IF YOU NEED ASEPTIC PACKAGING, BLOW-FILL-SEAL IS THE SOLUTION.

Would you like to fill your liquid or semisolid pharmaceuticals in a more reliable, more economical, and more user-friendly way than is possible with conventional methods? Then it’s high time for blow-fill-seal technology from Rommelag. Our bottelpack systems enable aseptic filling in application-optimized plastic containers, which are directly produced, filled, and sealed by the system. These shatterproof containers are free of contamination and correspond to the filling quantities that you and your clients need. More information on blow-fill-seal technology and your personal contact partner can be found on our website.

www.rommelag.com
COVER STORY
14 Mass Spec Sheds New Light on Biologics Drug Development
Although limitations must be overcome, mass spectrometry is having a great impact on biologic development and manufacturing.

EXCIPIENTS SOURCING
20 Collaboration Key to Meeting Excipient GMP Requirements
Drug manufacturers need to work closely with excipient suppliers to ensure supply chain safety.

FORMULATION
24 Advancements in Extrusion-Spheronization
More agile techniques are improving the development of multiparticulate drug-delivery systems.

EQUIPMENT MAINTENANCE
34 A Risk-Based Approach to Stainless Steel Equipment Maintenance
Laboratory tests can determine critical cleaning parameters for passivation treatments used to prevent rouge on GMP stainless-steel equipment.

EXTRACTABLES AND LEACHABLES TESTING
39 Evaluating E&L Studies for Single-Use Systems
Extraction studies demonstrate approaches for evaluating single-use biopharma manufacturing materials.

COLD CHAIN DISTRIBUTION
46 Cold Chain: Zeroing In on the Last Mile
Longer packouts are becoming the rule.

Peer-Reviewed
26 Establishing Blend Uniformity Acceptance Criteria for Oral Solid-Dosage Forms
This article introduces the concepts of pooled variance and the central limit theorem, which are intended for establishing acceptance criteria for blend uniformity data of granular powder blends when a significant degree of sampling bias is involved.

Columns and Regulars
5 GMP/GDP Inspections
The GMP/GDP Inspections Landscape—Part II: Considerations and Opportunities

10 European Regulatory Watch
Moving Forward with Adaptive Licensing

12 Outsourcing Review
Viewpoint: Challenges and Opportunities for CDMOs

49 Ask the Expert
Ensuring Sterility in Small-Scale Production

50 Ad Index

Join PTE’s community
Join the Pharmaceutical Technology Europe group on LinkedIn™ and start discussing the issues that matter to you with your peers.
Go to PharmTech.com/linkedin
The GMP/GDP Inspections Landscape—Part II: Considerations and Opportunities

The European Federation of Pharmaceutical Industries and Associations (EFPIA) conducts an annual survey of inspections among its member companies, which are research-based pharmaceutical firms. The data (1) generated demonstrated the workload, the use of resources, and the outcome of inspection practices for the oversight of good manufacturing practice (GMP) and good distribution practice (GDP) by domestic and foreign regulatory authorities. Member companies are confronted with more inspections of their manufacturing sites by authorities from other countries (i.e., foreign inspections). Part II of the article describes additional challenges and opportunities to improve inspection efficiency, based on data from the survey (1).

Facts on inspections

Industry and regulators have made the point that inspections are resource-consuming. Here are some calculations based on the data (1).

Estimated resources involved in inspections

Based on data from the EFPIA survey, an estimation of resources per foreign on-site inspection is given in Table I. For on-site inspections, many companies were asked to submit documents prior to inspections. The data showed that the submitted documents helped to focus and reduce the inspection time on-site. The preparation effort might additionally be driven by specific requirements from individual inspectorates. Compared to the regulators, the inspected companies needed 10 times more resources for preparation, conduct, and follow-up of inspections.

Resources calculated as the duration of inspections

The average duration of foreign inspections by country, where more than four inspections were performed (not including paper-based inspections), is shown in Figure 1. Based on the 2015 data of inspections at manufacturing sites, the following can be calculated:

- On average, two inspectors come for each inspection
- Foreign inspections last, on average, 4.1 days at the site, requiring 8.6 inspector days
- Domestic inspections use, on average, 3.1 days per site, requiring 6.4 inspector days
- The industry requires approximately 160 person days for preparation, conduct, and follow-up of inspections
- An average inspection fee is assumed to be €30,000.

For inspectorates, it is assumed 20 person days per inspection (including pre- and post-inspection and travel for experts and participants from corporate departments). For the 486 inspections in 2015, the sum is estimated to be up to 9720 person days.

The 2015 survey (1) asked seven questions on specific and general issues related to inspection practice. These questions covered, for example, noticeable change regarding how inspections have been conducted; unique question content in the scope of inspection that had not been expected; topics raised in inspections that are beyond the announced scope of the inspection; the approach taken by inspectorates to identify data-integrity topics; and if the national agency implemented a risk-based approach for scheduling/conducting inspections.

A summary of the received responses on all the specific questions conclude the following priorities of inspection practices:

- Data integrity with focus on quality control laboratories, pharmacovigilance data, and the manufacturing environment, including the corporate environment

*Stephan Rönninger is director, External Affairs, Amgen (Europe) GmbH; Johanna Berberich is senior manager, Quality Audits & inspections, Bayer; Véronique Davoust is senior manager, Global Quality Intelligence, Pfizer; Peter Kitz is vice-president, Global Pharmaceutical Quality, Bristol-Myers Squibb; and Andreas Pfenninger is member of the management team, Registration, Production, Quality, Environmental Protection, Interpharma.

*To whom all correspondence should be addressed.
GMP/GDP INSPECTIONS

Establishing GDP and oversight
Sterile manufacturing processes and operations
Approaches for application of new and revised or not yet implemented guidelines. Some answers reflected this area to be an "unusual inspection practice" that might represent an opportunity for inspectorates for training of new staff or to challenge regulations in practice.

Considerations to optimize inspection practice
After 12 years of data collection, EFPIA recognizes that there are significant opportunities for better use of resources and suggests the following points for consideration to optimize inspection practice:

- Inspections should be scheduled and conducted using a risk-based methodology. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) model for risk-based inspection planning in the GMP environment could be used as a basis for inspection planning. Regulatory authorities should give first priority to ensuring that manufacturers and affiliates in their own territory are compliant through adequate local oversight.
- Regulatory authorities should give first priority to ensuring that manufacturers and affiliates in their own territory are compliant through adequate local oversight. To this end, information in the EudraGMDP database should be kept up-to-date.
- Foreign inspections should be conducted only if deemed necessary. First of all, such inspections can be facilitated through application of the principle of mutual reliance. Where possible, regulatory authorities should aim to rely on the partner authority’s supervisory oversight, based on risk and best use of resources.

Mutual recognition and mutual reliance
Currently, the exchange of inspection reports and company responses does not seem to reduce the number of inspections; instead, this information is used often as a preparation step for upcoming inspections. Resources could be better leveraged by mutual recognition or reliance on inspection outcomes from trusted inspectorates, for example, from PIC/S member inspectorates. In 2013, EFPIA proposed in a position paper that PIC/S member inspectorates should agree on equivalence of the domestic GMP requirement. This approach could lead to opportunities to reduce the number of redundant inspections by relying on inspections previously conducted by other members who maintain harmonized standards.

Statutory agreements, in the form of mutual recognition agreements (MRAs) or memoranda of understanding (MoU), also offer an opportunity to reduce the number of inspections. For example, the United States is committed to bilateral and multilateral dialogue with other countries (e.g., in form of a MRA with the European Union independent of the Transatlantic Trade and Investment Partnership [TTIP]).

In the longer term, inspection reports along with the inspected company’s responses could be shared in an international inspection database, provided confidentiality issues are addressed and respected.

Increase inspection efficacy
The EFPIA position paper of 2014 proposes effective and balanced risk-based regulatory oversight to improve the use of resources. Inspection efficiency can be improved by harmonization of standards and regulatory processes including:

- Certification process for regulatory inspectorates
- Risk-based approach to inspection

Table I: Estimation of the resources involved in an inspection.

<table>
<thead>
<tr>
<th>Resources</th>
<th>inspector focused approach</th>
<th>Industry holistic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation for specific requirements by individual inspectorates</td>
<td>4 person days (experience from industry audits)</td>
<td>90 person days</td>
</tr>
<tr>
<td>On site</td>
<td>8 person days (on average 2 inspectors for 4 days)</td>
<td>55 person days</td>
</tr>
<tr>
<td>Post-inspection</td>
<td>4 person days (experience from industry audits)</td>
<td>15 person days</td>
</tr>
<tr>
<td>Sum</td>
<td>16 person days</td>
<td>160 person days</td>
</tr>
<tr>
<td>Travel/Fee</td>
<td>+4 person days (2 inspectors for 2 days)</td>
<td>approximately €30,000</td>
</tr>
</tbody>
</table>

Figure 1: Average duration of foreign inspections by country (2015 data; where the European Union is counted as one country). Paper-based inspections are not included.
Veltek Associates, Inc. offers two garment product lines, which are both pre-folded in our EasyGown system. Comfortably styled and fitted with elastic thumb loops to reduce shifting, as well as tunnelized elastic wrists and ankles.

1600 Garments
- Breathable
- Comfortable
- High bacterial efficiency

1700 Garments
- High filtration efficiency
- Low particulate and shedding performance
- Excellent water repellency

Face Masks
- Breathable
- Reduces goggle fogging due to absorption efficiency
- Soft and comfortable

www.sterile.com
Figure 2: Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) facilitates cooperation.

<table>
<thead>
<tr>
<th>PIC/S Member Inspectorate</th>
<th>233/503 inspections (46%) of all foreign inspections in 2015 (32% in 2013; 53% in 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIC/S (pre) Accession Inspectorate</td>
<td>214/503 inspections (23%) of all foreign inspections in 2015 (19% in 2012; 31% in 2013; 18% in 2014)</td>
</tr>
</tbody>
</table>

Sites located in countries of PIC/S Member Inspectorates

Planning and scheduling
- Standard data packs for on-site and paper-based inspections for faster provision of information as well as better facilitation and use of resources
- Standard terminology for categorization and ranking of observations, and standard reporting template
- Globally accepted GMP/GDP certificate format to document compliance of an inspected site
- Global database for sites approved by certified inspectorates. The EudraGMDP database is a source of compliance information of sites inspected globally. EFPIA encourages regulatory agencies from outside the European Economic Community (EEC) and MRA countries to use this platform. EFPIA further suggests global product numbers (International Organization for Standardization [ISO] Identification of Medicinal Products [IDMPI]) could be incorporated into this database.

Interaction with and within industry
- It is proposed that shared inspection outcomes may avoid duplication of effort and help facilitate early access to markets. The reasons for performing unannounced inspections are well understood; however, comparison of the outcomes from the EFPIA survey shows no difference, either for domestic or foreign inspections. The only difference is that unannounced inspections need longer to gain access to experts than announced inspections.

Paper-based inspections
- EFPIA has proposed the development of a standardized preparation documentation package to enable faster provision of information and better facilitation and use of resources (4). This package could include:
  - Site-related information: site master file (PIC/S SMF)
  - Product-related information: annual product/annual quality reviews
  - Quality system-related information: quality manual (reflecting quality management system)
  - Additional compliance information: GMP/GDP certificates for the site, list of inspections, list of internal audits and number of customer/contractor audits, major changes, rejected batches, out of specifications, and others.

Interaction with and within regulators
- Interaction between regulatory authorities might facilitate waivers for inspections. Time to market could be improved if inspectorates exchanged data on inspection activities, including pre-approval inspections. The industry would benefit from a harmonized guidance for inspectorates defining documents to send for a paper-based inspection prior to an on-site inspection.

Interaction with and within inspectorates
- EFPIA encourages PIC/S member inspectorates to rely on conclusions from domestic inspections by PIC/S members. The industry understands that PIC/S does not have a legal obligation to share information, but PIC/S membership does have the opportunity to increase mutual reliance. The data show the potential to take advantage of resources that could be redirected to domestic oversight or higher risk sites. As shown in Figure 2, 46% of foreign inspections were conducted by PIC/S member inspectorates; these inspections resources could be saved by relying on the results of inspections already conducted, such as the GMP certificate of an inspectorate that is a member of PIC/S. To create greater efficiencies, while maintaining an effective programme, the authors believe it is worth encouraging PIC/S member inspectorates to rely on conclusions from domestic inspections by PIC/S member inspectorates.
- Furthermore, the existing EU/EMA joint inspections process can be extended to include the local regulatory authority in foreign countries to provide greater efficiency with the same inspection. The continued use and success of risk-based approaches as applied by long-time PIC/S members can be a role model for new PIC/S member inspectorates to continue building confidence in other PIC/S member inspectorates.
- PIC/S member inspectorates could reference PIC/S–GMP requirements in their inspection report or in a comparison table with the local requirements. In addition, another aspect that the authors believe to be worth considering, is to extend the sharing of inspection reports among PIC/S member inspectorates at a harmonized platform (e.g., EudraGMDP). Continuous education is encouraged, and useful sources include PIC/S trainings/seminars and the PIC/S Inspectors Academy, which can help to build trust among inspectorates. Finally, PIC/S could facilitate mutual reliance on inspections by adopting local statutes.

Conclusion
- The pharmaceutical industry has become increasingly global, and
new risks have emerged, such as falsification of medicines. Although increased cooperation between regulatory agencies has been noted, there is still significant duplication of inspection oversight at manufacturing sites. Avoidance of inspection duplication would allow resources to be directed towards higher risk areas of the supply chain.

Although the number of foreign inspections has not increased, it has levelled at a high number (1). In the 2015 survey, 640 sites from innovative medicine manufacturers received foreign inspections, costing more than 75,000 regulator hours and €80,000,000 spent by EFPIA member companies.

Globally accepted certification systems have proven to be efficient and effective in other industries, such as aviation, nuclear energy, and food. EFPIA advocates the use of a globally accepted GMP/GDP certificate format to demonstrate compliance of an inspected site. Such certificates should be available on a public database. EFPIA suggests that harmonization of inspections of pharmaceutical products is possible, in which the right quality in the lifecycle of inspections is balanced through making best use of resources.

Acknowledgements
Data were evaluated by the following members of the EFPIA GMP network reporting to the Technical Development Expert Group (TDEG): Stephan Rönninger, Amgen (Moderator); Johanna Berberich, Bayer; Véronique Davoust, Pfizer; Peter Kitz, Bristol-Myers Squibb; and Andreas Pfenninger, Interpharma.

Support was provided by Gerd Fischer, Boehringer Ingelheim. The authors thank Michele Hunter for technical writing.

In addition, authors thank the companies that provided input to the survey in 2015 and before: AbbVie, Almirall, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Biogen, Bristol-Myers Squibb, Eli Lilly and Company, Grünenthal GmbH, GlaxoSmithKline, Johnson & Johnson, Merck (MSD), Merck Serono, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Servier, Takeda, and UCB.

References
2. PIC/S, A Recommended Model for Risk-Based Inspection Planning in the GMP Environment, PI037-1 (January 2012).
Early access schemes are bringing in a new regulatory procedure for commercialization of innovative drugs in Europe—both at the national and European Union levels. The EU’s European Medicines Agency (EMA) has given the biggest impetus to accelerated access with its decision in 2016 to press ahead, after the completion of a pilot project, with an adaptive pathway (AP) programme. However, the position of the development of processes for the production of the new drugs within early-access systems remains unclear, especially for biologics whose manufacture is expensive and complex. This is particularly the case for advanced therapy medicinal products (ATMPs)—somatic-cell and gene therapies and tissue-engineered medicines.

The main focus of early access projects is on making medicines for unmet needs, such as rare diseases or conditions that have inadequate treatments on the market, available to patients faster than the normal approval timespan. Under AP, the new drugs are fast tracked through clinical trials to be given marketing authorization with the proviso that the approval will have to be confirmed by real-world data (RWD) once on the market—such as electronic health records, prescription databases, patient registries, claims databases, and patient surveys.

Gathering evidence
The APs programme being adopted by EMA emphasizes the pre-planning of the evidence generation in support of the new medicines—from the preclinical to the post-authorization stages. This planning is done at an early point in drug development, not just by the regulators but with the participation of other stakeholders, such as patient organizations, healthcare professionals groups, and health technology assessment (HTA) organizations that recommends newly approved drugs for reimbursement.

EMA, which is responsible for the EU’s centralized approval of medicines, stresses that the AP is not a new route to marketing authorization. Instead, it offers a new approach to product development and data gathering. Drugs going through the AP procedure will still be approved under existing early access regulations such as those for conditional authorization or compassionate use.

EMA has concluded that a two-year pilot project completed in 2016 had shown that the AP system can be an effective means of bringing different stakeholders together so that they can plan a product’s development in a way that ensures all the evidence needed are obtained. This can be achieved by using real-world data and evidence to complement information from randomized clinical trials (RCTs).

Although the use of APs is not suitable for all products, it is particularly appropriate for supporting the development of medicines in therapeutic areas where evidence generation is challenging, such as infectious diseases, Alzheimer’s disease, degenerative diseases, and rare cancers, according to EMA.

EMA stresses that the AP is not a new route to marketing authorization.

The AP system is based on an iterative approach to drug development. As more evidence is accumulated and more is learned about the benefits of a medicines, the regulator will approve broader applications. “The medicine will first be authorized in a patient population that is likely to benefit most from the medicine,” explained an EMA spokesman to Pharmaceutical Technology Europe. “Then, additional evidence is gathered over time, which potentially results in changes to the marketing authorization—for example, through (process) variations—reflecting the expanded knowledge acquired.”

High costs and lack of funding
Nonetheless, AP and national early-access schemes pose difficulties for companies dealing with the high cost of developing processes for making new biological and other advanced medicines. Companies are expected to provide the drugs free when participating in early access schemes, usually after a Phase III, or even a Phase II, clinical trial. But at this stage, they cannot be sure what reimbursement price the medicine will be given. Furthermore, with some ATMPs especially, all the GMP standards or even regulations for new medicine technologies are still not in place.

“ATMPs can be seen as a type of product where an adaptive approach might be both beneficial and challenging,” the EMA spokesman commented. “In some cases, the acceleration of clinical development might be competing with the refinement of the data on chemistry, manufacturing, and controls (CMC),”
In a report (1) issued in 2016 on its AP pilot project, EMA acknowledges that CMC evolves continuously before and after authorization. “In the context of the lifecycle approach, certain validation and/or upscaling/change activities may be agreed to be conducted post-marketing with the use of appropriate regulatory tools available—e.g., post-approval change management protocols,” says the report (1). “The acceleration of development time presents challenges in delivering a product of appropriate quality for the conduct of clinical studies and reliable supply to the patient,” it continues. “The product used for the clinical trial needs to be representative of the product that will be submitted for approval.”

Many of these difficulties can be eased during the early stages of R&D when companies have the opportunity to discuss plans for a product’s development, including CMC, with the regulator and other stakeholders such as HTA agencies. “The impact of any manufacturing changes must be proactively explored,” EMA explains in the report. “This is particularly true for ATMPs, where initial development costs are high, and logistics complex. It is important to agree on a strategy that ensures that initial clinical data are not invalidated by subsequent manufacturing changes.”

Having to work out the course of CMC development as early as the preclinical phase, however, could push up the production costs of an innovative medicine even further. Some companies have been deterred from entering the United Kingdom’s Early Access to Medicines Scheme (EAMS) because of financial uncertainties stemming from high production costs, according to a review (2) of the two-year-old scheme by PricewaterhouseCoopers (PwC), the London-based professional services company.

The BioIndustry Association, London, representing UK biotechnology companies, has complained about the absence of public sector financial support for product development for projects like EAMS. “The lack of funding poses a barrier to many small biotech companies from engaging with (EAMS),” Steve Bates, BIA chief executive, told Pharmaceutical Technology Europe. “Other nations have funded early access schemes that allow companies to recover some of the costs of engagement.”

Companies which are reluctant to enter early access projects, tend to be SMEs, which have to tread carefully with the development of drugs with high production costs. Only a small proportion of the 18 products selected to participate in the EMA’s AP pilot scheme came from SMEs with those progressing to the final stages of the pilot being developed predominantly by multinationals.

**Gene and cell therapies**

Among the most problematical of new technologies for SMEs and start-ups created by universities and other academic research institutes are gene and cell therapies in which the development of production processes and logistics seems to be lagging behind the progress of the science. They are even proving to be difficult for multinational pharmaceutical manufacturers.

At a London conference on ATMPs development in December 2016, jointly organized by EMA and the Brussels-based trade association European Biopharmaceutical Enterprises (EBE), Steven Howe, head of process research at the Cell and Gene Therapy Platform of GlaxoSmithKline (GSK), Stevenage, UK, listed several production challenges just in ex-vivo autologous gene therapies. These challenges include the scale-up and scale-out of vector production and ex-vivo cell processing, the approach to comparability in production change management, and logistics and supply chain issues.

A major dilemma facing the gene-therapy sector is whether to opt for centralized or decentralized models for the processing and transfer of cells to patients. A regional hub solution could involve not only manufacturing in hospitals but by the bedside of the patient.

“Close collaboration between industry, academia, and regulatory agencies is needed to bring these transformational medicines to a wider patient population,” Howe said. For smaller players in gene and cell therapy and other advanced medicines, there is, on the other hand, greater hope of receiving state funding. Governments are willing to give research grants not necessarily with the objective of helping to provide treatment of unmet needs but to progress development of novel technologies in a new area of medicine.

**Centres of excellence**

Several European countries are anxious to establish centres of excellence for gene and cell therapies in what is predicted to become a fast growing pharmaceutical sector. The UK now has 22 GMP-compliant manufacturing units for gene- and cell-therapy products, many of them in state-funded universities and National Health Service (NHS) facilities. In neighbouring Ireland, GE Health of the US is investing €150 million ($160 million) in an ATMP and biopharmaceuticals project in Cork with staff being trained with the help of the state-funded National Institute for Bioprocessing Research and Training (NIBRT), Dublin.

What role AP and early access procedures will play in the scientific and commercial progress of new advanced technologies remains uncertain. There is a lot of scepticism about AP in Europe among healthcare professionals, patient groups, and academics whose worries include increased risks to patients, doubts about the quality of RWD, and whether drug companies will honour their obligations to provide it and the reversibility of marketing approvals.

APs and other early access systems have a lot to prove—not only that they can work successfully on the regulatory front and can provide positive benefits to patients. They also have to win over a lot of doubters in key areas of healthcare.

**References**

Viewpoint: Challenges and Opportunities for CDMOs

The outlook for the CMO and CDMO industry may be affected by ever-changing politics.

In mid-2016, consolidation, IPOs, pharma-spinouts, and facility selloffs were the major themes in pharmaceutical outsourcing. In the aftermath of the US presidential election, pharma stocks (and other industrials) went up. This giddiness among pharma investors lasted less than a month, ending when President-Elect Trump told Time magazine, in his Person of the Year interview, “I’m going to bring down drug prices. I don’t like what’s happened with drug prices” (1).

There was no elaboration for several weeks, and industry, investors, and the general public alike were in the dark about what he meant and how he might achieve that goal. No one was prepared for his 11 Jan. 2017 press conference (2), in which he complained that pharma companies are “getting away with murder” and said that Medicare should be negotiating with drug companies for better prices. A few days later, he expanded that notion, calling for Medicaid to also have authority to negotiate prices, despite the fact that it expanded that notion, calling for Medicaid to also have authority to negotiate prices, despite the fact that it has “best price” entitlement under current law.

The future of the CMO/CDMO sector

In recent months, the contract manufacturing and contract development organization (CMO/CDMO) industry has seen a major acquisition in Lonza–Capsugel; a significant one in Asahi Glass–CMC Biologics; a pair in which Pharma & Biopharma Outsourcing Association (PBOA) member Catalent acquired two potential PBOA members in Accucaps and Pharmatek; and a large IPO by Samsung Biologics, which seems to value that company as bigger than Catalent and Patheon’s combined market cap.

Where is the CMO/CDMO sector headed in 2017 and beyond? Making predictions is pretty inane at the moment, but the industry should see more efforts at integrating “one-stop” CDMO concepts, along the lines of Patheon’s OneSource model, and that may entail more mid- to large-scale acquisitions, along with strategic purchases for specific technologies.

Regarding the new administration in the United States, the industry is in wait-and-see mode. With the Republican party controlling both houses of Congress and President Trump in the White House, the Republicans will be in a position to implement business, industrial, and healthcare policy that can trickle down to affect the CDMO sector.

Tax reform seems to be the top priority for the GOP (after repealing the Affordable Care Act, the process for which has turned out to be a minefield). Along with a drop in the corporate tax rate, they have pushed for a tax holiday that would allow US-headquartered companies to bring overseas profits into the country at a reduced tax rate, along the lines of the American Jobs Creation Act of 2004, which lowered the tax rate from 35% to 5.25% for a one-time repatriation.

What effect could a large-scale influx of funds by major pharma companies have on CDMOs? Those pharma companies may simply pay out higher dividends to shareholders, but this repatriation could also trigger a wave of mergers and acquisition activity among domestic players, which could lead to shifts in outsourcing allocation. In concert with the GOP’s idea of a border adjustment tax, there may be greater investment in US R&D and manufacturing facilities by in-house pharma, as well as a potential shift from ex-US facilities to domestic CDMOs for products intended for the US market.

Anti-immigration sentiment could become problematic if it keeps high-value scientific personnel from coming to the US. More than one CDMO has expressed concern about potential visa restrictions and their impact on the labour pool.

FDA reform

The US Congress has talked about accelerating generic drug reviews to provide another outlet for bringing drug prices down. While more generic approvals could benefit the CDMO sector, based on this author’s experience inside the GDUFA II negotiations, the US Food and Drug Administration (FDA) does not have a lot of margin to shave from review times.

The appointment of a new FDA commissioner could certainly shape policy in ways that benefit or hinder pharma and CDMOs, but FDA is awfully big, and it’s not the sort of organization that can change direction on a dime. Top-down policy decisions may impact discrete areas (will quality metrics survive the administration’s push for deregulation?), but the day-to-day functions of the agency overall may not reflect the priorities of a new administration very quickly.

It’s all too uncertain at this point, and no Magic 8-Ball is going to point out the correct path. But one can hope that the new administration recognizes the value that the pharma industry brings to the US healthcare ecosystem, the financial and innovative engines that they represent, and the importance of the CMO/CDMO sector. PBOA’s members provide pharma and biotech companies with...
the advanced dose forms, regulatory-compliant manufacturing, and supporting development services that help them develop and manufacture drugs, biologics, vaccines, and other treatments safely and cost-effectively, and I hope we can work with the new administration to continue to bring value to American patients.

**References**


**Impact of New US Administration on Pharma**

For more information on how the new Trump administration may affect the pharma industry, visit PharmTech.com to read the following:

- **President Trump Meets with Pharma Manufacturers**
  www.pharmtech.com/president-trump-meets-pharma-manufacturers-0
- **Pfizer Reacts to Trump’s Comments and Discusses Pipeline in its Q4 Earnings Call**
  www.pharmtech.com/pfizer-reacts-trump-s-comments-and-discusses-pipeline-its-q4-earnings-call-0
- **Does Pharma Really Want to Overhaul FDA?**
  www.pharmtech.com/does-pharma-really-want-overhaul-fda
- **US Election Puts Health Policy in Play**
  www.pharmtech.com/us-election-puts-health-policy-play-0
- **Pharmaceutical Manufacturers Gear Up for Political Change**
  www.pharmtech.com/pharmaceutical-manufacturers-gear-political-change-0

**CALL FOR PAPERS**

Pharmaceutical Technology Europe and Pharmaceutical Technology cover all aspects of pharmaceutical drug development and manufacturing, including formulation development, process development and manufacturing of active pharmaceutical ingredients (both small molecule and large molecules) and finished drug-products (solid dosage, semisolid, liquids, parenteral drugs and topical drugs), drug-delivery technologies, analytical methods development, analytical testing, quality assurance/quality control, validation and advances in pharmaceutical equipment, machinery, instrumentation, facility design, and plant operations.

We are currently seeking novel research articles for our peer-reviewed journal as well as manuscripts for our special issues. For peer-reviewed papers, members of the Editorial Advisory Board of Pharmaceutical Technology Europe and Pharmaceutical Technology and other industry experts review manuscripts on technical and regulatory topics. The review process is double-blind. Manuscripts are reviewed on a rolling basis.

Our single-themed issues, which include literature reviews and tutorials, address excipients and ingredients, analytical testing, outsourcing, solid dosage and more.

Please visit our website, www.PharmTech.com/pharmtech-author-guidelines-and-editorial-calendars, to view our full Author Guidelines. Manuscripts may be sent to Editorial Director Rita Peters at rita.peters@ubm.com.

We look forward to hearing from you.
Mass spec sheds new light on biologics drug development

Although limitations must be overcome, mass spectrometry is having a great impact on biologic development and manufacturing.

Mass spectrometry (MS) is a powerful and sensitive technique used to detect, identify, and quantify molecules separated by their mass to charge (m/z) ratio in the gas phase. In a recent publication by the US Food and Drug Administration (FDA) reviewing MS usage trends over the past 10 years of biologic license application (BLA) filings, the agency determined that MS is now ubiquitous in filings and that the number of ways it is being used is increasing. The demands of life-sciences applications have led to the improvement of MS technologies and rapid growth of new types of instruments that feature powerful analytical capabilities—sensitivity, selectivity, resolution, throughput, mass range, and mass accuracy, according to Gang Huang, vice-president of analytical development and regulatory affairs with WuXi Biologics. In the biopharmaceutical industry today, mass spectrometry finds applications at the earliest discovery stages (e.g., imaging of biomarker/protein binding in cells), during process development, and for product characterization throughout the development cycle, including for release testing.

Challenges with sample preparation and data processing remain, however. Biologics manufacturers and analytical laboratories are working closely with instrument suppliers to address these issues. Improvements are continually introduced, and as a result the potential for additional use of this analytical technology for biologic drug development and manufacturing is significant.

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

Mass spectrometry is widely used for the characterization of protein therapeutics in the development stage. More specifically, MS is an effective tool for intact protein analysis (measurement of the molecular weight of the protein), fragment analysis, peptide mapping, and identification of post-translational modifications (PTMs), according to Tiffani Manolis, segment manager for pharma at Agilent Technologies. As a characterization tool, MS is used to assign the primary structure of biologic drugs, including amino acid sequencing for peptides/proteins, disulfide bond mapping, N-glycan profiling of monoclonal antibodies (mAbs), and nucleotide sequencing for oligonucleotides, adds Jie Ding, associate director of mass spectrometry services at PPD Laboratories’ GMP laboratory.

Peptide mapping can also be applied for determination of other critical quality attributes (CQAs), such as physicochemical properties of oxidation, glycosylation, deamidation, and isomerization and the presence of N-terminal cyclization as well as confirmation N- and C-terminal groups, according to Hillary Schuessler, an investigator with GlaxoSmithKline (GSK) R&D Platform Technology & Science. She adds that characterization of product variants and higher-order structure (HOS) analysis via hydrogen–deuterium exchange (HDX) are also important applications of MS.

In addition, MS can be used for media and feed characterization, such as quantitative targeted metabolomics for amino acids, vitamins, lipids,
Scientists for developing a tailored valuable information to process abundant HCP species provides MS. “The identification of the most (HCPs) is another application for impurities such as host-cell proteins,” says Greg Kilby, manager of biopharma analytical sciences with GSK R&D.

Proiling of process-related impurities such as host-cell proteins (HCPs) is another application for MS. “The identification of the most abundant HCP species provides valuable information to process scientists for developing a tailored process for removal of these critical impurities,” notes Huang. Sanofi uses MS to support process development and manufacturing, including impurity identification and tracking and the collection of detailed, high-level, advanced structural information to confirm that the product is as intended, according to Jianmei Kochling, director of analytical science and technology for the company.

Sequence variant analysis of production cell lines used for biologic production is an important part of process development. The potential presence of sequence variants, which can result from DNA mutations and amino acid misincorporations, is analyzed at the protein level using high resolution MS and data analysis software. From multiple candidate clones, the one without mutations or low level mutations will be chosen as the final clone for further development, according to Huang.

At early development states, MS is used in cell imaging applications, and for characterization of biomarkers and determining drug metabolism and pharmacokinetic (DMPK) profiles (clearance/lifetimes).

These applications are just the beginning, however. “The roles for MS are rapidly expanding to more hybrid qualitative/quantitative applications and the examination of higher-order biotherapeutic structure,” notes Scott J. Berger, senior manager of biopharmaceuticals in the Waters Corporation’s pharmaceutical business group.

Other newer applications include biosimilar development, where MS is an enabling technology to show that an innovator and biosimilar have identical sequence and comparable variant profiles. Similarly, Berger says, the rise of antibody-drug conjugates (ADCs) has required more advanced liquid chromatography (LC)–MS laboratory workflows for challenging separations, mass detection, and data processing to determine the average number of drug conjugates (DAR) on a molecule, their distribution across the many possible sites of reaction, and individual occupancy levels for each of these sites on these hyper-complex molecules.

**Mass spectrometry is a more targeted method that provides detailed information about protein structure/conformation.**

**Why MS?**

Mass spectrometry is a preferred analytical technique in many of these applications because it is a more targeted method that provides detailed information about protein structure/conformation, whether for the desired product or impurities like HCPs that are present at low concentrations.

The sensitivity and specificity, high mass accuracy at low part per million levels, and ability to return precise chemical information on the molecule of interest are main drivers for using mass spectrometry, according to Kilby. Additional attractive characteristics include compatibility with most chromatographic methodologies, the ability to gain both qualitative and quantitative [relative and absolute] information, and the lack of any theoretical limitations on the size of proteins that can be analyzed.

“MS is an ideal tool for supporting process development and a quality-by-design approach. For process impurity identification, it is much more specific than ELISA (enzyme-linked immunosorbent assay) testing, which is the conventional method (and is still used for rapid product release),” Kochling says.

Mass spectrometry is also preferred in these applications because it offers superior sensitivity and specificity without the need for a large volume of samples, according to Ding. “Furthermore,” she adds, “there is a plethora of knowledge and well-established procedures for LC–MS/MS analysis of biologic drugs, from sample preparations to software-assisted data interpretation.”

Berger also notes that MS provides more confident qualitative mass analyses and makes it possible to identify a single peptide or modified peptide in the presence of the many other peptides that are generated in the digest of a biotherapeutic protein, even if that peptide is fully or partially co-eluting with other components. “Monitoring of multiple mass channels simultaneously allows for monitoring of several components at the same time, and in many cases without the need for optimizing the separation conditions to get valuable quantitative information,” he says.

In addition, the ability to detect components at levels lower than optical detection-based assays expands the dynamic range of detection of an assay for the peptide mappeak of a peptide or its variant, according to Berger.

Overall, observes Manolis, MS is an indispensable tool for peptide and protein analysis due to its speed, sensitivity, and versatility. “MS is particularly useful for gaining knowledge about the location of disulfide bonds and amino acid sequences,” asserts Kochling. Adds Mario DiPaola, senior scientific director for Charles River Laboratories: “No other analytical technique can provide the extent of information obtained by mass spectrometry, nor the selectivity or sensitivity. Previously it would have taken months to determine or confirm the entire sequence of a protein by first collecting enzymatic digests and then performing Edman degradation, but now the
same analysis can be performed in a matter of days with mass spectrometry while using micrograms of product rather than milligrams.”

**Continuous improvement**

Several advances in technology have been enabling the wider use of MS. Examples include developments in high-resolution mass spectrometry, such as quadrupole time-of-flight (QTOF) and orbitrap technology, and workflow-driven software development, according to Ding. Ion mobility methods have made MS useful for HOS analysis, cysteine variant determination, and N-Glycan profiling, while top- and middle-down analyses, which have been made possible through the introduction of electron transfer dissociation (ETD) fragmentation, are useful for determination of CQAs and identification of product variants, says Schuessler.

While not very recent, DiPaola points to the introduction of tandem mass spectrometry and the electrospray ionization (ESI) interface as key advancements in the field of mass spectrometry. ESI has allowed for easy coupling of a high-performance LC (HPLC) system to a mass spectrometer, as a key advancement because it permits separation of species followed by direct in-line mass analysis. Hybrid mass spectrometry has made it possible to obtain very detailed information on PTMs and protein primary structures.

The introduction of a variety of other alternate methods to collisional induced dissociation (CID), including electron capture dissociation (ECD), higher-energy collisional dissociation (HCD), electron transfer in the higher-energy collisional dissociation (EThC), ultraviolet photodissociation (UVPD), and surface induced dissociation (SID), among others, have led to significant improvements in fragmentation technology, according to DiPaola. Some of these fragmentation methods can be used independently or in-series to garner as much information about protein analyte as possible.

One of the most powerful developments in the evolution of MS technology, says Huang, is the commercialization of hybrid instruments. “Hybrid MS instruments are made by combining two different types of mass analyzers together in tandem; one can choose almost any combination of quadrupole, time-of-flight, or ion-trap hybrids. These hybrid instruments promise the ability of combining the best features from the different components and allow tandem mass spectrometry experiments and unique scanning modes that are not possible on a single instrument,” he explains.

Berger adds that the increasing focus on hybrid quantitative/qualitative workflows favours TOF-based platforms that do not suffer the lower-end dynamic-range limitations of automatic gain control (AGC)/orbitrap-type instruments. “Time-of-flight and quadrupole time-of-flight MS technology has been the primary high-resolution MS tool used for biopharmaceutical characterization and monitoring due to its ability to maintain high resolution and sensitivity independent of the mass of a species, and the ability to do so with increasingly rapid LC and CE (capillary electrophoresis) separations on the front end of these analyses,” he explains.

**Hybrid instruments and bioinformatics tools are advancing research using mass spectrometry.**

Various bioinformatics tools associated with MS analyses, such as pathway mapping/analysis, network association, and ADC calculators, have had an impact on the use of MS as well, notes Kilby. “Each major instrument vendor has software that works specifically with its instrument and uses complex algorithms to process its proprietary data files. Vendors constantly seek feedback from users to improve software features, such as chemical intelligence, batch data process, automation, report generation, US Title 21 Code of Federal Regulations Part 11 compliance, and so on,” agrees Ding.

More specifically, Manolis notes that dedicated data analysis software has been developed for biopharma applications, and the workflow-specific design this software has streamlined the process. “In addition,” she says, “walkup software has been developed to enable MS novice users, such as biologists, to have access to high-end MS instruments. Special consideration has also been given to providing total workflow solutions to address sample preparation all the way to reporting.”

Overall, Berger believes that the expanded use of MS in more targeted biotherapeutic CQA monitoring experiments, even in later (regulated) development and quality control (QC) environments, is related to the increased robustness of the instrumentation, growing usability of these systems, and deployment on informatics platforms designed for regulated environments. “The ability to follow specific product variants in a peptide map, intact mass profile, or released glycan profile enables targeted quantification of the amount of that modification as an organization develops and matures its manufacturing processes or sets specific limits of a variant in a QC release test,” he explains.

The other area of great expansion has been in HOS analysis, according to Berger. The development of ion mobility MS has introduced the ability to measure collisional cross-section (CCS) data for molecules, bringing an added level of separation to MS analysis and generating data based upon gas-phase cross-sectional area and shape, in addition to the traditional mass and charge characteristics measured by a mass spectrometer. Biologic folding interactions and stability can be screened and assayed using this type of ion mobility information. In addition, Berger notes that more resolving HOS information can now routinely be provided by hydrogen deuterium exchange MS (HDX–MS), which measures the accessibility of backbone amide hydrogens to exchange with deuterated water in solution. HDX–MS is being used to define the interaction of a mAb and its target (epitope mapping) for intellectual property (IP) filings and to demonstrate structural...
Lonza has been a reliable partner in the life sciences industry for over 30 years. Our experience in biological and chemical development and manufacturing has allowed us to create a broad platform of technologies and services for fine chemicals, advanced intermediates, active pharmaceutical ingredients (APIs), functional ingredients, biologics, cell and viral therapies.

We are committed to continued innovation with a focus on future scale-up technologies and emerging markets. Whether you are an established pharmaceutical company or an emerging biotech, Lonza is prepared to meet your outsourcing needs at any scale.

Why Outsource with Lonza?

- Full range of services from preclinical risk assessment to full-scale commercial manufacturing
- Advanced technologies and optimized processes to streamline your product pipeline
- 10 contract development and manufacturing sites worldwide
- Experience with worldwide regulatory authorities
- Track record in meeting accelerated timelines associated with breakthrough therapy designated products
- Dedicated project teams committed to comprehensive and timely communications
- Lean, sustainable processes that minimize waste and environmental risk

For more information, contact us at:
North America: +1 201 316 9200
Europe and Rest of World: +41 61 316 81 11
custom@lonza.com

www.lonza.com/oursites
Comparability between innovator and biosimilar biotherapeutics.

**Workflow Limitations**

With current MS technology, there is a disconnect between the practical and actual time it takes to complete complex analyses, according to Kochling. “The analysis of proteins is very complicated, and even with current mass spec instrumentation and software, a significant amount of manual labour is required, and in some cases it can take up to one month to complete an analysis, which is not practical in an industrial setting,” she states. “Although mass spec technology has been ever improved in sensitivity and dynamic range, the hardware capability is ultimately limited by the complexity of samples. Sample preparation technology and procedure improvement can compensate for the instrument capability in sensitivity and dynamic range,” she continues.

Current mass spectrometers were designed and optimized for the analysis of smaller molecules, and as a result large protein molecules often suffer from poor data quality resulting from limited resolution, sensitivity, and mass range, adds Manolis. She notes that additional alternative and optimized fragmentation methods for large molecules for top-down and middle-down analysis are desired. On the other hand, Berger believes that MS systems are designed to be general-purpose platforms for both large- and small-molecule studies, with compromises on some specific performance attributes for large molecules to accommodate a wider range of applications in the lab.

At GSK R&D Platform Technology & Science, poor parallelization is an issue; currently it is not possible to highly multiplex MS analyses without buying extra mass spectrometers (compared with genomic and microarray technology, for example). In addition, as resolution and scan speed increase, files sizes are getting very large such that current informatics suites struggle with data analysis, especially for large experiments, according to Schuessler. “With the enormous volume of data being generated, data processing and analysis become increasingly important and remain a bottleneck,” agrees Huang.

Furthermore, according to DiPaola, the analysis of these files requires sophisticated and expensive software, as well as highly skilled and knowledgeable users. “Both of these scenarios present recruiting and financial challenges for laboratories and companies,” he asserts.

**Buffer Incompatibility, Complex Software, and the Need for Skilled Users Present Workflow Challenges for Biologics Applications.**

Kilby also points to the incompatibility of MS with commonly used biologic matrices/buffers/detergents, issues with samples that have extended dynamic ranges (HCPs, serum proteomics, etc.), integration in process analytical technology and continuous flow manufacturing, and the fact that response factors are not universal (unlike for UV, charged-aerosol, and evaporative-light-scattering detectors).

The need to label or spike analytes with an appropriate isotopically labelled species to obtain highly quantitative results due to the ionization variability of species is one issue for DiPaola. Another is the difficulty of detecting low-level impurities (<1–2% in abundance) in biological samples without some prior knowledge of their type. A third issue for DiPaola is the need to confirm isobaric amino acids when conducting sequencing by MS/MS using Edman degradation, which becomes a bottleneck because the peptides containing such isobaric amino acids must be collected and individually sequenced.

Finally, DiPaola notes that the high cost of mass spectrometers presents another obstacle, especially when dealing with high-resolution, tandem systems. “Affordability is a sizable issue for small laboratories and companies with limited financial capacity. Additionally, these systems are rather complex and delicate, so that any repairs can only be performed by skilled engineers, adding additional costs,” he explains.

Berger asserts that many of these limitations with mass spectrometry today do not involve the instrument itself, but other elements of the analytical workflow that interact with the system. “Faster and more robust sample preparation is needed to match the improvement in back-end data processing throughout for many applications of MS in the biopharmaceutical industry,” he notes.

For instance, Berger points to clone screening and other early development activities, where reproducible microscale and nanoscale separations remain a challenge to many MS users. “Waters has developed a chip-based microfluidic platform, the ionKey/MS System, that simplifies the process of microscale LC–MS of proteins and peptides, but the industry is looking for further innovations that raise usability of systems at the microscale to that of analytical scale LC–MS,” he observes.

**MS Technology Developments Underway**

To address throughput issues, there is, according to DiPaola, an effort to transition from serial data acquisition to parallel acquisition. “In combination with novel data interpretive software tools, this move should make possible the multiplexing of data acquisition and analysis for peptides, intact proteins, and whole protein complexes,” he says. He also expects new data formats, compression methods, and storage architectures to be introduced to address file size, storage space, retrieval, and speed of data analysis issues.

Researchers at GSK R&D Platform Technology & Science are excited about a number of new developments in MS technology, including platform-neutral, multi-vendor solutions such as the software suite for biopharma applications from Protein Metrics; integrated analyzers for process monitoring, such as the Waters ACQUITY QDa Mass Detector; commercial solutions for ion mobility, HDX, and ETD fragmentation; and...
capillary electrophoresis devices that can be attached directly to the MS source such as 908 Devices’ ZipChip, which are fast and sensitive and offer the potential for rapid CE–MS analysis of peptide maps, intact proteins, charge variants, and metabolites, according Kilby.

DiPaola also expects high-resolution, top-down or bottom-up systems combined with novel fragmentation techniques and improved analysis software to be available in a year or two that will overcome the isobaric amino acid issue for de-novo protein sequencing by mass spectrometry. He also notes that new dissociation methods such as CID, HCD, ETD, and infrared multi-photon dissociation (IRMPD) are generating new acquisition paradigms that require more systematic data collection. “New software tools and algorithms with compliance to 21 CFR Part 11 requirements are in development to address these new data acquisition paradigms,” he asserts.

In essence, major developments efforts can be divided into two disciplines, according to Manolis. “From a physics perspective, significant advances in instrument design are very close to release that will greatly improve not just the capability to analyze large biomolecules, but also the reproducibility of such analyses. On the biology front, advancements in data analysis software that can make clear biological sense of the rich data collected by mass spectrometry is critical for multiple applications. Combining these efforts with the latest capabilities in automated sample preparation and separation techniques allows for a big step forward in the total confidence in using mass spectrometry for biopharmaceuticals,” she states.

More advances expected long-term

Despite the advances in MS technology achieved to date, those in the industry expect further notable improvements in the long term. “Research in electron transfer dissociation (ETD), top-down and bottom-up proteomics, high-resolution mass spectrometry (HRMS), and software-assisted structural elucidation will have lasting impact on biologics analysis,” Ding observes.

Huang also believes that multi-attribute methods that utilize LC/MS for separation, identification, and quantification of post-translational modifications will have potential to replace multiple purity methods currently used for protein product release testing. “With this approach, there will be fewer methods for product release testing but richer product critical quality attribute information obtained,” he comments.

Despite advances in mass spec technology to date, industry experts expect further improvements in the long term.

While current MS technology has been primarily limited to the analysis of in-vitro proteins, proteoforms, and multi-protein complexes, the future drive in mass spectrometry is to study the same entities in vivo to determine native biological structures and their dynamics within biological processes, according to DiPaola. “New MALDI [matrix-assisted laser desorption ionization] imaging spectrometers are available and more advanced models will be soon introduced for spatial mapping of entities of interest, including proteins, signaling molecules, etc., in tissues and eventually in single cells,” he says. Data files for imaging experiments are starting to approach “Big data” definitions, though, and thus challenge most existing software tools, according to Kilby.

In a similar vein, Kilby notes that the application of MS to quantitative whole body imaging, which is currently very expensive and requires the use of radiolabelled compounds, would allow analysis of all compounds present in a given location, not just the radiolabelled ones, without the need for radiation. “There is a long way to go, however, to extend dynamic ranges and improve compatibility with salts and other materials present in untreated biologic samples, and it is not yet known whether it will be possible to return quantitative results,” he says.

One of the biggest challenges Waters is taking on, according to Berger, is to enable more people in biopharmaceutical organizations to leverage the resolution, sensitivity, and dynamic range offered by mass spectrometry. “We also want to raise the dependability of higher-performance instruments to match that of optical detectors that are routinely used in biopharmaceutical labs today. Photodiode array UV/Vis detectors were once viewed as too complicated for regulated environments, but today we rarely give them a second thought about their applicability for the analysis of pharmaceuticals. My hope is that high-performance MS analysis will soon be seen the same way,” he says.

The goal on the horizon, according to Manolis, is to extract the most information for the least amount of effort. “Can we get to a point where we can directly analyze a biopharmaceutical sample without any time-consuming sample preparation and get all the information about the sample we need?” she asks. “To do so will require improved fragmentation techniques, greater dynamic range, and software tools that can pull more information out from a single sample, as well as aggregate data across the development cycle,” Manolis asserts.

Kochling certainly expects greater applicability for mass spectrometry in the biopharmaceutical industry. “MS is already providing great benefits to biologics development and manufacturing. Although improvements in data processing software for throughout enhancement are still needed, mass spec technology has advanced dramatically in the past 25 years. It is exciting to think about how its capabilities will be expanded over the next 25.”

Reference

Recently adopted regulations in the European Union, United States, and Japan require pharmaceutical manufacturers to ensure that the excipients they use are produced in compliance with current good manufacturing practice (cGMP) regulations. Doing so can be quite challenging; however, drug makers can use hundreds of excipients from as many different suppliers. In addition, the pharmaceutical market accounts for only a fraction of the sales for many excipient producers. Several different voluntary standards and guidance materials have been developed by industry to help both drug companies and excipient suppliers meet GMP requirements, and regulatory agencies encourage the use of third-party auditing of excipient suppliers against these standards to ensure that they are using excipients that meet cGMPs. Adding to this challenge is the continual development of excipient regulations in emerging markets, such as China and Brazil.

Meeting these more stringent and evolving global requirements for excipients requires close collaboration between pharmaceutical companies and their excipient suppliers. Two-way exchange of information is necessary to ensure transparency and security of the excipient supply chain.

Significant recent developments

There has been an overall increase in regulation of the pharmaceutical market, some of which impact excipient use, according to Christian Becker, pharmacist, regulatory and external affairs for the global segment management pharma solutions at BASF. “There are new regulations that directly apply to the manufacturers of pharmaceutical excipients (e.g., the bundling procedure in China) but more often, excipient manufacturers are indirectly affected by guidelines that apply to drug manufacturers. To comply with such guidelines, drug manufacturers depend on forming close collaborations with reliable excipient manufacturers,” he says.

The US FDA Safety and Innovation Act (FDASIA) and the European Falsified Medicines Directive (FMD) are probably the most far-reaching regulations impacting pharmaceutical excipients in recent years, according to James Morris, director, pharma biotech with NSF International. “The need under FMD to complete formalized excipient risk assessments by March 2016 set an aggressive timeline for the pharmaceutical industry. And while risk assessment guidance is available, it is up to pharmaceutical excipient customers to ensure that excipients purchased meet the appropriate GMP requirements for the products they manufacture,” he observes.

The International Council for Harmonization Q3D Guideline for Elemental Impurities (ICH Q3D) (1) has also presented issues for excipient suppliers and their customers. It applies a risk-based approach that creates challenges with respect to determining how to assess and quantify risks with non-API materials, including excipients, according to Patricia Rafidison, global regulatory compliance manager with Dow Corning.

Excipient manufacturers are expected to provide a risk-management plan or analytical data on intentionally added elements to enable drug manufacturers to comply with the guideline; however, the declaration of metal catalysts may become an issue if the identity of the metal constitutes crucial production know-how, according to Becker. “Many discussions are ongoing to determine the best risk management/risk assessment approaches and the most effective strategies to be adopted by the pharmacopoeias around the world,” Rafidison says.

Changes in excipient regulations are also occurring more rapidly than expected in developing regions, often with adoption of regulations modeled after those in the US and Europe, according to Rafidison. For instance, the new Chinese regulation came into force in August 2016 and replaces the existing Import Drug License (IDL) system for excipients imported into China. Going forward, excipients will be reviewed only in conjunction with a drug approval application (bundling), similar to the process in the US and Europe.

In addition, Rafidison notes that pharmacopoeias have now been established in many different countries, and despite some...
MEGGLE’s monodispersed combination of alpha-lactose monohydrate, MCC and starch is the world’s first high-functionality, triple co-processed excipient. It is specifically designed to ease oral solid dosage form development and manufacture, and is highly suited for direct compression (DC). The benefits speak for themselves. And for CombiLac®:

- Excellent compactibility
- Excellent flowability
- Fast, hardness-independent tablet disintegration for effective API release
- Low friability
- Overcomes individual ingredient compaction and handling limitations

CombiLac® from MEGGLE:
Combining the best of both.
Excipients Sourcing

Successful harmonization efforts most have differing specifications, which presents difficulties for companies looking to sell their products in multiple markets. Overall, there has been a greater focus on excipient quality and the security of the total excipient supply chain. “Drug manufacturers are actively working to comply with newer regulations, which has translated into increased requirements for excipient suppliers ranging from the completion of numerous questionnaires to greater numbers of customer audits,” states Rafidson. She adds that voluntary industry standards, such as NSF/IPEC/ANSI 363: Good Manufacturing Practices (GMPs) for Pharmaceutical Excipients (2) and the EXCIPIACT GMP and GDP standards are helping companies overcome compliance challenges and providing opportunities for drug manufacturers and excipient suppliers that proactively implement them.

Communication is essential

“It is important to keep in mind that new regulations generally are introduced to enhance patient safety or otherwise improve things for patients, and the entire supply chain is responsible for meeting the new requirements,” asserts Gary Lord, global strategic marketing director, medical solutions, with Dow Corning. He adds that the best relationships involve two-way dialogues, with excipient suppliers providing more than products at the lowest cost. “Everyone needs to be vested in helping develop the best medicines for treating unmet patient needs,” he says.

Indeed, in the highly regulated pharmaceutical market, both parties depend on a close and forward-looking collaboration to be successful, according to Becker. “Reliability is key for long-term partnerships, which are beneficial in a business that involves protracted processes such as drug development and approval,” he notes.

Another ongoing difficulty, according to Morris, is the fact that the pharmaceutical sector represents a small portion of the total excipient market, since excipients are also used in foods, cosmetics, and other products. “Even so, regulators expect pharmaceutical companies to justify their selection of excipients and ensure that excipients are manufactured in compliance with appropriate GMPs. In practice it is often not easy since the pharmaceutical client may represent a small fraction of the excipient manufacturer’s total sales,” he observes.

Third-party certifications

To be able to justify excipient selection during development, therefore, pharmaceutical companies must form strong partnerships with their excipient manufacturers. “It is incumbent on both suppliers and their buyers to establish mutually beneficial supply agreements and leverage third-party audit and certification programmes to meet regulatory expectations in a cost-effective manner,” Morris concludes.

The regulatory requirement to perform supplier risk assessments, in fact, warrants the use of excipient GMP certification schemes to demonstrate ongoing assurance that the most current GMP requirements are being met by the excipient manufacturer, according to Morris. “GMP certification by an accredited certification body provides a level of quality assurance which will, in many cases, satisfy and preclude an on-site company audit,” he asserts.

Pharmapack Europe announces 2017 award winners

Advances in pharmaceutical packaging were recognized on 2 Feb., 2017 as the winners of the 2017 Pharmapack Awards at Pharmapack Europe in Paris, France.

Pharma Compliance Pack from August Faller GmbH & Co., which incorporates perforated tabs that are removed before a tablet is taken, received the Best Exhibitor Innovation for Patient Compliance. The blisters can only be withdrawn in portions, ensuring the patient takes the medication at the right time, in the correct order, and in the prescribed amount.

Intuityject by EVEON, selected as the Best Exhibitor Innovation for Ease of Use and Patient Compliance, is an automated injector that adapts to vials. The platform provides automated preparation and administration, with a modular design to adapt to primary containers.

Multi-Color Corporation’s SMART Packaging Solution, which includes interactive touchpoints for use throughout the drug supply chain, was recognized as Best Exhibitor Innovation for Patient Safety. The solution offers security and logistics management for traceability and tamper evidence.

Nemera’s Safelia, awarded Best Exhibitor Innovation for Patient Centricity and Customization, is an autoinjector used for the delivery of 1-mL and 2.25-mL prefilled syringes that administers both high volumes and high viscosities through thinner needles. Safelia provides automatic needle insertion, injection, and needle retraction and can be customized to specific patient cohorts and formulations.

Otezla (apremilast) Titrition Pack by Celgene was recognized in the health products category. The Titrition contains three different strengths of Otezla pills (10mg, 20mg, 30mg) and promotes patient adherence and compliance to the dosing regimen.

The Compact Box, created through a partnership of Sanofi Pasteur and Campak, was also recognized in the health products category for a design that improves patient compliance to titration-dosing schedules. The Titrition contains three different strengths of Otezla pills (10mg, 20mg, 30mg) and promotes patient adherence and compliance to the dosing regimen.

“The Compact Box, created through a partnership of Sanofi Pasteur and Campak, was also recognized in the health products category. The technology reduces packaging volume by 50% and eliminates the need for PVC blisters. The cold chain benefits of the Compact Box include a 30% improvement in distribution costs.”

–The editors of Pharmaceutical Technology Europe
Follow the leaders
Leaders, including large and small companies committed to the pharmaceutical industry, actively seek open communication and transparency with their excipient suppliers. They also clearly define the intended applications for the excipients they purchase, according to Rafidison. “It is essential for the excipient supplier to understand the intended use so the appropriate grade/product can be recommended. There must be trust in the supplier-customer relationship, limited information sharing leads to limited understanding, which only creates further issues,” she notes.

These companies leverage industry resources through IPEC, NSF International, and Rx-360 to understand and comply with the new regulations, according to Morris. Drug manufacturers that are proactively working to comply with the newer excipient regulations are also organized and typically have systems in place to conduct supplier risk assessments, either themselves or through third-party certification programmes. “These companies are working closely with suppliers like Dow Corning to find mechanisms for minimizing the work load and optimizing the output,” asserts Rafidison.

Lord would like to see harmonization/standardization of questionnaires and quality agreements, so that resources could be freed up for more important work. Becker, meanwhile, would like to see regulatory-affairs groups on both sides becoming involved at earlier stages of new development projects not only to help identify solutions for potential regulatory hurdles in advance, but also to allay ungrounded concerns.

Choose the right excipient suppliers
Selecting the right excipient supplier is crucial given the heightened emphasis on ensuring security of the entire excipient supply chain. Suppliers should be knowledgeable about the unique needs of the pharmaceutical industry and its complex regulatory landscape and share that knowledge through active participation in industry conferences, working groups that influence the development of new regulations, and trade associations that prepare guidance documents and tools, according to Rafidison. The best excipient suppliers also willingly provide information needed for customers to complete risk assessments and take the initiative to ensure compliance through the establishment of comprehensive quality programmes. Morris adds that pharmaceutical manufacturers should look for excipient suppliers that have proactively evaluated their level of GMP compliance against one or more of the voluntary industry standards and ideally sought certification from an accredited certification programme. “These excipient suppliers will ultimately reduce their audit burden, increase GMP awareness internally, and increase the value they offer,” states Morris.

Suppliers should be knowledgeable about the unique needs of the pharmaceutical industry and its complex regulatory landscape.

Many excipient suppliers are constantly working hard to improve the quality of their materials, according to Keith Horspool, vice-president of pharmaceutical development in the US for Boehringer Ingelheim Pharmaceuticals. “They are also making robust efforts in conjunction with the US Food and Drug Administration (FDA) to improve the content of the Inactive Ingredient Database (IID),” he adds.

Suppliers with long-term experience in the development and manufacture of excipients, a broad product portfolio that provides solutions for nearly any formulation problem, and a good reputation with regards to high quality standards and regulatory compliance will be the best choice for drug manufacturers to be successful in a highly regulated and competitive market, says Becker. “Instead of pure product supply, we support our customers with expertise in R&D, drug formulation, and regulatory affairs,” he adds. Asserts Rafidison: “Working with excipient suppliers who invest in innovation and provide targeted expertise can help pharmaceutical companies speed up new drug development and shorten time to market all around the world.”

Need for novel materials
In fact, novel excipients are taking on increasing importance as enablers of product development, according to Horspool. “The need for such materials has never been greater based on the ability of new excipients to improve product profiles (more consistent performance), to facilitate new product processing concepts such as continuous manufacturing, and to enable new therapeutic entities to be formulated into efficacious products,” he states.

To realize the potential and value of novel excipients, however, the regulatory process for their acceptance needs to be modernized. At present, novel excipients are approved as part of a new drug approval that creates a huge challenge and risk to excipient developers and pharma companies in adopting a new excipient in conjunction with an important new therapeutic. “This situation is becoming increasingly difficult and is leading innovators in new excipients to question whether investments in this area are commercially viable. Both pharma/biotech and excipient developers regard this as a critical topic to address and a joint IQ/IPEC-Americas Initiative is ongoing to solicit support from FDA to revise current regulatory processes that are an impediment to future development and adoption of important novel excipients,” observes Horspool. In addition, a request has been made for a Critical Path Initiative Meeting in 2017 to discuss a potential qualification process in early clinical development for novel excipients outside of the drug approval process.

References
2. NSF International, NSF/IPEC/ANSI 363: Good Manufacturing Practices (GMPs) for Pharmaceutical Excipients (December 2014). PTE
Pellets have gained considerable popularity as multiparticulate delivery systems. Widely demonstrated to enable more even and predictable distribution and transportation of APIs, they also contribute many therapeutic advantages, such as lowered risk of side effects and less irritation in the gastrointestinal (GI) tract. At the same time, they can offer a range of technological advantages, including ease of capsule filling due to better flow properties, ease of coating, enhancement of drug dissolution, and the production of less friable dosage forms. In addition, pellet-based delivery systems can be used to develop combination products. A combination of drugs can be blended and formulated in a single dose, offering the potential to enhance patient compliance.

Depending on the type of equipment and processes selected, pelletized dosage forms can be prepared through a number of techniques, such as extrusion and spheronization, rotogranulation, solution and suspension layering, dry powder layering, and spray drying. This article looks at the extrusion-spheronization technique, its advantages, and the steps, skills, and technologies involved. It also assesses some of the drawbacks related to traditional extrusion-spheronization methods, and how recent developments in the preparation of pelletized dosage forms are bringing technical agility, simplicity, and speed to the development processes.

**Pellet drug-delivery systems**

Pellets, or multiple unit dosage forms (MUDF) as they are widely known, are small, free-flowing, spherical particulates manufactured by an agglomeration process that converts fine powders or granules of bulk drug substances and excipients into spherical units. Ranging from 0.5 mm to 1.5 mm in diameter, they can be consumed directly or may be formulated in tablets or capsules. Pellets consist of a drug core surrounded by layers of other excipients and covered by a polymer coating. Depending on the type of polymers used, various release profiles can be achieved including targeted, moderate, sustained, or pulsed release.

**The benefits of pelletization**

Pellet technology offers many benefits when compared to simple tablet or capsule delivery methods. Applicable to a wide range of therapeutic indications, it can provide a high degree of flexibility in the design and development of unique oral dosage forms. Pellet formulations are most commonly used for modified-release applications due to the technique’s ability to create different release rates using the same drug substance. The technique also offers the capability to administer one or more drug substances in a single dose form, which means substances with known incompatibilities can be combined into a single product (e.g., 50% of the pellets in a capsule could be for one condition, and the remainder for another). These drugs can then be delivered to the same site or at different sites within the GI tract. The technique also allows the combination of pellets with different release rates of the same drug in a single dose form.

**The technique also allows the combination of pellets with different release rates of the same drug in a single dose form.**

Pellets disperse freely in the GI tract because of their small size, invariably maximizing drug adsorption, while reducing peak plasma fluctuation. They also minimize side effects without reducing bioavailability. Finally, pellets offer the potential to overcome patent challenges in the manufacture of generic products by providing a new way to deliver a particular drug.

**Extrusion-spheronization**

The most widely used pelletization technique for controlled-release applications is extrusion-spheronization. The technique produces pellets with a high drug loading capacity, which makes it particularly effective for poorly soluble APIs.
The multi-step process includes seven stages to convert a pharmaceutical formulation into a spheronized product:

- **Dry mixing**—The dry mixing of ingredients achieves a homogenous powder dispersion.
- **Wet massing**—A wet granulation method is then used to produce a sufficient plastic mass for extrusion.
- **Extrusion**—During the extrusion stage, rod-shaped particles of uniform diameter and shape are produced from the wet mass. These particles are known as extrudate.
- **Spheronization**—The extrudate is placed on a rotating friction plate where it is broken up into smaller cylinders with a length equal to their diameter. These cylinders are then rounded as a result of frictional force.
- **Drying**—The drying stage achieves the desired final moisture content. Pellets can be dried at room temperature or at an elevated temperature in a fluidized-bed drier.
- **Screening (optional)**—In this final stage, pellets are screened to achieve a targeted mean size.
- **Coating (optional)**—Any additional coating applications (whether functional or cosmetic) that may be necessary are then added.

**Pellets offer many unique advantages both in terms of manufacturing and therapeutic benefits.**

**The benefits of extrusion-spheronization**

Extrusion-spheronization creates a highly efficient and streamlined pathway to the development of pellets. Besides the fast processing capabilities and simplified design, pellet formation by this technique produces more spherical pellets and offers more advantages than any other process. Indeed, one of the primary benefits is particle size distribution controls that ensure less variability and improvements in flow properties. In addition, ease of operation, high-throughput with low wastage, and the production of pellets with low friability, all bring their own unique advantages.

The technique offers the ability to incorporate higher levels of APIs without producing excessively large particles. Two or more actives can be combined in any ratio, in the same unit. Physical characteristics of the active ingredient can also be easily modified, to produce particles with high bulk density, low hygroscopicity, and a smoother surface.

**An alternative to the multi-step extrusion-spheronization technique is rotogranulation, direct pelletizing, where spheroids are produced directly from powder.**

Although the extrusion-spheronization process is a highly promising technique for the creation of pellets, one of the major challenges is that it is a multi-step batch process, making it more labour-intensive than other techniques. There is significant scope for improvement, in terms of minimizing the number of process steps and instrumentation used, which could then create greater economical, technical, and commercial benefits for pharmaceutical manufacturers.

An alternative to the multi-step extrusion-spheronization technique is rotogranulation, direct pelletizing, where spheroids are produced directly from powder. The powder is mixed and moistened in a single-unit spheronizing system consisting of a rotating disk. This disk provides a centrifugal force. The impact and acceleration forces that occur in this process result in the formation of agglomerates that become rounded out into uniform and dense pellets, which are then dried. While offering the advantages of combining the different steps of pelletization into one processing unit, this technique is still not widely adopted in the industry due to factors such as cost and availability of equipment.

**New advancements**

Recent advancement in pellet technology primarily centre around the development of improved coating methods. Because the nature of the polymer coating, including the thickness of the polymeric film, can influence a pharmaceutical product’s release pattern, new techniques are being developed, which offer enhanced flexibility and a higher degree of stability. Wurster fluidization, a bottom-spraying technology that has been widely recognized for its precise film coating capabilities, is one of these techniques. Its unique features include the use of an air distribution plate and a partition that together organize the fluidization of particles through a coating zone. The spray nozzle is mounted at the bottom of the product container and is centered on the coating zone. A short distance between the coating materials and the particles during the coating process minimizes the need for spray-drying and contributes to high uniformity and coating efficiency.

**Conclusion**

Pellets offer many unique advantages both in terms of manufacturing and therapeutic benefits. Improved flow, more even and predictable distribution and transportation in the GI tract, narrow particle size distribution, and ease of coating, all contribute to enhanced pharmaceutical products. At the same time, they eliminate the build-up of high local concentrations of bioactive agents that might irritate the GI tract, while also reducing the variability of plasma profiles between subjects and within the same patient. Although there are multiple techniques that can be used to produce pellets today, extrusion-spheronization arguably brings the greatest advantages.
Establishing Blend Uniformity Acceptance Criteria for Oral Solid-Dosage Forms

Pramote Cholayudth

In 2013, the US Food and Drug Administration (FDA) withdrew its draft guidance on blend uniformity (BU)—Guidance for Industry: Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment (1), in which Sections V and VII no longer represented the agency’s current thinking (2). Section V recommended taking at least three replicate samples from each of at least 10 locations within the blenders (tumbler mixers; or 20 locations in convective mixers). However, it only required that one sample from each location be tested to assess BU as part of first-stage testing, and the current FDA preference is to analyze all of the three replicates from each location (i.e., at least 30 blend samples at each of the three blending time points are tested) (2). It should be noted that the BU data for the three time points are intended to demonstrate the blending process robustness.

As discussed in Bergum et al. (2), the use of nested sampling plans and testing of all replicate samples from each location allows the data to be subjected to variance component analysis in which the “between-location” and “within-location” variances are taken into account. The first type of variance is the variability across the sampling locations in a blender or during tablet compression and encapsulation processes, and the second is the variability between blend samples within a given sampling location.

High between-location variances will indicate non-uniformity within the blender (due to poor mixing) or reflect blend segregation during sampling (i.e., sampling bias) especially for granular blends. High within-location variances will indicate sampling bias (granular blends) or incomplete mixing during dosage forming steps such as tablet compression.

With the current technologies for powder blend sampling, blend segregation during sampling (sampling bias) especially for granular blends will unavoidably occur, resulting in deviated (biased) blend assay results. In this case, it is no use evaluating the biased data using the variance component analysis approach.

This article introduces the concepts of pooled variance and the central limit theorem, which are intended for establishing acceptance criteria for BU data of granular powder blends when a significant degree of sampling bias is involved. FDA preference on testing all of the replicate blend samples from each location is recommended to demonstrate the blending process robustness.
samples (i.e., at least 30 blend samples) is still taken into account in this article.

### Knowledge gained in the past

While taking blend samples by any sampling devices, the blend mass at the sampling location (i.e., in the blender) will be segregated due to the effect of the sampler movement. A blend is composed of the granules embedded with the active ingredient(s) and fine powders partly comprising lubricants and disintegrants; as such, the granular and fine powder portions are not always collected proportionally into the blend samples taken. Consequently, the overall blend uniformity in each of the blend samples may be diluted or concentrated, and therefore, be different from the true uniformity in the batch. Such a blend segregation caused by the sampling is referred to as sampling error or sampling bias resulting in biased mean and standard deviation values of the BU data. The magnitude of the bias may be extended such that non-normality of the BU data may occur.

Actual case study data are illustrated in Table I where the pre-mix blend uniformity data are excellent due to the fact that the fine powder blends are marginally segregated while sampling. All the final blends (granular + fine powders) in the same process validation (PV) batches, however, will exhibit poor uniformity data due to the blend segregation as earlier discussed. However, in the tablet compression stage (of process validation batches), all the content uniformity and blend uniformity (i.e., weight-corrected) data are excellent. This observation implies that sampling at the final blend stage (granular) is biased.

Another real case is that all fine-powdered materials (i.e., non-granular) directly blended for further capsule filling appear to have no sampling bias, as illustrated in Table II. One of the lessons learned is that there is practically no sampling bias in fine powder blends, although a much higher degree of sampling bias exists in the granular blends. The acceptance criteria introduced in this article are intended for those granular blends where the blend sampling bias,

---

**Table I: Blend uniformity data of pre-mix and final blend samples (wet granulation in tablet product).**

<table>
<thead>
<tr>
<th>Process validation lot #</th>
<th>Stages</th>
<th>Blend assay results and acceptance criteria (Tablet)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Pre-mix (n = 10)</td>
<td>104.82</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td>Final blend (n = 10)</td>
<td>103.77</td>
<td>6.78</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Pre-mix (n = 10)</td>
<td>103.06</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td>Final blend (n = 10)</td>
<td>104.72</td>
<td>7.32</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Pre-mix (n = 10)</td>
<td>104.18</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Final blend (n = 10)</td>
<td>99.83</td>
<td>14.63</td>
</tr>
</tbody>
</table>

Red area = failed, green area = passed.

Pre-mix: in high speed mixer/granulator, final blend: in V-shaped blender.
The acceptance criteria mean ± 10% (absolute) and standard deviation (SD) limit of not more than 3.84 for n = 10, based on standard deviation prediction interval (SDPI) method, are suggested in the Parenteral Drug Association Technical Report 25 (3).
especially at higher degree, is unavoidable.

The data of the two cases were evaluated because the compendial relative standard deviation (RSD) limit of not more than (NMT) 6% (n = 10) for content uniformity was official where the standard deviation prediction interval (SDPI) method was based on this particular RSD limit.

The pooled variance approach
Because variability of content uniformity (CU) data is influenced by a combination of those of BU and mass uniformity (MU) data, the approach to establishing the SD limit for BU data solely based on CU data variability such as the SDPI method is no more valid. In fact, variability of MU data should be taken into account. Such MU data would be available during the optimization phase in tablet compression or the encapsulation step. As an alternative, MU data may be obtainable upon using the placebo blends.

According to Sanford Bolton (4), the expression $\sigma_{CU}^2 = \sigma_{BU}^2 + \sigma_{MU}^2 + \sigma_{AM}^2$ implies that CU variance is equal to the sum of BU, MU, and analytical method (AM) variances. Given that the AM variance is marginally low or usually determined as zero, Equation 1 is obtained:

$$\sigma_{CU}^2 = \sigma_{BU}^2 + \sigma_{MU}^2 \tag{1}$$

The Acceptance criteria mean ± 10% (absolute) and standard deviation (SD) limit of not more than 3.30 for n = 6, based on standard deviation prediction interval (SDPI) method.

### Table II: Blend uniformity data of final blend samples (direct mixing in capsule product).

<table>
<thead>
<tr>
<th>Process validation lot #</th>
<th>Stages</th>
<th>Blend assay results and acceptance criteria (Capsule)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Final blend (n = 6)</td>
<td>Mean 102.14, Min – Max 101.17 – 103.16, Acceptance Limit 92.14 – 112.14, SD 0.73</td>
<td>Passed</td>
</tr>
<tr>
<td>2</td>
<td>Final blend (n = 6)</td>
<td>Mean 103.16, Min – Max 102.56 – 104.10, Acceptance Limit 93.16 – 113.16, SD 0.73</td>
<td>Passed</td>
</tr>
<tr>
<td>3</td>
<td>Final blend (n = 6)</td>
<td>Mean 102.48, Min – Max 101.62 – 103.48, Acceptance Limit 92.48 – 112.48, SD 0.64</td>
<td>Passed</td>
</tr>
</tbody>
</table>

Green area = passed.
Final blend: in cubic blender.
The acceptance criteria mean ± 10% (absolute) and standard deviation (SD) limit of not more than 3.30 for n = 6, based on standard deviation prediction interval (SDPI) method.

### Figure 1: Sample variance distributions with population variance estimation.

\[\sigma_{CU}^2 = \sigma_{BU}^2 + \sigma_{MU}^2\]
pooled variance). Figure 1 illustrates and confirms that the means of sample variance distributions are equal to the population or lot variance.

When Equation 1 is rearranged, the expression is as follows (Equations 2 and 3):

\[ \sigma_{BU} = \sqrt{\sigma_{MU}^2 - \sigma_{CU}^2} \]  
\[ \sigma_{BU} = \sqrt{3.75^2 - \sigma_{MU}^2} \]  

In establishing the acceptance criteria limits for BU SD, it is necessary to pre-establish the lot \( C_{pk} \) at 1.33 (i.e., lot SD = 3.75 [lot variance = 3.75^2 = 14.0625] using upper and lower specification limits [USL and LSL] of 115 and 85% label claim [LC], respectively) as the process baseline where it is found to provide the maximum acceptance value (AV) result marginally falling within the compendial limit of not more than 15. The simulated AV distributions demonstrating the justification of this particular baseline are illustrated in Figures 2 and 3 where the coverages for AV NMT 15 are at least 99%.

Two scenarios are introduced and discussed. Scenario 1 where lot MU SD < lot BU SD is illustrated in Figures 2, 4, and 5. Scenario 2 where lot MU SD > lot BU SD is illustrated in Figures 3, 6, and 7. From Figure 4, if lot MU SD is 2.15 and lot CU SD is fixed at 3.75 (from Equation 3 above), then lot BU SD is 3.0725 (calculated using Equation 3). The upper bound (UB) for BU SD (90% confidence interval) in tumbler mixers (n = 10) is 3.9 (in Excel, =3.0725*(CHIINV(0.1,10-1)/(10-1))^0.5). In convective mixers (n = 20), and the UB for BU SD is 3.7 using the same calculation method. So the BU SD limits will be 3.9 and 3.7 for n = 10 and 20, respectively. Now it can be seen that the BU SD limits are subject to variability of MU data. One can see that Equation 1 is proven by Figures 4–7 (i.e., where the lot \( C_{pk} \) values for CU data are 1.33).

In Figure 6, the SD limits are calculated to be 2.9 (n = 10) and 2.7 (n = 20) which are also illustrated in Figure 8. Figures 5 and 7 illustrate the relationship between the sample variance distributions for MU, BU, and CU data. Figure 8 provides the relationship between the three SD data as a quick reference for BU SD determination.

Based on the FDA recommended blend sampling plan, three replicate blend samples from each of not less than...
10 locations are taken. The agency prefers that all the samples be tested and evaluated rather than one sample from each location as in the past. Based on the simulation test results (see Table III), the two-stage acceptance criteria, on which the decision criteria summarized also in Table III, are introduced as follows.

Acceptance criteria stage 1:
For each of replicates 1, 2, and 3, blend data is evaluated.

- Mean ± 10% (absolute)
- SD ≤ P where SD is standard deviation for each replicate data and P is the calculated SD.

Acceptance criteria stage 2:
For each of average data sets*, the average data of the blend samples at the same locations are evaluated (* i.e., three sets from replicates 1 and 2, 2 and 3, and 1 and 3).

- Grand average ± 10% (absolute), i.e., grand average for each average data set.
- SD_average ≤ P where SD_average is standard deviation for each average data set and P is the calculated SD_average.

A good practice in granular blend sampling should be taken into consideration so that the sampling is not too biased (i.e., the true blend data is not rejected by mistake). A scenario of granular blends is presented in Table IV and plotted in Figure 9 where locations 2 and 4, having wide spreads of BU data (12.76 and 14.23 ranges, respectively), are likely to create the non-normality that causes the failure in stage 1. In the scenario, the overall requirement (although failed in stage 1) is met and, finally, it passes the acceptance criteria.
Discussion
Based on the simulation test results in Table III, the various magnitudes of errors represent the various degrees of blend sampling errors. The tabulated test results (% occurrence) demonstrate justification of the decision criteria to accept the BU data and also confirm validity of the established acceptance criteria. From these particular test results, having the two-stage acceptance criteria seems to be discriminative enough to accept only the conforming BU data, leading to successful CU data (i.e., the non-conforming data are rejected). The average data for three replicates, if established as stage 3, would be too normalized, and the poor and non-normal BU data may be accepted.

To demonstrate the mixing robustness, blend sampling was performed on three different blending time points (i.e., a large number of up to at least 90 blend samples are taken and tested). The introduced acceptance criteria were also intended to handle a great number of data so that the failure result will occur only when the granular blending process is truly poor.

In case of fine powder blends, such as pre-mixes prior to wet granulation or direct blends prior to direct compression, there are also three replicate blend samples where each of the replicate data is required to meet the acceptance criteria in stage 1 (i.e., stage 2 is not necessarily applied to the fine powder blend data). It may be also required that the three replicate data (fine powder) are subjected to variance component analysis (5). The detail on this statistical tool is out of the scope of this article.

Figure 7: Simulated blend uniformity (BU), mass uniformity (MU), and content uniformity (CU) variance distributions.

Figure 8: Relationship between lot mass uniformity (MU) standard deviation (SD) vs. lot blend uniformity (BU) SD and upper bound for BU SD.

Figure 9: Plotted blend uniformity data (three replicate granular blend samples).
BU during tablet compression or encapsulation stage (i.e., available as weight-corrected data in process validation batches) may not totally reflect the true uniformity in the final blend stage because of blend segregation during the dosage forming steps. The data, however, is still useful to support that BU during the final blending step is at least not poor.

**Table III: Decision criteria on meeting granular blend uniformity acceptance criteria.**

<table>
<thead>
<tr>
<th>Stage #</th>
<th>Simulation test results (lot CpK = 1.33)</th>
<th>Occurrence case 1</th>
<th>Occurrence case 2</th>
<th>Occurrence case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Passed</td>
<td>Failed</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Passed</td>
<td>Passed</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>Decision criteria</td>
<td>Acceptable if 2 stages are successful.</td>
<td>Acceptable if stage 2 is successful.</td>
<td>Not acceptable.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simulation test results (% occurrences)</th>
<th>0% error</th>
<th>15% error</th>
<th>30% error</th>
<th>50% error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% error</td>
<td>74%</td>
<td>100%</td>
<td>98%</td>
<td>65%</td>
</tr>
<tr>
<td>15% error</td>
<td>40%</td>
<td>58%</td>
<td>75%</td>
<td>62%</td>
</tr>
<tr>
<td>30% error</td>
<td>15%</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% error</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The simulation test is challenged using various magnitudes of true blend uniformity (BU) standard deviations (SDs) (1.0–3.7) with various errors (0–50%). For example, in 15% error, the magnitudes of SDs challenged are increased by 15%. This is provided that the BU SD limits are based on the original (non-biased) true BU SDs. Note that, with the same percentage error, the various magnitudes of SDs will generate about the same success and failure rate results.

**Table IV: Blend uniformity data (three replicate granular blend samples).**

<table>
<thead>
<tr>
<th>Stage #</th>
<th>Replicate #</th>
<th>Location #</th>
<th>Mean</th>
<th>Max</th>
<th>Min</th>
<th>Standard deviation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1, 6</td>
<td>101.82</td>
<td>100.90</td>
<td>101.82</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2, 7</td>
<td>102.60</td>
<td>102.07</td>
<td>99.94</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3, 8</td>
<td>101.69</td>
<td>103.29</td>
<td>99.35</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4, 9</td>
<td>103.29</td>
<td>99.94</td>
<td>95.10</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5, 10</td>
<td>95.10</td>
<td>95.10</td>
<td>95.10</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.47</td>
<td>103.29</td>
<td>99.35</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>110.47</td>
<td>90.47</td>
<td>3.80</td>
<td>2.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90.47</td>
<td>3.80</td>
<td>2.48</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1, 2</td>
<td>101.82</td>
<td>96.98</td>
<td>102.74</td>
<td>99.99</td>
<td>100.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.90</td>
<td>97.46</td>
<td>102.07</td>
<td>99.94</td>
<td>95.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96.94</td>
<td>91.36</td>
<td>103.78</td>
<td>96.70</td>
<td>101.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.75</td>
<td>97.02</td>
<td>99.01</td>
<td>104.23</td>
<td>103.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99.38*</td>
<td>99.09</td>
<td>107.30</td>
<td>98.11</td>
<td>109.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101.97</td>
<td>99.03</td>
<td>107.30</td>
<td>98.11</td>
<td>109.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>97.46</td>
<td>100.54</td>
<td>102.08</td>
<td>99.32</td>
<td>100.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.74</td>
<td>99.99</td>
<td>102.74</td>
<td>99.99</td>
<td>100.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96.98</td>
<td>99.99</td>
<td>102.74</td>
<td>99.99</td>
<td>100.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.74</td>
<td>99.99</td>
<td>102.74</td>
<td>99.99</td>
<td>100.48</td>
</tr>
<tr>
<td>3</td>
<td>2, 3</td>
<td>95.33</td>
<td>97.74</td>
<td>101.23</td>
<td>92.88</td>
<td>100.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.29</td>
<td>99.00</td>
<td>99.02</td>
<td>105.76</td>
<td>100.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>97.77</td>
<td>103.36</td>
<td>100.19</td>
<td>96.18</td>
<td>99.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101.36</td>
<td>99.43</td>
<td>100.55</td>
<td>103.62</td>
<td>96.60</td>
</tr>
</tbody>
</table>

Example: * in location # 1 (101.82+96.94)/2 = 99.38, supposing that SD limit is calculated to be 3.80.

**Passed** | **Failed** | Decision: Passing acceptance criteria

Essential elements for the acceptance criteria establishment include:
- FDA’s current thinking is taken into account (i.e., 30 BU data for 3 replicate blend sample data from at least 10 locations are evaluated).
- Experience and lessons learned show that granular blend
data are readily non-normal because of a significant degree of sampling bias.

- For granular blends, the non-normal data needs to be handled and accepted by normalizing the data using central limit theorem method.
- The concept of pooled variances is introduced using the expression \( \sigma_C^2 = \sigma_B^2 + \sigma_M^2 \) as the science-based approach to acceptance criteria establishment by demonstrating the inter-relationship between \( \sigma_B^2 \), \( \sigma_M^2 \), and \( \sigma_C^2 \) to confirm that sample variance distribution means (for any sample sizes) are equal to the corresponding lot variance and also confirm that \( \sigma_C^2 \) is equal to \( \sigma_B^2 + \sigma_M^2 \).

- Process baseline is pre-established by using processes with lot C pK for CU data pre-set at 1.33 where the coverage for AV results NMT 15 is up to at least 99%.
- Simulation test challenged with sampling errors is performed to demonstrate and confirm that the acceptance criteria are justified and robust:
  - Robustness of the acceptance criteria is demonstrated through challenging with different magnitudes of lot BU SDs with varied values of errors.
  - Discrimination is built into the acceptance criteria using the two-stage acceptance criteria rather than the three-stage; and poor data will be rejected.

**Conclusion**

To meet the FDA’s current thinking, there may be several proposed options for BU acceptance criteria. The proposal in this article is scientifically based on process benchmarking (lot C_pK at 1.33), central limit theorem, and pooled variance, which are supported by the simulation test results illustrated in Figures 2 to 7 and Table III. Such illustrations will demonstrate that meeting the established BU acceptance limits, especially for granular blends for oral solid-dosage forms, will guarantee with a high assurance (i.e., 90% confidence interval) that the CU data will pass the test at a high probability (i.e., at least 99% coverage for \( n = 10 \)).

**References**

A Risk-Based Approach to Stainless Steel Equipment Maintenance

Laboratory tests can determine critical cleaning parameters for passivation treatments used to prevent rouge on GMP stainless-steel equipment.

Elizabeth Rivera is a technical services manager; Paul Lopolito is a senior technical services manager; and Dijana Hadziselimovic is a senior technical services associate, all at the Life Sciences Division of STERIS Corporation in Mentor, Ohio.

Stainless steel is usually the preferred substrate for good manufacturing practice (GMP) applications, and it constitutes the majority of GMP product-contact surface areas. The austenitic stainless-steel series (e.g., 304L and 316L) has been popular in pharmaceutical applications because of its high stain and corrosion resistance and affordability. Although stainless steel is named “stainless”, it is really “stain resistant”. This property comes from its ability to naturally form an oxide-rich, passive layer on the surface.

Passivation is a process in which a passive layer forms on the stainless-steel surface; this layer occurs naturally in the presence of oxygen when the surface has been cleaned of exogenous matter (1–3). The passive layer on the stainless-steel surface becomes the primary means of protection to prevent corrosion. Stainless steel can corrode, however, when the chromium-to-iron ratio has been significantly reduced, resulting in the oxidation and subsequent release of iron oxides that form deposits on surfaces.

Rouge is the commonly used term for the visible corrosion product of stainless steel; it can be composed of several forms of iron oxides, with ferric oxide being the predominant form (4–7). Rouging is typically found in water generation systems, process tanks, and pipeline systems that are routinely exposed to corrosive solutions. Rouge seems to be a common problem. Regulatory agencies such as the US Food and Drug Administration (FDA) have cited in at least one warning letter that corrosion is unacceptable in direct-contact pharmaceutical systems (8).

The reasoning is that rouge on product-contact surfaces can create an environment for process residues and microbes to tenaciously adhere to the rouged area and become more difficult to clean and sanitize (9–11). Residues and microbes might also reside within the rouge layers, where the routine cleaner and sanitizer may not be able to penetrate.

Preventive and corrective maintenance

Considering the risk associated with rouged surfaces, manufacturers would benefit from focusing more attention on treatments that prevent rouge from happening. Some companies take a reactive approach and wait until rouge has been detected or has impacted production before taking corrective action. Process attributes such as elevated temperature, extreme pH solutions, or surface damage (e.g., from poor quality welding) can corrode stainless-steel surfaces (4–7). If a process or surface condition is expected to lead to corrosion at some point during the life of the equipment, then an effort should be made to investigate and prevent that corrosion from occurring.

Unlike preventive maintenance, which is done to mitigate the cause of the potential problem or undesirable situation, corrective maintenance is done to correct a problem or fault once it has been detected. With a stainless-steel preventive maintenance procedure, for example, an operator knows exactly what needs to be done at a predefined schedule. On the contrary, in the case of a corrective maintenance, the critical parameters and overall procedure would depend on what is found. Corrective maintenance often requires evaluation of the severity of the rouge problem before any treatment can be recommended. This evaluation is referred to as a risk assessment, and includes a review of the potential impact to the patient, product, personnel, and equipment (12).

Once the rouge is formed, there may be unknown variables associated with it and correcting the problem typically takes much longer than a preventive task. Many published references about stainless-steel corrosion are focused on corrective maintenance (3–11, 13–15).

When assessing the risk of the corrosion or rouge to the quality of the next product or batch, one should ask the questions about risk and mitigation actions summarized in Table I.

Passivation

There is no globally accepted test to guarantee that a stainless-steel surface has been adequately passivated. Generally, when stainless-steel equipment has been exposed to a passivation treatment, some documentation should be generated describing the passivation procedure with emphasis on the critical parameters. A test matrix has been suggested to be used as a guide for acceptance criteria and to confirm that a surface is passivated (3). The overall scope of these test methods is to either...
Passivation treatments are employed for the experiment:
- Alkaline cleaning (either single pass or recirculated) to remove all contaminants, oils, and foreign material.
- Water rinse
- Acid treatment (either single pass, recirculated, or immersed) to dissolve any free iron and sulfides and to expedite the formation of the oxide layer.
  - Water rinses
  - Drying
  - Visual inspection and tests, as appropriate.

**Laboratory test model and verification of test conditions**
Laboratory testing has been successful in determining critical cleaning parameters for passivation of stainless-steel surfaces. A formulated phosphoric/citric acid detergent and a formulated citric/oxalic acid detergent were used to treat 316L stainless-steel coupons in the passive layer evaluation experiments described as follows.

The following procedure was employed for the experiment:
- 316L stainless-steel coupons (1"x3") were cleaned in a laboratory washer.
- Cleaned coupons were treated with concentrated hydrochloric acid for 30 seconds to remove the passive layer.
- All the coupons were tested with an electrical pen technique to make sure that all coupons were not passive.
- Coupons were rinsed with ambient water for injection and subsequently exposed to the different cleaning agents, concentration, time, and temperature.
- After exposure, the coupons were rinsed with deionized water and left to dry for 60 min.
- Coupons were tested with an electrical pen technique to determine whether the treatments resulted in a passive condition.
  - The electrical pen technique indicates a passive range between (-200 mv) – (-400 mv) and registers pass/fail status via an indicator light (see Figure 1).
  - Final confirmation testing was performed using copper sulfate and salt spray cabinet techniques (see Figure 1).
  - The parameters tested were:
    - cleaner (formulated phosphoric/citric acid detergent or formulated citric/oxalic acid detergent);
    - concentration (5, 7, 8, 10, and 15% v/v); temperature (45, 60, 70, and 80 °C); and time (20, 30, 45, 60, 90, and 120 min).
  - Testing included the electrical pen, copper sulfate, and salt spray cabinet methods to verify the passive layer on stainless-steel coupons.

The experiments showed that the following parameters resulted in passivated coupons:
- 8% v/v formulated phosphoric/citric acid detergent at 80 °C for 120 min.
- 10% v/v formulated phosphoric/citric acid detergent at 70 °C for 30 min.
- 10% v/v formulated phosphoric/citric acid detergent at 60 °C for 60 min.
- 10% v/v formulated phosphoric/citric acid detergent at 80 °C for 30 min.
- 10% v/v formulated citric/oxalic acid detergent at 70 °C for 30 min.
- 10% v/v formulated citric/oxalic acid detergent at 80 °C for 20 min.
- 15% v/v formulated citric/oxalic acid detergent at 60 °C for 120 min.

### Table I: List of questions to help assess risk.

<table>
<thead>
<tr>
<th>What might go wrong?</th>
<th>The process solution blended or stored in a 304 or 316 stainless-steel vessel or equipment may be corrosive to the surface.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the likelihood it will occur?</td>
<td>The frequency of occurrence is dependent on the concentration, temperature, and nature of the process solution and the composition, roughness, and uniformity of the stainless-steel surface.</td>
</tr>
<tr>
<td>What is the likelihood it will be detected?</td>
<td>The frequency of detection is high, provided visual inspection is performed by trained personnel on the vessel between products and batches. Visually clean is a universal GMP requirement for product contact surfaces. The frequency of detection is low in hard-to-access areas such as centrifugal pumps and piping.</td>
</tr>
<tr>
<td>What are the consequences?</td>
<td>The presence of corrosion, such as micro-pitting, and rouge can adversely impact visual inspection, cleaning, and sanitization of the surface and, if untreated, can also affect the integrity of the surface and product manufactured.</td>
</tr>
<tr>
<td>What are the mitigation actions? (Corrective action)</td>
<td>Notify third party or perform in-house mechanical polishing, electropolishing, or chemical rouge removal and passivation procedures.</td>
</tr>
<tr>
<td>What are the mitigation actions? (Preventive maintenance)</td>
<td>Perform risk assessment to identify root cause through analysis and evaluation of laboratory testing. Submit change control to eliminate the root cause or develop frequency for chemical passivation treatments.</td>
</tr>
</tbody>
</table>

Verify that the surface has been passivated by removal of exogenous matter (e.g., free iron or hydrophobic films) or by direct measurement of the quality of the passive layer. Table II summarizes the advantages and disadvantages of common passivation test methods (2–3). Representative coupons of similar material and finish to the production equipment can be used to validate a passivation protocol.

Passivation treatments are dependent on the chromium content, surface finish, and machinability characteristics of the grades in each family of stainless steel. The chemical treatment should help restore the inert oxide layer in a consistent, faster-forming passive layer than found naturally. Passivation treatment using citric acid blends and phosphoric acid blends are highly effective for a large number of stainless-steel families. The conventional nitric acid passivation methods and others are summarized in Table III. The choice of passivation chemistry and method depends on the acceptance criteria imposed by the end-user as well as corporate, local, and national waste regulations. Typically, a passivation process includes the following steps:

- Alkaline cleaning (either single pass or recirculated) to remove all contaminants, oils, and foreign material.
- Water rinse
- Acid treatment (either single pass, recirculated, or immersed) to dissolve any free iron and sulfides
### Table II: Summary of popular tests to assess the effectiveness of passivation treatment.

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Water-wetting and drying (also known as water immersion) | - Laboratory test  
- Visual evaluation determines presence of staining                   | - Not quantitative  
- Results subject to visual interpretation                                                                                   |
| High humidity                              | - Laboratory test  
- Visual evaluation determines presence of staining                   | - Performed in laboratory only  
- Not quantitative  
- Results subject to visual interpretation                                                                                       |
| Salt spray cabinet                         | - Laboratory test  
- Visual evaluation determines presence of staining  
- Standard test method that can be automated                   | - Not quantitative  
- Results subject to visual interpretation                                                                                       |
| Copper sulfate                             | - Laboratory test  
- Visual evaluation determines presence of staining                   | - Not quantitative  
- Not effective at detecting small, discrete, free iron particles  
- Requires use of hazardous reagents  
- Results subject to visual interpretation                                                                                       |
| Potassium ferric cyanide–nitric acid       | - Sensitive laboratory test  
- Visual evaluation determines presence of staining                   | - Not quantitative  
- Requires use of hazardous reagents  
- Safety concerns about exposure to highly toxic hydrogen cyanide gas  
- Results subject to visual interpretation                                                                                       |
| Electrical pen                             | - Test kit for laboratory or field use  
- Calibrated hand-held device  
- Measure corrosion potential directly on the tested surface  
- Relatively inexpensive                   | - Proprietary technology  
- Generally used as a pass/fail test based upon a light indicator (preset values from manufacturer)                           |
| Cyclic polarization                        | - Measures corrosion resistance as critical pitting potential or breakdown potential  
- Other values are corrosion potential, size, and quality of the passive region, and current density at the breakdown potential  
- Relatively inexpensive                   | - Laboratory test only  
- Requires a software package to make the measurements  
- Personnel must be trained; high level of expertise required                                                                       |
| Auger electron spectroscopy (AES)          | - Provides quantitative analysis by using AES technology to determine the elemental composition of the metal surface to a depth of 2–20 Angstroms  | - Laboratory test only  
- Relatively expensive  
- Instrument not widely available  
- Expertise needed for instrument use and data interpretation                                                                             |
| Glow-discharge optical emission spectroscopy (GD-OES) | - Provides quantitative analysis by using GD-OES technology to determine the elemental composition of the metal surface  
- Particularly useful for thick and thin film structures                   | - Performed in laboratory only  
- Relatively expensive  
- Instrument not widely available  
- Expertise needed for instrument use and data interpretation                                                                             |
| X-ray photoelectron spectroscopy (XPS) or Electron spectroscopy for chemical analysis (ESCA) | - Provides quantitative analysis by using XPS technology to determine the elemental composition of the metal surface to a depth of 10–100 Angstroms  | - Laboratory test only  
- Relatively expensive  
- Instrument not widely available  
- Expertise needed for instrument use and data interpretation                                                                             |

### Case study I
A large biotech manufacturer consistently observed rouge in select 316L stainless-steel buffer preparation and storage tanks. Based on solubility profiles of the buffer components, purified water should have been effective at removing the buffer residue. Persistent rouge, however, impacted the use of the equipment. Upon visual inspection of the tanks, obtaining a third-party service provider specializing in stainless steel cleaning and maintenance was required. This process resulted in increased maintenance costs and decreased production time due to equipment downtime. The biotech manufacturer investigated their cleaning and maintenance procedure to develop a scientific, risk-based approach to equipment preventive maintenance. The objectives for the investigation were as follows:
1. Confirm cleaning of the buffer residue
2. Confirm condition of exposure that resulted in loss of passive layer
3. Confirm that passivation treatment protects the surface from buffer exposure.

The testing of condition 1 was performed by applying 1 mL of buffer onto a precleaned, 304 stainless-steel coupon with a 2B finish. The treated coupon was dried at ambient temperature for a prespecified dirty hold time. The coupon was then cleaned with deionized water for 5 min. at 65 °C or 80 °C. The coupon was determined to be cleaned if it met the characteristics of: visually clean, water-break free, and no weight change (by gravimetric testing).

The testing of condition 2 was to evaluate the effect of buffer condition on a passive 316L stainless steel coupon using periodic checks of the passive layer with an electrical pen technique and copper sulfate test kit. Final confirmation was performed with salt spray cabinet test. If the passive layer was damaged, additional testing was performed using frequent rinses of low concentration of a formulated acid detergent to maintain the passive layer on the 316L stainless steel surfaces. Testing was performed in replicates. Control coupons were passivated with 10 % v/v formulated acid detergent at 80 °C for 60 min. prior to exposure to the buffer.

**Investigation results.** Deionized water was effective in cleaning surfaces with dried buffer A (60 mM sodium phosphate, 2 M Chloride, pH 5.6) after 5 min. at either 65 °C or 80 °C. Coating the coupon with Buffer A and drying it overnight resulted in a non-passive surface. Treatment using concentrations of 10–15% v/v formulated citric/oxalic acid detergent at times of 20–60 min. at 80 °C or at times of 40–60 min. at 65 °C were effective at passivating the buffer exposed surfaces and maintained a passive condition for at least a 24-hour buffer exposure. Specifically, surfaces maintained their passive state under the following buffer exposure time:

- Up to 48 hours after passivation with 10% v/v formulated citric/oxalic acid detergent at 65 °C for 40 min.
- Up to 72 hours after passivation with 15% v/v formulated citric/oxalic acid detergent at 65 °C for 60 min.
- Up to 24 hours after passivation with 10 % v/v formulated citric/oxalic acid detergent at 80 °C for 20 min.

The additional testing found that the decrease in chloride concentration in Buffer A from 2M to 1M extended the buffer storage condition exposure from 96 to 120 h. Water is effective at cleaning Buffer A with 2M or 1M chloride. However, dirty hold time and solution storage time can affect the passive properties of the stainless steel surfaces when evaluated using the electrical pen test and cyclic polarization (not reported). The citric/oxalic acid detergent passivation conditions

---

**Table III: Agents commonly used in stainless steel passivation treatments.**

<table>
<thead>
<tr>
<th>Passivation agent</th>
<th>Performance</th>
<th>Health and safety considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphoric acid and blends (5–25% w/w, 1–4 h heated)</td>
<td><em>-Good for routine use</em>&lt;br&gt;<em>-Excellent rouge and scale remover</em></td>
<td><em>-Must be neutralized before disposal</em>&lt;br&gt;<em>-May be concerns due to phosphates</em></td>
</tr>
<tr>
<td>Citric Acid and blends (3–10% w/w, 1–4 h heated)</td>
<td><em>-Great for routine use</em>&lt;br&gt;<em>-Good passivation agent; not as effective for rouge removal</em>&lt;br&gt;<em>-Takes longer to process than mineral acids</em></td>
<td><em>-Must be neutralized before disposal</em></td>
</tr>
<tr>
<td>Nitric acid (10–40% w/w, 30–90 min at ambient or higher)</td>
<td><em>-Good rouge and passivating agent</em>&lt;br&gt;<em>-May be effective at ambient temperatures</em></td>
<td><em>-Must be neutralized before disposal</em>&lt;br&gt;<em>-Highly hazardous to occupational health</em></td>
</tr>
<tr>
<td>Electropolishing (parameters vary according to a qualified procedure)</td>
<td><em>-Removes metal from the surface</em>&lt;br&gt;<em>-Mostly limited to components than installed systems</em>&lt;br&gt;<em>-Rinsing step must ensure the removal of residual film that may adversely affect the surface</em></td>
<td><em>-Must be neutralized before disposal</em></td>
</tr>
</tbody>
</table>

---

**Figure 1: (Left to right) Copper sulfate test kit, electrical pen kit, electrical pen handheld device, and an automated salt spray cabinet.**
(time, temperature, and concentration) can affect the passive layer and the duration of buffer storage time. A passivation treatment of at least 5% v/v of a formulated citric/oxalic acid blend at 80 °C for 90 min. provided a passive surface when evaluated with the electrical pen, cyclic polarization, and X-ray photoelectron spectroscopy (XPS) or electron spectroscopy for chemical analysis (ESCA). The passivation of the stainless-steel coupon with 15% v/v citric/oxalic acid detergent maintained a passive surface using the electrical pen test for greater than 96 h when exposed to the 1M chloride buffer.

This information enabled the manufacturer to place timers on select buffer storage and product hold tanks to inform the operators when a passivation cycle is needed.

Case study II

The second case study is similar to the first. A multinational plasma-fractionation product manufacturer was observing micro-pitting and rouge in select 316L stainless-steel buffer preparation tanks. The buffers included 0.1M sodium chloride, 0.15M sodium chloride, 1 M sodium chloride, 3 M sodium chloride, 20M sodium acetate, 2.1M sodium CAP (N-cyclohexyl-3-aminopropanesulfonic acid) buffer, pH 5 acetate, 1M acetic acid, and 1M acetic acid with 1M sodium chloride.

The objectives for the investigation were the same as in the first case study and were tested in a similar manner.

All the buffer solutions, when air dried onto a 304 stainless coupon with a 2B finish, were effectively cleaned using deionized water within 5 min. at ambient temperature in a low-mixing, agitated immersion bath.

The pH 5 acetate and 1M acetic acid with 1M sodium chloride buffers exposed to 316L stainless-steel passivated coupons affected the passive layer between 72 and 96 hours as determined by electrical pen test and confirmed using copper sulfate and salt spray cabinet testing.

Washed and rinsed 316L stainless-steel coupons, passivated with a 10% v/v formulated phosphoric/citric acid detergent at 80 °C for 40 min., were then rinsed with water and air-dried at ambient temperature for one hour before testing. The coupons were exposed to the pH 5 acetate or 1M acetic acid with 1 M sodium chloride buffers, and every 3 to 4 days the coupons were removed from the buffer, rinsed with water, and washed with a low concentration phosphoric/citric acid detergent (0.5% v/v, 80 °C for 10 min.). The surfaces remained passive throughout the 31-day test period.

Water is effective at cleaning the buffers evaluated. However, the 1M acetic acid with 1 M sodium chloride dirty time and solution storage time can affect the passive properties of the stainless-steel surfaces when evaluated using the electrical pen test, copper sulfate, and salt spray testing. An acid wash treatment of at least 0.5% v/v formulated phosphoric/citric acid detergent every 3 to 4 days at 80 °C for 10 min. provided a passive surface over 31 days, while the non-acid washed controls failed around 72 h.

Conclusion

The material of choice for most reusable vessels and equipment in GMP manufacturing facilities is 316L stainless steel. The surface material should be selected based on its application and defined in the user requirement specifications. Sometimes this engineering review is overlooked, manufacturing conditions are changed, or new products are added. Substrate compatibility issues, such as corrosion and rouge, can directly impact visual inspection, cleaning, sanitization, particulate generation, material integrity, and possibly personnel safety. Upon inspection of vessels and equipment, if repeated substrate compatibility issues arise, then a quality risk assessment should be performed and data collected based on experimental models, such as those presented in this paper. A corrective action can be performed based on a justifiable, risk-based, scientific approach. Understanding the root cause of the corrosion issue and significantly reducing or eliminating its occurrence through effective preventive maintenance will reduce unscheduled corrective action activities, manufacturing delays, and adverse impact to product quality or to patients.

References

Biopharmaceutical companies have increased the adoption of single-use systems (SUS) and components (i.e., polyethylene bags, filters, tubing, connectors, etc.) for manufacturing processes, in addition to multi-use (MU) materials (i.e., glass bottles, stainless steel tanks, etc.) (1). Regulatory guidelines require that the product contact items “shall not be reactive, additive, or absorptive” to assure drug product quality and safety (2). The manufacturer is, therefore, responsible to examine various materials used in manufacture of both drug substances and drug products to ensure that the materials are appropriate in terms of efficacy (process performance and product quality) and safety for the final drug product.

Suppliers are advised by the BioPhorum Operations Group (BPOG) and Bio-Process Systems Alliance (BPSA) to provide comprehensive extractables test data. Many companies have now adopted the BPOG extractables protocol (3) as their user requirement.

Extractables and leachables evaluation
An extractables and leachables evaluation should begin with a risk assessment of the materials to determine whether there is a significant risk that may require additional studies on all or part of the product contact materials (4).

A risk rating is determined by applying three main factors: the severity of the harm caused by substances leaching from the manufacturing component; the probability that leaching will occur; and the probability of detecting the leached substances through in-process manufacturing controls.

The risk analysis of each product contact material used in the process takes into account variables including:
- Proximity to the API/drug substance and final drug product
- Extraction capability of the solvent/solution
- Contact time
- Temperature
- Product contact surface area
- Material pre-treatment
- Material compatibility/resistance.

It is presumed that any impurity entering the production stream can have a negative impact on the product quality and the severity of such a failure mode is considered to be high. A process-specific assessment takes into account the production stream in which the component is used in and accordingly, it assigns a risk rating. As the production process advances towards the final drug product state, the risk to the patient, represented by any leachable, increases (Figure 1). Therefore, polymeric components used in process steps closer to the drug substance or the drug product will carry a higher risk rating compared to the earlier steps of the process. For example, a bag or a filter used for the final filtration of bulk drug substance will have a significantly higher rating compared with the components used in the upstream process steps.

The BPOG Best Practices for Mitigating Risk from Leachables in Single-Use Systems suggests a risk assessment rating (5) that companies can use to develop their own risk assessments (see Table I) (5). The risk ratings of each factor will be weighted as in the BPOG example and summed to obtain the final risk score that is then categorized as low, medium, or high. If the risk is classified as low, it may be sufficient that the material meets the compendial requirements. If the risk is medium, in addition to the low-risk requirements, the company should evaluate available extractables data from the supplier, or generate in-house study data for a toxicological risk assessment. If the risk is classified as high, in addition to the medium risk requirements, a process-specific leachables risk assessment must be carried out; if data are not available from the supplier, or the data do not correspond to the processing conditions, a dedicated extraction study and/or leachables study will be necessary.

A dedicated extraction study representative of the processing conditions should define the worst case in-use parameters in terms of type of solvents, duration, and temperature of contact, and surface-to-volume ratio.
Finally, the definition of the study design is a very important and crucial step. Different extraction study design options are available for the manufacturing process contact materials:

- Perform an extraction study on the process parts as an on-site assembly (i.e., for each process step, combining all the materials included in each skid).
- Perform an extraction study singularly on each product contact material part, eventually bracketing materials of the same type/composition.
- Reproduce a small-scale assembly of the manufacturing process, which includes the most at risk materials (based on preliminary risk assessment).

These approaches have been applied in three case studies and are summarized here, highlighting the advantages and the difficulties of each study design option (Table II). It is important to note that the case studies described in this paper are not to be intended in contrast with BPOG Standardized Extractables Testing Protocol for SUS in Biomanufacturing, which Merck adopted as single-use requirements. The extraction and leachables simulation study conditions presented here were designed to compensate for the insufficient/inadequate extractables data supplied by vendors and were intended to mimic the worst-case scenarios of use of the materials for their intended application within the company’s specific manufacturing processes.

### Analytical methods

In the three case studies, the following analytics were applied:
- Headspace sampling/gas chromatography/mass spectrometry (HS/GC/MS) and gas chromatography/mass spectrometry for volatiles and semi-volatiles
- Ultra-high performance liquid chromatography/MS/MS for semi-volatiles/non-volatiles
- Graphite furnace atomic absorption spectroscopy (GF/AAS) for silicone
- Inductively coupled plasma–mass spectrometry (ICP–MS) for elemental impurities
- Total organic carbon (TOC) on aqueous carbon only.

### On-site assembly extraction study

The on-site assembly option was applied to a downstream manufacturing process. Due to the complexity of the equipment and the single-use and multi-use materials involved, the extraction study was carried out by bracketing the different skids separately, according to the worst-case in-use conditions of each specific purification step, following the risk assessment.

Extractables studies on the chromatographic resins were already available from the vendors so all resins involved in the purification process were disconnected and excluded from the extraction study, thus simplifying the study.

The worst-case organic and aqueous solutions selected as model solvents for the process skids extraction were the following: ethanol 20% in water, acetonitrile 50% in water, acetonitrile 50% with 0.1% trifluoroacetic acid (TFA), sodium hydroxide (NaOH) 0.1M and 0.5M, and a solution of NaOH 0.5M and sodium hypochlorite (NaClO) that was used to sanitize the line (Table III). These solutions were recirculated in each skid for a few hours up to seven days at normal process temperature, then sampled and analyzed by performing the different techniques. The reference solutions, before starting the recirculation process, were sampled and tested as well.

Analytical studies detected a variety of volatile and semi-volatile organic compounds; several plastic/rubber additives such as phenolic antioxidants; plasticizers (e.g., phthalates/adipates); amides, and other plastic/rubber formulation related components (e.g., residual solvents, silicon polymers, glycols, and alkanes).

Having extrapolated from what was detected in the study to the real-case conditions of use of the process materials (namely, by taking into account the dilution factor), a safety assessment was made considering the daily dose of the final product (<1 mL in this case). The result was that the potential daily exposure of the patient to the species detected in this extraction study was below 1.5 μg/day, which is the safety threshold for genotoxic impurities. Therefore, no safety concern was determined for the materials used within the process.

### Critical aspects and lessons learned

This experiment raised some difficulties within the execution and the analytics, and revealed some lessons learned:

- Due to the impact of contamination from the on-site solution preparation step (e.g., contact with plastic bags/bottles), there is a need to establish the right mindset within the manufacturing site.
- Many artifacts and analytical interferences were generated by strong/reactive solutions (as NaOH/NaClO), causing difficulties in the analyses and data interpretation; the use of strong saline/reactive solutions should be
reconsidered and replaced with fit-for-purpose solutions.

- The impact of the already-used materials should be taken into consideration. Traces of residual compounds from previous manufacturing runs and from cleaning processes (e.g., ethanol) were also detected.

**Single-parts extraction study**

The single-parts option was applied to fill/finish manufacturing process parts. New parts (e.g., tubing, gaskets, valves, connectors, etc.) were used and extractions were done singularly within the laboratory, without involving the entire production area. Therefore, this option seemed simpler to perform. Furthermore, as most of the materials are used in different processes, a goal of the study was to use the extraction profile obtained from each material for all other processes in which the same material was involved, potentially reducing other extraction study efforts in the future. Therefore, for these fill/finish processes, a dedicated simulation study, with the drug product buffer/placebo as extracting solution, may be sufficient to complete the extractables and leachables data package. In addition, the data generated in this approach are useful for future changes of materials.

All the materials present in the process were evaluated and classified, grouping them by their main components (e.g., silicone, rubber, plastic type) resulting in 12 groups of materials. These materials were extracted with aqueous solutions only (NaOH, Table I: Example of risk assessment from BioPhorum Operations Group (5).
Extractables and Leachables Testing

Table II: Advantages and difficulties of the different extraction study designs.

<table>
<thead>
<tr>
<th>Option 1: On-site assembly study</th>
<th>Advantages</th>
<th>Difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easier to perform: the solvents re-circulate in the system loop.</td>
<td>• The samples may be contaminated from several materials and buffers.</td>
<td></td>
</tr>
<tr>
<td>• Fewer samples to test.</td>
<td>• Data interpretation may be difficult.</td>
<td></td>
</tr>
<tr>
<td>• Large volumes in use.</td>
<td>• Big volumes in use.</td>
<td></td>
</tr>
<tr>
<td>• Correlation between extractable compound and the source of material may be needed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option 2: Singular material study</th>
<th>Advantages</th>
<th>Difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extraction data for each single part of the process may useful for future material changes.</td>
<td>• Management of the extraction of small parts, O-rings, or filters is difficult.</td>
<td></td>
</tr>
<tr>
<td>• Less volume in use.</td>
<td>• Increased number of samples to analyze.</td>
<td></td>
</tr>
<tr>
<td>• Less number of samples to analyze.</td>
<td>• Smaller volume used.</td>
<td></td>
</tr>
<tr>
<td>• More practical and representative of the real case, though can simplify the analytics and the extraction preparation.</td>
<td>• Increased number of extractables species and more complicated data interpretation.</td>
<td></td>
</tr>
<tr>
<td>• Need for scaling the results to the real in-use conditions.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option 3: Small-scale assembly</th>
<th>Advantages</th>
<th>Difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easier to perform</td>
<td>• No direct correlation between extractable compound and the source of material, though Option 3 can be easier than Option 1.</td>
<td></td>
</tr>
<tr>
<td>• Can be adapted in the laboratory to the real needs; possibility to exclude some parts to avoid sample contamination and to simplify data interpretation.</td>
<td>• It may be necessary to repeat the study or at least the simulation study for a different product.</td>
<td></td>
</tr>
<tr>
<td>• Less volume in use.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Less number of samples to analyze.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• More practical and representative of the real case, though can simplify the analytics and the extraction preparation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.1M; HCl, 0.1M; water; and drug product buffer as a simulation of the real-case conditions, because no organic solvent was foreseen to be used within this process (Table IV). The extraction was carried out by soaking the single pieces, with the selected model solutions, while the tubes were filled and closed at both ends. The volume of the extracting solutions reflected a surface-to-volume ratio ranging from 6:1 to 4:1. A light agitation was applied and the overall extraction was carried out in a climatic chamber under controlled temperature conditions.

A much higher number of samples were analyzed in this option, though the solutions chosen for the extractions were more compatible with the analytical techniques with reduced artifacts and contaminations. The main organic extractables identified were rubber and plastic materials formulation/manufacturing (polymer fragments, glycols, etc.) and additives (plasticizers, vulcanizing agents, lubricants, solvents, antioxidants, etc.). By using this extraction approach, it is worth noting that for some product contact items (i.e., ethylene-propylene diene monomer diaphragms), trace element results were affected by the presence of some metallic parts such as screws/external connections that were not supposed to come into contact with the product but were impossible to remove before the extraction, thus generating biased results.

Finally, the results were extrapolated to the normal operating volumes of solution in contact with the same materials, resulting in an overall dilution factor of 600 (surface-to-volume ratio <0.1). For this reason, the overall levels of organic/inorganic extractables/potential leachables identified in this study were negligible when referred to the final drug-product solution under normal operating conditions.

Critical aspects and lessons learned. This experiment raised the following difficulties within the execution and the analytics:

• It was difficult to extract small pieces or parts whose geometry was not completely compatible with the selected volume of the extracting solution.
• Higher numbers of samples had to be analyzed.
• Data evaluation and correlation with the process step volumes were difficult as the materials used in the different steps of the process.
• The possible contribution of external parts that do not normally come into contact with the product, but may affect the overall results, must be evaluated.

Small-scale assembly extraction study

The small-scale assembly option was applied to a fill/finish manufacturing process that involved the use of a single-use polyethylene mixing bag, sterile filter, pump, tubing, and connectors. These materials were considered most at risk as they are the closest to the final product and no further dilution is applied to obtain the final drug product. In this case, there was the possibility to use new items and to scale down the system to mimic the real conditions, dealing with less volume and a more friendly sample preparation.

The study was designed as a small-scale assembly within the manufacturing site, using materials that were representative of the real-case production. Based on the
preliminary risk assessment and on existing information (from other extraction studies and from the supplier), some items were excluded from the small-scale assembly, simplifying the study and the data interpretation. In particular, the assembly was performed using a scaled-down 10-L bag (same type and supplier of the one used in production), silicone tubing, polypropylene connectors, and a pump with a Teflon head that contains rubber gaskets that come into contact with the product solution.

This small-scale assembly was extracted with three different model solutions (i.e., water, 0.01M hydrogen chloride, and 50% ethanol in water), covering the real worst-case conditions in terms of surface-to-volume ratio as well as contact time and temperature conditions. A scaled-down volume corresponding to the minimum batch size was used, and a dynamic extraction for 48 hours at 35–40 °C in a climatic chamber was performed. In addition, for a leachables simulation study, a simplified placebo solution was used as a model solvent. Separate extractions were carried out by using different equipment parts each time for each solution. The extraction experiment is shown in Table V.

The analytical results highlighted a few organic species (i.e., series of siloxanes and traces of some phenolic antioxidants related species) were detected as extractables from the plastic and rubber materials in contact with the product during the fill/finish operations. The quantity in the extracts was extremely low, however, especially in the simplified placebo (simulation study).

Table III: Extraction study design for option 1, on-site assembly for downstream processing. BPOG is BioPhorum Operations Group.

<table>
<thead>
<tr>
<th>Process steps</th>
<th>Solutions</th>
<th>Volumes</th>
<th>Conditions</th>
<th>Total number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatography capture 1</td>
<td>Worst-case material contact solutions selected (working conditions as well as the cleaning and storage considered)</td>
<td></td>
<td>Recirculation for 7 days at normal process temperature</td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration 1</td>
<td>Different contact solutions per different steps:</td>
<td></td>
<td>Chromatography resins excluded as data were available from suppliers.</td>
<td></td>
</tr>
<tr>
<td>Chromatography capture 2</td>
<td>• Sodium hydroxide (NaOH) 0.1M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromatography capture 3</td>
<td>• NaOH 0.5M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration 2</td>
<td>• NaOH/Sodium Hypochlorite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromatography capture 4</td>
<td>• Ethanol 20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membrane filtration</td>
<td>• Acetonitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acetonitrile and trifluoroacetic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surface: Volume ratio 6:1 was applied in accordance with BPOG protocol.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Different volumes used:</td>
<td>Min: 0.5 L Max: 5 L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table IV: Extraction study design for option 2, extraction of the single parts for fill and finish. BPOG is BioPhorum Operations Group.

<table>
<thead>
<tr>
<th>Items</th>
<th>Solutions</th>
<th>Volumes</th>
<th>Conditions</th>
<th>Total number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Glass bottle</td>
<td>Four aqueous solutions selected:</td>
<td></td>
<td>7 days at 40 °C in closed container under mild agitation</td>
<td></td>
</tr>
<tr>
<td>Group 2: Stainless steel tank</td>
<td>• Sodium hydroxide 0.1M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3: Polyvinylidene fluoride (PVDF) filter membrane</td>
<td>• Hydrogen chloride 0.1M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4: Ethylene propylene diene monomer (EDPM) valve</td>
<td>• Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 5: EPDM diaphragm</td>
<td>• Sample buffer (simulation study)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 6: EPDM and polytetrafluoroethylene (PTFE) diaphragm</td>
<td>S/vol. ratio 6:1 and 1:1 for filters was applied as per BPOG protocol.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 7: EPDM O-ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 8: Silicone gasket</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 9: PTFE silicone hose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 10: Silicone hose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 11: Polycarbonate and silicone hose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 12: Polystyrene connectors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group体积: 0.5 L Max: 5 L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table V: Extraction study design for option 3, small-scale assembly for fill and finish.**

<table>
<thead>
<tr>
<th>Items</th>
<th>Solutions</th>
<th>Volumes</th>
<th>Conditions</th>
<th>Total number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene bag</td>
<td>Four aqueous solutions selected:</td>
<td>Lowest scaled-down processing volume:</td>
<td>48 h recirculation at</td>
<td>48 samples</td>
</tr>
<tr>
<td>Silicone tubing</td>
<td>• Ethanol 50%</td>
<td>2.6 L for a 10 L bag</td>
<td>35–40 °C</td>
<td>(per analytical technique)</td>
</tr>
<tr>
<td>Pump head</td>
<td>• Hydrogen chloride 0.1M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connectors</td>
<td>• Water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sample placebo (simulation study)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on these results, it was possible to conclude that no safety concern arises from the SU materials used during the fill/finish operations. It is important to highlight that in this type of extraction study design, if no dilution is applied from drug substance to drug product, the results in terms of concentration of the detected compounds are used as-is.

**Critical aspects and lessons learned.** The third option revealed the following considerations:

- The scaling down of the system had to be representative of the actual process and simulate worst-case conditions that mimicked the higher surface-to-volume ratio under normal operating conditions.

- As in the first assembly approach, there was no direct correlation between extractable compounds and the source of material, though in this experiment, the data interpretation was easier than in the first study. The small-scale option used less aggressive solutions and applied a simpler design assembled in the laboratory, with much lower risk of contamination.

- This last approach was considered to be the best way to conduct the extraction study on the manufacturing materials; it is friendlier to carry out and the conditions are more representative of the real situation.

**Considerations and conclusion**

The evaluation and practical study approaches of extractables and leachables for manufacturing process product contact materials concludes that each study should be carefully established case by case. Every extractables and leachables evaluation should begin with a risk assessment of the materials involved prior to the study design. Extraction studies should be as simple as possible. Model solvents should mimic the worst-case conditions, should be fit for the scope, and should not be too aggressive to avoid artifacts, sample contaminations, and difficult data interpretation. In addition, the authors recommend that special consideration should be given to the preparation of samples, especially if situated in the manufacturing areas instead of dedicated laboratories.

**Acknowledgements**

The authors offer special thanks to colleagues at Merck Serono: Pascal Candillon, Nourredine Boudiaf, Patricia Boinon, Isabelle Locatelli, and Bernard Anthoine from MS-Aubonne; Luke Woodford, and Christian Menzel from MS-Vevey; Francesco Iacobazzi from MS-Bari, and Francesca Cutillo from MS-Guidonia.

**References**

2. FDA, Code of Federal Regulations 21 Part 211.65 and §211.94.

**Contract laboratory expands E&L testing capabilities**

SGS, a bio/pharmaceutical analytical contract solutions provider, has made investments in extractables and leachables (E&L) testing facilities on both sides of the Atlantic. In January 2017, the company announced investments at its North American Center of Excellence for E&L in Fairfield, NJ USA.

Two new instruments, a liquid chromatography–mass spectrometry (LC–MS)/MS and gas chromatography (GC)–MS with head-space capability are high resolution and high-throughput systems, allowing for improved and rapid identification of trace unknown extractable compounds.

In September 2016, the company opened a 500-square-meter facility in Wiesbaden, Germany as a Global Centre of Excellence for the testing of extractables and leachables for pharmaceutical products. The Wiesbaden facility replaced operations previously done at the company’s laboratory in Taunusstein, Germany. Equipment and instruments from Taunusstein, as well as newly acquired instruments, were qualified and validated at the Wiesbaden laboratory. SGS reported that the space vacated at Taunusstein will be used to expand quality control release testing capabilities.

—The editors of Pharmaceutical Technology Europe
CHECK OUT NEW PHARMACEUTICAL TECHNOLOGY’S ALL NEW MARKET RESOURCE!

Pharma Marketplace is your online resource to connect with pharma manufacturing suppliers around the world.

Find global suppliers and resources for:
- Analytical Instruments
- Chemicals, Excipients, Ingredients & API
- Contract Services
- Facility Design and Operations
- Laboratory Instruments, Equipment & Supplies
- Manufacturing, Processing Equipment & Supplies
- Aseptic/Sterile Processing
- Drug Delivery Technology
- Packaging Equipment & Accessories
- Information Technology
- Compliance & Validation

www.pharmtech.com/marketplace

CONTACT US TODAY!
As manufacturers move into new markets and launch new clinical research programmes, including work in the development of cell, gene, and tissue therapies, ensuring the integrity of the cold chain has become more important, and more challenging, than ever. Success involves careful partner selection and logistics planning, as well as proactive communication with shippers, freight forwarders, and logistics specialists. It also depends on new temperature-control technologies, a number of which have recently been commercialized (see Sidebar).

In 2016, UPS bought Marken Technologies, which specialises in clinical trial shipments, to strengthen its capabilities in this area. In this article, Dan Bell, vice-president of quality, compliance and technical affairs at Marken, discusses overall trends as well as insights into some of the challenges posed by cell and gene therapies. Also commenting are Ron Swistock, director of global healthcare strategy at UPS, as well as Mike Sweeney, senior director of global service development, and James Klingelhofer, regional sales director, both of whom work for World Courier.

More efficient insulation

PTE: What recent advances have been made in packaging equipment for cold chain?

Bell (Marken): A few advances we are seeing in packaging equipment include more efficient insulation using nano-technology to improve the thermal resistance, or ‘R’ factors of vacuum-insulated panels, which allow for greater payloads and longer validation times without compromising weight.

Also, a greater focus is being placed on pallet size and unit load device (ULD) solutions utilising passive technology. We’re seeing a push toward lower temperatures as alternatives to dry ice, and competitively priced solutions for controlled room temperature (CRT) (15 °C to 25 °C). Another advancement is integration of technology, especially global positioning system (GPS) tracking and remote reporting from environmental sensors.

Sustainable materials

PTE: How are the industry’s packaging needs changing?

Swistock (UPS): Pharmaceutical companies are under increased pressure to understand carrier ambient environments in order to develop or justify their transportation methods and risk mitigation plans. You’ll see more efforts placed on sustainable materials, and demand will grow for carriers to offer more temperature controls within their networks to minimise packout complexities, costs, and requirements. An increasing number of pharmaceutical companies are also innovating and collaborating with reputable third-party logistics companies to create better efficiencies for shipping biopharmaceuticals as well as clinical trial specimens.

PTE: What specific changes are you seeing?

Swistock (UPS): Reusable shippers are getting more interest. These may be more expensive up front but they enable a ‘just-in-time’ business model. For the receiving laboratory, this approach not only offers environmental disposal advantages, but saves floor space because the lab no longer has to store used shippers.

PTE: What improvements are you seeing in pack-outs?

Bell (Marken): We are seeing a shift to universal packout configurations that remove the need for phase change materials at different temperatures and reduce the risk of user error during conditioning and assembly. Another example of packout improvements is the addition of chemical indicators to phase change plates to ensure correct conditioning prior to assembly and deployment.

Swistock (UPS): Temperature-control technology is improving, and packouts can be much longer than they were in the past. Traditionally, the packout standard has been 24 hours up to 48 hours, but now we are working to bring that up to 96 hours. If shippers can provide this level of protection for a two-day trip, it will ensure safety in case of transportation and weather delays.
capabilities include replenishment of dry ice and ensuring the integrity of shipment. UPS works closely with its business partner, Cryoport, and uses Cryoport’s dewars, and shipments can be initiated from either Cryoport’s or UPS’ websites.

**Impact of serialisation**

**PTE:** How is serialisation affecting packaging equipment design and features?

**Bell (Marken):** In packaging, we are seeing a greater focus on security around seals and tamper-evident closures along with greater use of GPS tracking and geofencing to address the US Drug Supply Chain Security Act (DSCSA) concerns for drugs in transit. From a technology standpoint, chain of identity solutions—based on the integration of GPS, radiofrequency identification (RFID), and Bluetooth technologies—are being built into packaging and linked to cloud-based tracking software. This becomes especially critical for cell, gene, and immunotherapy products that are patient-specific or derived from patient initially.

**New biologics pose new challenges**

**PTE:** What role are new biological treatments (e.g., cell and gene therapies) playing in the clinical trial logistics business today, and how does planning for trials with these products differ from planning for traditional clinical trial logistics?

**Swistock (UPS):** These treatments are still a small part of the clinical trials business, but they require a disproportionate amount of front-end planning. Over the past few years, we’ve seen that sponsors really want to know how integration can play a greater role.

These studies require cryogenic shipping, so the question is how many more dewars can be accommodated in our network. This work is also highly specialised. For example, we need to perform special studies for autologous compounds, which require cryogenic shipment on two legs of the journey. In general, these projects require a very complex and integrated network.

**Sweeney (World Courier):** Cell and gene-therapy products require extensive logistical planning. In the case of autologous cell therapies, the patient’s cells are the active pharmaceutical ingredient used in the manufacturing of the end therapy. Therefore, the patient becomes a part of the supply chain, and he or she can be directly impacted by delays or problems during the logistics process.

Additionally, particularly with consideration to the severity of the patient’s illness, the logistics timelines are always extremely tight. Any deviation can have a far reaching impact on the clinical team, end-therapy manufacturer, and patient.

When contrasted with small-molecule or biologics products, we find that there is much less margin for error with the logistics of cell and gene-therapy products. Scoping suitable time, critical routings, and educating airlines on the special nature of these products are all parts of the process.

**Best practices**

**PTE:** How should sponsors and contract partners approach collaboration for these projects?

What questions are critical to ask logistics and shipping specialists, and what specific functions should each partner assume?

**Swistock (UPS):** Important questions should revolve around service partners’ experience and safety record with dewars, as well as packouts and how long the shipments will remain viable without taking additional steps.

**Klingelhofer (World Courier):** Sponsors and contract partners should collaborate in early planning stages for both early clinical and commercial development. Although early clinical-stage development requires careful planning, when the scale is increased to commercial application, it is absolutely imperative that sophisticated scheduling and tracking is put into place. It is extremely beneficial for logistical plans for both early clinical-stage development and commercial development to be discussed during the planning phases.

Questions can range widely and should include the following, all of which must be addressed at the onset of planning:

- How many sites, countries, and cities are involved?
- What is the estimated number of patients?
- What is the nature of the contents—i.e., are they kits, packaging, or apheresis samples?
- Is temperature control management required?
- What is the nature of required chain of custody tracking, or are there any special shipment handling requirements involved (e.g., is x-ray permitted?)

### Last-mile temperature control

An example of a new cold chain temperature-controlled shipping technology is Cocoon, which was commercialised in November 2016 and designed for use with pallet-sized shippers. Cocoon, which eliminates the need for an external power source, was developed by World Courier’s Climate Optimization Research and Engineering (CORE) laboratories. Composed of vacuum-insulated panels in a honeycomb design, Cocoon weighs 15–30% less than comparable packaging products, covers European and US pallet sizes, and supports three temperature range requirements: -15 °C to -25 °C, 2 °C to 8 °C, and 15 °C to 25 °C. The vacuum-insulated panels, coupled with Cocoon’s phase-change materials, provide a high-level of thermal protection and stability for temperature-sensitive pharmaceutical products throughout long-distance deliveries. According to World Courier, Cocoon packaging solution maintained its internal temperature throughout a two-week delivery from Austria to Baghdad, Iraq, which included 10 days of storage in uncontrolled warehouse temperatures.
In both development and commercial projects, experts point to the need for sponsors and partners to collaborate on cold chain as soon as possible. Among the difficult, but necessary, points to address are:

- Number of sites involved in the clinical trial
- Estimated number of patients taking part
- The nature of the contents being transported, whether they are kits, packaging, or samples
- Temperature control management requirements
- Details on the required chain of custody tracking, and whether any special shipment handling is involved (e.g., x-ray).

**Klingelhoefer (World Courier):** Generally, it will help sponsors to have a basic understanding of the shipping lanes, transit time requirements, and temperature-control parameters to be able to anticipate potential issues and allow solutions to be pre-emptively created. For example, if the end therapy is going to be transported in a liquid nitrogen dry shipper, then who is going to provide the liquid nitrogen shipper? And, who is going to ensure that the dry shipper unit is properly charged with liquid nitrogen? The answers to these questions will help determine responsibilities, a plan of action, and timeframes.

**Autologous therapies**

**PTE:** What are the unique challenges of moving autologous, as compared with non-autologous cell and gene therapies, and other personalized medicines?

**Swistock (UPS):** With autologous therapies, the biggest complexity is that, not one, but two really high-performance shipments are involved. There can be challenges, for instance, when the patient visits a facility where blood is collected. Often these trials are run in dispersed locations. In some cases, there will be fewer labs available to send the blood. In general, with autologous treatments, planning is particularly important for the journey’s second leg. Line between two points.

**PTE:** With the circular supply chain, there is generally more of a need for careful coordination between apheresis and manufacturing slots. With allogeneic, there is likely more room for maneuvering because it relates to the time between when the therapy is manufactured and the time it is needed for infusion into a patient. The more complex circular supply chain for autologous requires precision planning with no room for error or delays. The straight line supply chain for allogeneic relies on experienced specialists.

**PTE:** What special temperature-control technologies, storage, and transportation options are required for these therapies?

**Klingelhoefer (World Courier):** This will vary on the product and pharmaceutical sponsor requirements. Sponsors often require temperature-controlled packaging for apheresis samples (typically 2 °C–8 °C packaging) and packaging for end-therapy product (typically liquid nitrogen dry shippers). In some cases, customers will ask for GPS tracking devices to help enhance visibility of their shipments.

**PTE:** Some clinical-trial materials are now delivered direct to patients’ (DTP) homes. Do you see that approach being used in the future for these types of materials, and how would that complicate the overall process?

**Bell (Marken):** Absolutely. The key with DTP in clinical trials is maintaining thermal integrity over the last mile. This is a critical link in the clinical supply chain and essential to the success of a clinical trial. Regulators are looking now at how to include and enforce standards around the last mile through good distribution practices (GDPs).

Further, with more pharma companies including both direct-to and direct-from patient homes as options in more of their protocols, we expect to continue to see increased demand. Finding packaging solutions that work well for delivery or collection from a patient at home, along with coordinating this service with in-home nursing care can be very challenging.

**Swistock (UPS):** We are seeing a relatively small amount of activity in DTP, but great interest. DTP exists for rare diseases, but the logistics for clinical trials, involving ambient temperatures, are easier. We’ve had success with these studies. Investigational medicinal products must be delivered on a regular basis, typically in one or two doses. In a clinical setting, they may be delivered less frequently. But if people have mobility problems, DTP studies open up potential business. So far, there have only been a few DTP studies involving cell and gene therapies, and they have required a lot of upfront work. In one case, the client had little compound available before each shipment, but doses had to be shipped 365 days a year. This required working with special operating places for Sundays and holidays, or when the patient was not home. Not every study is a good candidate for this type of approach, but we do expect DTP to become more important in the future.

**Sweeney (World Courier):** At the moment, the majority of shipments would be beyond the scope of home coordination. For many situations, the end-therapy product must be sent at frozen temperatures, including some cryogenically frozen material, which then requires a sophisticated thawing process before infusion. Currently, it is unrealistic to expect a DTP scenario for most cell and gene-therapy products. PTE
Ensuring Sterility in Small-Scale Production

Susan Schniepp, distinguished fellow at Regulatory Compliance Associates, discusses how to ensure sterility when manufacturing small-scale parenteral batches.

Q. I am a small-scale parenteral manufacturer and have been approached to support a clinical programme through Phases II and III. What considerations are important for the small-scale production lots?

A. This situation always raises some interesting discussions. The statistical assurances for sterility for normal commercial lots are not available because of the usually small lots during clinical production. At the same time, the need to minimize any unanticipated clinical risks remains high. The best advice is to consult the regulations and determine what requirements you must meet to help ensure the clinical material you are manufacturing is safe.

Clinical-trial material batches can range from as few as 200 to as many as 5000 units or more. It may not be feasible for these small-size batches to be produced on a traditional manufacturing line. In fact, some of the batches might be manufactured under a laminar flow hood by manual aseptic processing. It is important to remember that sterility assurance of the product must be maintained even when the clinical-trial materials are being prepared by hand because of the small lot sizes required. For these small-scale batches, manufacturers need to adhere to the recommended requirements for control of the environment as defined in the US Food and Drug Administration’s (FDA) aseptic processing guidance (1), the Parenteral Drug Association’s Technical Report #62 (2) on manual aseptic processing, and in EudraLex Volume 4, Annex 1 (3). In other words, the environment must be maintained and monitored with the recommendations specified in the documentation governing aseptic processing.

Properly maintaining an environment suitable for the manufacture of aseptic drug products regardless of batch size is not as clear-cut as it seems. Quality personnel responsible for batch release need to take into consideration a number of factors before the lots in question can be released. These factors include assuring appropriate use of disinfectants before, during, and after manufacturing; proper gowning and aseptic technique of the operators; and making sure the environmental and qualification data support the operations.

Creating sterility programmes

So, what does this all mean? It means the company must have a robust programme in place to support the sterility of the batch regardless of the lot size. There needs to be a cleaning programme defining the proper use of disinfectants/sporocides before, during, and after processing. It means there should be a gowning qualification/requalification programme for personnel responsible for the product manufacturing. The gowning programme should define how operators are initially qualified, how they are monitored for microbiological excursion during gowning, during manufacturing, and upon completion of manufacturing activities. It should also define how operators will be periodically requalified and how operators will be requalified in the event of an out-of-specification result. Operator aseptic technique should be tested through the conduction of media fills representative of the actual manufacturing runs. At a minimum, media fills should be performed annually.

Components used in the manufacture of aseptic processing on a small scale need to be rendered pyrogen free before being introduced into the manufacturing area.

There also needs to be a facility maintenance programme that challenges the appropriateness of the air handling system. Establishing a periodic maintenance programme for your high-efficiency particulate air (HEPA) air filtering system and performing periodic smoke studies to make sure the airflow is suitable for aseptic operations should provide the assurance that the airflow system is in control and is functioning appropriately.

In addition to the above recommendations, the company should have a programme to control incoming components. Components used in the manufacture of aseptic processing on a small scale need to be rendered pyrogen free before
being introduced into the manufacturing area. Small-scale batches will not be taking advantage of continuous processes associated with large-scale lot manufacturing, so consideration must be given to how the materials and components will be introduced manually into the manufacturing area. This will require even greater emphasis on operator technique. In some instances, the manufacturing equipment used in small-scale batch production is portable, so this programme should also encompass the introduction of the necessary manufacturing equipment into the production area.

Properly maintaining an environment suitable for the manufacture of aseptic drug products regardless of batch size is not as clear-cut as it seems.

There needs to be an established environmental monitoring programme. The environmental monitoring programme for small-scale batch production should provide the information on the quality of the aseptic processing environment including any ancillary areas such as the equipment/component processing area, gowning rooms, laminar flow hoods, floors, ceilings, walls, and equipment surfaces including those that come into contact with the product components as well as the product itself. Determining the appropriate monitoring locations should be determined through a comprehensive risk evaluation that should periodically be reviewed and updated to reflect the most current operating conditions.

Finally, there needs to be consideration to final product testing and the appropriate number of samples needed to ensure the product is sterile and safe for patients. The samples needed for testing should be taken from the beginning, middle, and end of the manufacturing run and the number taken should be reflective of the batch size.

Successfully manufacturing small-scale parenteral batches suitable for patients requires many of the same procedures and controls needed for large-scale parenteral manufacturing. If you keep in mind—regardless of batch size or manufacturing process—that the ultimate goal is to assure the sterility of the product throughout the manufacturing run and you use the data collected to determine the suitability of your processes, you should be able to produce any size batch in accordance with regulatory expectations.

References

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.

More on sterile manufacturing
Visit PharmTech.com to read more articles on sterile manufacturing, including the following:
- **Airlocks for cGMP Facilities**
  www.pharmtech.com/airlocks-cgmp-facilities

- **Defining Risk Assessment of Aseptic Processes**

- **Parenteral Advisory: Outmoded Fill/Finish Technology**
  www.pharmtech.com/parenteral-advisory-outmoded-fillfinish-technology-0

- **Designing Flexible Aseptic Containment Systems**
  www.pharmtech.com/designing-flexible-aseptic-containment-systems

Ad Index

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalent Pharma Solutions</td>
<td>52</td>
</tr>
<tr>
<td>EBD GmbH</td>
<td>33</td>
</tr>
<tr>
<td>Lonza Clinical Development &amp; Licensing</td>
<td>17</td>
</tr>
<tr>
<td>Meggle Group Wasserburg</td>
<td>21</td>
</tr>
<tr>
<td>Peter Huber Kaltemaschinenbau GmbH</td>
<td>9</td>
</tr>
<tr>
<td>Rommelag AG</td>
<td>2</td>
</tr>
<tr>
<td>Shimadzu Europe</td>
<td>51</td>
</tr>
<tr>
<td>Starna Scientific</td>
<td>13</td>
</tr>
<tr>
<td>Veltek Associates Inc</td>
<td>7, Outsert</td>
</tr>
</tbody>
</table>
Shimadzu’s LCMS-8060 makes a real difference to working better and faster. The LCMS-triple-quadrupole combines all UF technologies and pushes the limits of LC-MS/MS quantitation for applications requiring highest sensitivity and robustness.

**World’s highest sensitivity**

based on the new UF Qarray technology, delivering new limits of MRM sensitivity and impacting full-scan sensitivity.

**Unmatched speed**

due to data acquisition with scan speed of 30,000 u/sec and polarity switching time of 5 msec.

**Outstanding durability**

achieving peak area response RSD of 3.5 %*, thus showing high robustness

*2,400 samples of femtogram levels of alprazolam spiked into protein-precipitated human plasma extracts over a 6 day period (over 400 samples were injected each day).
As the #1 global leader in drug development and delivery, we have a passion to help you bring better treatments to your patients, faster. Our broadest expertise and superior technologies helped optimize thousands of molecules from pre-formulation through all development stages. Our integrated analytical, clinical, and manufacturing services along with patient-centric dose design streamlines and accelerates your path to patients.