers were finding it difficult to scale up to service the number of production lines required by the various pharmaceutical companies. As a result, many serialization service providers have had to hire hundreds of employees in a short time frame to meet demand.

The major hubs in the United States are in the San Francisco Bay Area, the Northeast, and of course, Research Triangle Park. Additionally, we see a large opportunity for external manufacturing in the Midwestern US. The beauty of cloud solutions is that they have unlimited scalability, so we are able to work with companies of all sizes and customize our solutions according to the size of the business. Further, Colombia and Brazil are emerging markets, while Canada will adopt serialization within the next five years due to changes in regulations.

PTE: Just a few months ago, many small to mid-sized manufacturers and CMOs had not even started formal serialization programs. Where are you seeing the greatest challenges?

Minaeff: The pharma industry's serialization implementations face the following challenges:

- Collaboration between thousands of parties
- An unstable regulatory landscape
- Management's view that serialization is a cost, not a benefit
- The need to share billions of terabytes of data.

PTE: There are already a number of cloud-based data management systems available for serialization. How is Adents' different?

Minaeff: Adents was established to explore the new generation of serialization software. The major challenge with serialization is not the actual marking or reading of serial numbers but rather the data management expertise that backs up the serialization. Over the past few years, Adents has created a new software suite, with an open architecture.

The first part of this software was released in 2010. This software-driven serialization solution took off very quickly in the European market. The solution is not only used in the pharmaceutical sector but also in the wine and spirits, and health and beauty sectors.

In 2012, pharmaceutical companies in the United States and Europe started to implement these processes and began to look into cloud-level solutions. Adents partnered with Microsoft in 2014 to codevelop Adents Prodigi, which was released in 2017. Adents has since grown to nearly 100 employees and more than half of its customer base consists of life-science companies.

Leveraging serialization efforts

PTE: What is needed to help more companies leverage the work that they have done to enable serialization to achieve broader business benefits?

Minaeff: As a serialization project progresses, there are many challenges that need to be faced and many sources of complexity. Serialization failures most frequently come from a failure to understand the scope of a serialization project, for example, failing to identify all stakeholders and their requirements (e.g., packaging, label change, supply chain, IT, and Enterprise Resource Planning [ERP]).

Essentially, five key elements are required for a successful track-and-trace serialization solution for the pharmaceutical sector:

- Configurability, so that no specific software development is needed,

in a platform that can be easily updated and upgraded, reducing human error.
- Scalability, so that after initial rollout, additional lines can be deployed seamlessly without having to duplicate the entire process.
- Interoperability (i.e., increased flexibility) so that users can choose the hardware that best fits their objectives, allowing them to use existing equipment when possible, and to minimize costs and delays in delivery.
- Site-level management capabilities to cope with change management. Having one centralized point from which configuration and processes can be managed can help to facilitate configuration management, data exchange, reporting, change management, and validation support as well as IT governance. Site-level management capability minimizes risks and help users prepare for future track-and-trace challenges.

PTE: How is the industry moving beyond serialization to the larger goal of traceability?

Minaeff: Modern software companies rarely look past three-to-five-year planning cycles, due to the rapid change of technology and business requirements. However, if we look at the current pace of change in automation, robotics, regulatory requirements, consumer demands (from both customers and manufacturers), we begin to see the increasing role that software must play in manufacturing, to provide lifecycle management and support 'right first time' production goals.

References

1. A. Shanley, "Pharma Serialization Nears a Tipping Point," 2 January, 2018. *pharmtech.com*, www.pharmtech.com/pharma-serialization-nears-tipping-point
2. PharmTech Editors, "FDA Pushes DSCSA Serialization Enforcement Deadline Back to 2018," 5 July, 2017. *pharmtech.com*, www.pharmtech.com/fda-pushes-dscsa-serialization-enforcement-deadline-2018
3. A. Shanley, "Serialization: So Close and Yet So Far," 5 April, 2018. *pharmtech.com*, www.pharmtech.com/serialization-so-close-and-yet-so-far
4. S. Milmo, "Meeting the EU Serialization Deadline," 1 June, 2018. *pharmtech.com*, www.pharmtech.com/meeting-eu-serialization-deadline
5. Press Release, "TraceLink Customers Receive EMVO Approval for Data Submission to the EU Hub," *prnewswire.com*, www.prnewswire.com/news-releases/tracelink-customers-receive-emvo-approval-for-data-submission-to-eu-hub-300660604.html
6. C. Henry, "Concern Voiced About Pharma's Serialization Readiness," 12 April, 2018. pharmalogisticsiq.com, www.pharmalogisticsiq.com/supply-chain-security-track-trace/news/serialization-progress
7. Press Release, "Adents and Microsoft Introduce Blockchain Serialization Solution," 20 June, 2018. *adents.com*, www.adents.com/release-adents-microsoft-introduce-blockchain-serialization-solution-supply-chain-security-3654.html
8. Serialization Innovation: Latest Technologies for the Pharmaceutical Industry, 24 May, 2018. *adents.com*, www.adents.com/article-serialization-innovation-latest-technologies-at-the-service-of-the-pharmaceutical-industry-3422.html **PTE**

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Seeking Regulatory Advice

Knowing and addressing regulatory expectations early on can avoid unexpected delays later, says Siegfried Schmitt, principal consultant at PAREXEL.

Q. Our company is a young, modern enterprise, and our management decided to apply modern, state-of-the-art technologies and methodologies in our manufacturing facility. We have installed automated systems that allowed us to establish process analytical technology (PAT) to formulate a quality-by-design (QbD) approach and enable us to perform parametric release. We intend to submit our application in the United States and in Europe in 2019 or 2020. We were advised by consultants to seek advice from the regulators to confirm that we are on the right track. However, our senior management rejects this idea. Can you give any advice on how to convince them otherwise?

A. First, let me congratulate your management on being a progressive company that embraces modern technology and science as promulgated by regulatory agencies around the world. Though regulators encourage the industry to leverage automation and new technologies, they themselves are not necessarily that familiar with these and may find it difficult to understand the full impact each of them has on product quality and, thus, patient safety. So the question is: when are you going to tell the agency about your innovative approach, at the time of the submission or before?

Regulatory agencies, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the national authorities, all offer scientific advice—all prior to an applicant submitting an application. There is a good reason for that, namely that the regulators are interested in assuring that when they receive an application, it not only complies with the regulations, but it also meets the agency's expectations. Though the healthcare regulations are detailed, they can never cover each and every aspect of the drug lifecycle. There is always room for ambiguity and interpretation. If these issues can be addressed well before an application, then so much the better, as they will not unnecessarily delay the approval of your drug. A win-win situation one should assume.

So why not take advantage of the offering? Maybe there is a thorough belief in one's capabilities and approach to compliance. Maybe you don't dare ask for fear of asking a silly question? Remember the old adage: There's no such thing as a silly question! Avoiding an uncertainty warrants certain disaster. Maybe you expect your questions will not be answered. You won't know until you have tried asking. Maybe you fear you may not like the answer. Isn't it a lot better to know about the agency viewpoint early on?

Clearly, there is a good case for seeking a meeting with the agencies to present your innovative approach. Yes, a lot rides on preparing thoroughly for such a meeting, making sure you present clearly, succinctly, and convincingly. Make sure you seek feedback on those areas that you think may get challenged.

Even if you still cannot convince your senior managers of the undoubtedly great benefits of seeking regulatory advice through such meetings, you can still pursue some alternative channels. These include attending conferences or workshops, where you can meet with peers and regulators, thereby exchanging views and seeking feedback. Or you could actively engage in (special) interest groups through industry associations. You may not get feedback from agency staff, but certainly from industry peers.

It's usually better to ask than to run into unexpected issues with regulatory agencies at the time of your submission. Every day your drug approval is delayed is not only a day of no revenue, it is one day more the patients have to wait for your product. **PTE**

Your opinion matters.

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

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