Packaging Trends 2017
From blister packaging to patient-centred fill/finish operations
SCHOTT Rigid Caps

IT’S YOUR TURN!

By offering our prefillable syringes portfolio for syriQ® and SCHOTT TopPac® with an intuitive screw-off closure system, we enable pharmaceutical companies to ensure improved stability and more ease of use.

What’s your next milestone?

www.schott.com/pharmaceutical_systems

IMPROVED STABILITY

IMPROVED EASE OF USE

syriQ®

SCHOTT TopPac®

SCHOTT
glass made of ideas
Features

FOCUS: PACKAGING TRENDS
16 Blister Packaging Moves Forward
Advances in materials and equipment for pharmaceutical blister packaging protect quality and enhance shelf life.

20 Packaging’s Flexible, Patient-Centred Future
Primary packaging and container design reflects a move to patient-friendly formulations and delivery systems, and more agile manufacturing processes.

22 New Packaging Solutions on Display at Pharmapack 2017
Manufacturers will display a variety of unique packaging solutions during Pharmapack Europe 2017.

2017 EUROPEAN BIO/PHARMA OUTLOOK
24 Solving the Post-Brexit Puzzle
As Europe’s bio/pharma market learns that breaking up is hard to do, it must address productivity, regulatory, and drug pricing challenges.

FORMULATION: OLIGONUCLEOTIDES
28 Characterization and Impurity Analysis of Oligonucleotide Therapeutics
Analytical technologies play a key role in the characterization and quantitation of oligonucleotide therapeutics.

SINGLE-USE MANUFACTURING
40 Validating a Method for Point-of-Use Leak Testing of Single-Use Bag Assemblies
The authors describe the development and validation of a highly sensitive point-of-use pressure decay test.

PROCESS OPERATIONS
44 Defining Quality: Joining the Quality Lab and the Plant Floor
As pharmaceutical quality metrics evolve, they will need to incorporate more of the principles of operational excellence, says consultant Prabir Basu.

Peer-Reviewed

32 A Statistical Decision System for Out-of-Trend Evaluation
The authors present a set of statistical decision rules based on linear regression models that can be implemented in an automated trend system to assist stability studies.

Regulars and Columns

6 GMP/GDP Inspections
The GMP/GDP Inspection Landscape–Part I: Data

12 European Regulatory Watch
The Evolving Role of HTA Bodies Sparks Scrutiny

14 Outsourcing Review
The Tide Stays High

46 Ad Index

47 Pharmapack Exhibitor Profiles

50 Ask the Expert
Staffing and Preparation for Audits

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 LinkedIn logo is a registered trademark of LinkedIn Corporation and its affiliates in the United States and/or other countries
IF YOU NEED ASEPHTIC 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
The GMP/GDP Inspection Landscape—Part I: Data

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has conducted an annual survey of GMP/GDP inspections at sites and affiliates among its member companies from 2003 until the present time. This article describes findings of the EFPIA annual survey of site inspections among its member companies.

**Good manufacturing practice (GMP) inspections** are fundamental for ensuring that medicinal products are produced to the high standards required for patient safety. The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents research-based pharmaceutical companies in Europe. For reasons of transparency, EFPIA conducts an annual survey of inspections among its member companies. The data generated demonstrate the workload, use of resources, and the outcome of inspection practices for oversight of 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). The purpose of this data collection is to create awareness and develop potential opportunities to redirect resources toward better site coverage and, therefore, protection of the patients. Part I of this article reports, for the first time, the results of the annual inspections survey. Part II will look at additional challenges and opportunities for improving inspection efficiency (1).

**Legal background**

According to the International Council for Harmonization of Technical Requirements for Human Use (ICH), inspections of a firm’s manufacturing operation are essential to evaluate commercial manufacturing capability, adequacy of production and control procedures, suitability of equipment and facilities, and effectiveness of the quality management system in assuring the overall state of control. Notably, pre-approval inspections include the added evaluation of authenticity of submitted data and link to dossier (2). Inspections of a firm’s manufacturing operations assess GMP and GDP compliance and are legally required for drug (medicinal) products in most countries worldwide. In some regions, inspections of API manufacturers are also mandatory. Furthermore, relevant regulations for quality systems (3) require companies to have an independent auditing scheme of their sites, contractors, and suppliers. Recent emerging regulations require regulatory authorities to inspect manufacturers in the countries where the medicines and APIs are produced.

**Objective, scope, and definition of the EFPIA survey**

The objective of the annual survey is to provide awareness of global health authority inspection activity, focusing on duplicate inspections as a means of determining the value to the patient while controlling risk. Through the annual survey, EFPIA aims to encourage regulatory authorities to focus their resources on activities that pose higher risks to patient safety and to drive a collaborative approach among health authorities in inspection practice and sharing of inspection outcomes. EFPIA recognizes that convergence in activities between regulators is essential to effectively evaluate commercial manufacturing capabilities.

The EFPIA member companies reported inspections at companies of research-based manufacturers. The numbers should be seen as a snapshot. Aspects of the survey are as follows:

- Regulatory GMP/GDP inspections conducted at manufacturing sites and affiliates, inside and outside the regulatory authority’s own borders, including related International Organization of Standardization (ISO) certifications (e.g., for combination products/medical devices) are included in the data.
- Only companies that own facilities are reported, as inspections of contract manufacturers might be counted twice.
- Sites that manufacture both human and veterinary
VIABLE AIR MONITORING IS JUST ONE TOUCH AWAY

SMA ONETOUCH® ICS
A FULLY INTEGRATED PLC CONTROLLED VIABLE MONITORING SYSTEM

FEATURES
- Precise and calibrated air sampling to each SMA atrium
- Real time monitoring and control of all sample parameters
- Immediate alarming function on any sampling location
- Full integration of facility maps and floor plans

LEARN MORE AT WWW.STERILE.COM

VELTEK ASSOCIATES INC
1-888-4-STERILE • SMA@STERILE.COM
products are included in the scope of this survey. Other inspection types (e.g., on pharmacovigilance aspects [GPvP], inspection on narcotics, and environmental safety) had been reported in some cases, but not assessed.

- Sites manufacturing exclusively veterinary products are not reported.

In addition to the data collection, there are specific questions concerning inspection activities that are adapted each year to reflect areas of particular interest to EFPIA. The definitions used in the survey are available online (listed online in Table I).

Data assessment
Over the span of the survey so far (2003 to 2015), data have been collected from approximately 660 manufacturing sites annually. Conducting and receiving inspections involve considerable regulator and industry resources. There were 486 foreign inspections and 693 domestic inspections, which required 3951 foreign inspector days and 4456 domestic inspector days. It should be noted that these days were spent by regulators only; industry resources are not included in the figures. Also, these days do not include resources used for paper-based inspections or inspections where no inspector days had been reported. Less than 10% of the inspections were reported as unannounced. Whether announced or unannounced, there was a high level of compliance (more than 95% of the inspections had positive outcomes, with no regulatory action required).

Inspectorates performing foreign inspections
Over the past 12 years, 64 countries have performed foreign inspections. In 2015, 34 countries performed foreign inspections, compared with 40 in 2014 and 31 in 2013. The survey results showed the number of foreign inspections per country in 2015 (see Figure 1). Group 1 is formed by countries performing more than 60 foreign inspections; Group 2 is for countries performing more than 20 and less than 60 foreign inspections. In addition to those shown in Figure 1, there were also seven countries where one foreign inspection was made.

The data show that countries in Group 1—the United States and the European Union (where all EU countries are counted as one inspectorate)—perform approximately twice the number of foreign inspections compared with countries in Group 2. A trend analysis of survey data from 2011 to 2015 revealed:

- A downward trend in the number of foreign inspections being performed annually by Group 1 and Group 2 countries from 2011 to 2015 with some exceptions.
- An upward trend in the number of foreign inspections being performed annually by other countries (e.g., China performed five foreign inspections in 2011 compared with 16 in 2015; Belarus performed three foreign inspections in 2011 compared with 12 in 2015).

Analysis of foreign inspection activity between the ICH founding members of the US, EU, and Japan in 2015 revealed the following:

- The US performed 62 foreign inspections in the EU, compared with 104 inspections in the previous year. It performed no inspections in Japan in 2015, compared with one inspection in 2014.
- The EU performed 35 foreign inspections in the US, compared with 36 in 2014; it conducted no inspections in Japan, compared with one inspection in 2014.
- Japan conducted 12 inspections in Europe in 2015, compared with 23 in 2014; it performed 10 inspections in the US in 2015, versus 19 inspections in 2014.

There were significantly fewer inspections from the US in Europe (approximately 40%) and from Japan in the EU (approximately 48%). Similar reductions had been reported in the 2014 data.

Number of on-site inspections at a site
The maximum number of inspections at a single site within one year has been reported to be 15, including seven foreign inspections. The same workload for foreign inspections had been reported by five sites. Overall, 52 sites received more than four inspections in 2015,
570 sites report having between one to four inspections in 2015, and 118 did not receive any inspections in 2015. Although the number of sites with no inspection is decreasing, indicating better overall coverage, there are still sites that are not inspected. This observation might suggest that resources could be better balanced.

The survey asked for specific data from sites receiving multiple inspections, with the aim of addressing the question: “Are multiple inspections driven by risk?” It was noted that one manufacturing site can have several manufacturing licenses, thus there can be a need for several inspections at the same geographical location. However, there was no clear indication that these multiple inspections were always driven by risk. The data also confirmed that there is always intensive domestic oversight.

**Inspections at a manufacturing site**
In general, the inspections cover drug products (64%, including 18% sterile operations), API (20%, including 10% biotech API sites), vaccines manufacturers (8%), others (5%), and medical devices (3%). The majority of foreign inspections target the drug product (see Figure 2).

The survey results confirm the split of product types inspected remains constant among the different inspectorates with the exception of Japan. The authors believe this could be a result of the specific mutual recognition agreement (MRA) between Japan and Europe.

**Operations inspected**
Of reported inspections, 85% were GMP related, 4% were GDP related, 3% covered ISO certification, and 8% were related to other GxP operations. The data show that:
- 79% of domestic inspections concerned GMP compared with 94% of foreign inspections
- 5% of domestic inspections examined GDP compared with 2% of foreign inspections
- 11% of domestic inspections examined other GxP compared with 4% of foreign inspections.

Foreign inspections focused largely on GMP processes. Inspection of distribution licenses was performed mostly by the domestic regulatory authorities.

**Considerations of GDP inspections**
For the purpose of the survey, a GDP inspection is defined as an inspection that covers systems and processes within the scope of the distribution license. A significant number of new regulations and guidelines (4–7) were published in recent years aiming at better control of distribution channels to prevent entry of falsified products in the legal supply chain. Inspections of GDP compliance are, therefore, deemed to be important. They can be performed at a manufacturing site and/or at an affiliate of the company in the country of destination or at a hub. The survey shows that more of these inspections are performed each year.

In the 2015 survey, 203 inspections were reported to include GDP in their scope:
- 91% were domestic inspections—81% at affiliates and 19% at manufacturing sites; 2% of the inspections covered APIs or API/sterile and 98% covered finished products; none of these inspections reported a follow-up with interruption of supply
- 9% foreign inspections were reported—58% of these inspections had been performed at manufacturing sites; 42% of these inspections at affiliates (15% of these included an ISO certification).

**Inspections at affiliates**
Out of the 22 companies surveyed in 2015, 16 reported inspections at affiliates. The majority of inspections were conducted according to distribution licence. Other topics covered are GMPs (e.g., supply chain verification by a responsible person, repackaging, relabeling), other GxP processes (e.g., pharmacovigilance), and ISO certifications. There were 309 inspections at affiliates; 93% were domestic inspections (performed by inspectorates from 99 countries), and 4% were foreign inspections:
- 83% of all inspections had no follow-up
- 10% of all inspections had follow-up without interruption of supply
- 6% of all inspections had follow-up with interruption of supply (e.g., distribution affected, import delay, delivery to customers affected)
- 1% of all inspections had no outcome reported/outcome pending.

The majority of inspections at affiliates named the GDP distribution license as the primary scope of the inspection and drug product as the product type inspected.

**Different forms of inspection**
The survey analyzed the different forms of inspections. In 2015, there were 160
inspections flagged as pre-approval inspections (PAI) of manufacturing sites (95 were foreign and 65 were domestic inspections).

Two joint inspections were reported in 2015, which were in fact, two inspections running in parallel at the same time and were thus “concomitant” inspections rather than joint inspections: one inspection in the US from the Food and Drug Administration (FDA) and EU, and one inspection in Australia by Australia’s Therapeutic Goods Administration (TGA) and US FDA.

In the past, the industry has described positive and negative views of joint inspections, with some companies questioning the benefits and reporting that it feels like two different inspections at the same time. From the regulators’ point of view, there is an open question if joint inspections will continue to be organized. Joint inspection pilot programmes were initiated by US FDA. Later, US FDA joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), shifting the exchange toward mutual reliance on inspection data from partner inspectorates. The PIC/S Joint Audit Programme could still be used for alignment and training purposes.

Paper-based foreign inspections

Twenty-four paper-based inspections were reported as foreign inspections in 2015. These inspections were conducted by China, Chinese Taipei, Germany, Japan, South Korea, Syria, and US FDA. Inspected companies felt a need to involve a lot of resources due to requests for specific inspection formats and questionnaires. This issue was compounded by the fact that institutionalized formats such as the PIC/S site master file were not accepted by the different regulators.

**Assessment of the outcome of inspections**

Data on compliance following inspections are shown in Figure 3. The data indicate that domestic and foreign inspections lead to similar outcomes.

**Conclusion**

Inspections are essential to evaluate commercial manufacturing capability, adequacy of production and control procedures, suitability of equipment and facilities, and effectiveness of the quality management system in assuring the overall state of control and can include the evaluation of authenticity of submitted data in a registration dossier. The results of the survey based on the 2015 inspection data and trends since 2003 demonstrate duplication, workload, use of resources, and the outcome of inspection practices for oversight of GMP and GDP inspections and certifications.

**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, the 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**

5. Good Distribution Practice of Medicinal Products for Human Use, Guideline 2013/C 343/01 (5 Nov. 2013).
Improved protein solubility and titres with the VB expression vector platform

Innovative solutions are required for the development of cost-effective API production processes in the highly competitive pharmaceutical industry. Vectron provides next-generation upstream technologies for increased protein titres and solubility in *E. coli* and other bacteria.

Contact us for feasibility studies for your protein.

Example study: Production of a challenging antibody fragment in HCD *E. coli* fermentation

![Graph showing solubility and plasmid copy number](image-url)

For more information, visit: www.vectronbiosolutions.com
The Evolving Role of HTA Bodies Sparks Scrutiny

Political pressure to closely examine the relationship between drug prices, R&D, and production costs has increased, but how involved should HTA bodies be in assessing cost effectiveness and reimbursements?

Governments in Europe are increasingly looking to health technology assessment (HTA) organizations to help them gain a tighter grip on expenditure within the region’s predominantly state-funded healthcare services. As a result, the pharmaceutical industry is having to deal with a rising number of HTA bodies. Currently there are more than 50 national and regional HTA organizations in the 28-member states of the European Union and in non-EU states such as Norway and Switzerland. Their main task is to assess the clinical effectiveness of a new medicine in relation to similar products on the market so that an HTA can help in the fixing of the drug’s price and of the level of reimbursement at the national level.

A broadening scope of responsibilities

Many of the HTA organizations tend to have different assessment procedures and criteria for judging the added value of a product. Furthermore, a growing number of HTAs are moving beyond the clinical domain to investigate aspects such as cost-effectiveness, budget impacts, ethical and legal issues, and broader social and economic questions. This shift is bringing HTAs into what some drug producers would regard as borderline areas such as consideration of preclinical R&D costs, process development, and choice of formulations.

With some new medicines, acquiring a positive HTA can be as big a challenge as gaining authorization from a regulatory agency. There can be gaps of several years between a drug being licensed in a country and being given the go-ahead for reimbursement within its healthcare system. There are widening disparities in patients’ access to new medicines across the EU due to delays in reimbursement decisions. To speed up assessments by minimizing unexpected complications during investigation procedures, HTA bodies have been allowed to join regulators in giving preliminary scientific advice early in the drug development process. The objective is that this HTA guidance should concentrate on issues relating to the planning and design of clinical trials so that they provide data relevant to requirements of a technology assessment.

The industry’s perspectives

Governments are under pressure, however, to encourage HTA bodies to broaden their expertise so that they can have an even greater influence on drug development beyond clinical trials particularly in areas such as cost effectiveness. But the pharmaceutical industry has made clear that this widening of responsibilities should not involve assessments of manufacturing processes and their costs.

“At present, HTA bodies do not hold the knowledge and understanding to provide scientific advice in respect of production processes, in particular bio-manufacturing processes,” a spokesman for the European Federation of Pharmaceutical Industries and Associations (EFPIA) told Pharmaceutical Technology Europe. He pointed out that the London-based European Medicines Agency (EMA) and national licensing authorities have specialist knowledge of how production processes can affect the quality, safety, and efficacy of medicines. “We would consider this kind of expertise [in HTA bodies] as unnecessary to assess the clinical benefit of a new medical technology, including new medicines,” he continued. “It would be a superfluous duplication of expertise, processes, and assessments, if HTA bodies were to set out to develop expertise on production processes.”

EFPIA and other representatives of research-based drug companies are also not keen about the idea of HTAs’ scope being extended to R&D costs when dealing with cost effectiveness and impacts on healthcare budgets. “R&D costs are [not] relevant in setting reimbursement levels,” says the EFPIA spokesman. “Including R&D costs [in assessments] is not only difficult practically, as R&D costs are not attributable to one single product or country, but are shared across multiple projects and multiple regions. It is also inefficient. Setting the reimbursement level in relation purely to the costs of development, including R&D, would mean rewarding inefficient research and production processes.”

Cost effectiveness and access to medicines

Nonetheless, HTA organizations are participating in discussions with drug companies about lowering their planned prices for new medicines by cutting costs, including process costs, to make the prices more acceptable. The United Kingdom’s National Institute for Health and Care Excellence (NICE), one of Europe’s largest and longest established assessment bodies responsible for HTAs in England, has been given the role by the British government of vetting new oncology drugs, whose reimbursements costs are covered by a Cancer Drugs Fund (CDF). Money available annually under the fund was recently increased by NHS England, part of the UK’s state-funded National Health Service (NHS), more than five-fold since 2010 to £340 million ($432 million) (1).

To make the CDF drugs more quickly accessible to cancer patients after they are licensed, they are assessed by NICE during their development on the basis of quality-adjusted life years (QALYs) or how many years a treatment adds to
a person’s life and the quality of those years. One QALY is equivalent to one year of perfect health so that if a patient’s state of health falls below that level, it is rated less than one QALY per year.

NICE has been setting a threshold of £20,000–30,000 per QALY when deciding whether a new drug is cost-effective and should be approved for widespread use, according to a study by York University’s Centre for Health Economics (2). But it has also been approving new technologies at more than £40,000 per QALY (2).

In October 2016, NICE jointly proposed with NHS England a tiered system of categorizing new medicines by their cost-effectiveness on the basis of QALYs (3). Medicines whose cost effectiveness ratio fell below £10,000 per QALY could be put through a “fast track” NICE assessment. Medicines based on highly specialized technologies, such as those for treatments of rare diseases, would be given an upper limit of £100,000 per QALY to qualify for an HTA. Drug companies have been having to lower their prices by cutting costs to bring their medicines within the QALY threshold.

NICE stresses that when calculating cost-effectiveness, it does not need to investigate production processes or overall R&D costs. “Consideration of cost effectiveness does not require consideration of R&D costs,” an NICE official told Pharmaceutical Technology Europe. “[Our assessments] are based on patient outcomes measured in QALY with cost effectiveness measured in cost/QALY. The evaluation of production processes is part of the role of the regulator and NICE does not need to consider this.”

Drug pricing, R&D, and production costs

However, the political momentum behind calls for closer examination of the relationship between drug prices and R&D costs as well as production costs has been gathering pace. The European Parliament’s environment, public health, and food safety committee (ENVI) has demanded greater transparency of research data and costs. “The cost of development and clinical trials is crucial in order to set fair prices,” noted Soledad Cabezon Ruiz, rapporteur of an ENVI report on EU options for improving access to medicines (4). “A fair price should cover the cost of the drug development and production, plus a margin of profit,” she added.

Amidst the potential for greater use of personalized medicines resulting from the application of advanced technologies such as gene and cell therapies, production is likely to take up a higher proportion of some individual drugs costs. As a result, these new technologies could raise the profile of manufacturing costs, in particular when inconsistencies in production performance in the early stages of development can raise total R&D costs.

Collaborations and joint assessments

The European Council, representing the EU member states governments, urged in 2015 the drawing up of central guidance and criteria on HTAs of personalized medicines. It also suggested that there should be more co-operation between HTA bodies in the assessment of the medicines (5).

Over the past few years, HTA agencies have been joining together through a European network (EUnetHTA) to carry out joint assessments so that they can share expertise more effectively, particularly in areas where there is a shortage of specialist knowledge within assessment bodies. “Collaboration and knowledge-sharing amongst HTA bodies can contribute to increased expertise and more efficient HTA systems,” Ancel.la Santos, policy advisor at Health Action International (HAI), a Dutch-based NGO campaigning on medicines access issues, told Pharmaceutical Technology Europe. “Cooperation can be particularly relevant in the context of more complex technologies and therapies,” she explained. “Collaboration between HTA bodies should preserve high quality standards, result in the improvement of methodologies and assessments where needed, and take into account local country specificities.”

EUnetHTA launched in June, 2016 its third and biggest joint action programme for the period 2016–2020 with the objective of carrying out, with the help of mainly EU funds of €20 million, 80 joint assessments or projects, compared to 20 under the previous programme (6). In an impact assessment of cooperation activities in HTAs, the European Commission, warned that the latest joint programme may be the last to be financed by the EU (6).

“The uptake of joint work at EU level (for use in) national decision-making processes has remained low, leading to duplication of work by national/regional HTA authorities,” said the commission’s study (6). “It is not rational to invest public funds into HTA co-operation at European level if the uptake of the work is not improved and the duplication of the efforts is not avoided.” The big difficulty is that the EU states cling on to their right to reach their own drug pricing and reimbursement decisions. This independence is undermining the benefits of HTA co-operation and holding back the broadening of the expertise in HTA bodies.

References

3. NICE and NHS England, Proposals for Changes to the Arrangements for Evaluating and Funding Drugs and Other Health Technologies Appraised through NICE’s Technology Appraisal and Highly Specialized Technologies Programme (London, October 2016).
A year ago, the outlook for contract services was a little uncertain. Equity markets’ appetite for public offerings from emerging bio/pharmaceutical companies had significantly diminished: valuations of emerging bio/pharma companies, as measured by the NASDAQ Biotechnology Index (NBI), had declined by 15% from their highs in mid-2015, and by mid-February, they were off another 28%. Because contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) get so much of their business from externally-financed companies, the negative energy surrounding emerging bio/pharma did not bode well for the industry.

The valuations and levels of public offering activity in 2014 and 2015 were not sustainable, and the NBI has never gotten back close to the levels it reached in 2015. Nevertheless, fundraising by emerging biopharma companies held its own in 2016. Financing for emerging bio/pharma from venture capital, public equity, and partnering sources was ahead of 2013 levels, and those companies showed no fear of spending liberally to progress their pipelines through clinical development. Public reports for more than 300 companies tracked by PharmSource show that R&D spending by those companies has risen every quarter since the beginning of 2015.

Not surprisingly, this has been great news for CDMOs and CROs. Most publicly-traded services providers achieved revenue growth well in excess of 10% in 2016 (based on interim results), especially in those services that cater to clinical development (clinical supplies manufacturing, analytical services, clinical packaging, and clinical research). Many CDMOs have told PharmSource that they are operating near capacity, and customers may have to wait as much as six months for a manufacturing slot.

The significance of external funding can be seen by looking at early-phase clinical trials sponsored by emerging bio/pharma companies. Phase I and II clinical trial registrations by emerging bio/pharma companies, as recorded in clinicaltrials.gov, were up 55% higher in the first half of 2016 versus the first half of 2012 (see Figure 1) (1). Just over half of those companies (55%) are publicly-traded companies, while 45% are funded by venture capital. Clearly the tide of early development by emerging bio/pharma companies has risen thanks to the robust external funding environment.

The bio/pharma industry’s recent performance is encouraging, but what is really important is what the industry can expect going forward. There is a sense that the outlook is positive but with some significant uncertainties.

**US election impacts**

Clearly, general economic sentiment since the November 2016 presidential election has been positive, with an expectation that the regulatory environment will be less restrictive and the United States Food and Drug Administration will be approving more drugs more quickly. There have even been suggestions that a venture capitalist might be appointed to run the agency (no appointments had been announced at the time this column was written). However, emerging bio/pharma investors haven’t been moved much by this news as the NBI has remained at the same level it has been at for the past 12 months.

Enthusiasm for the bio/pharma industry may have been dampened by the president-elect’s campaign promise to go after high drug prices, including allowing Medicare to directly negotiate drug prices. The dismantling of Obamacare could further reduce spending on drugs, especially in hospitals and other institutional settings. Coupled with the aggressive efforts by pharmacy benefit managers to reduce private sector spending on drugs by reducing utilization and prices, overall drug spending is likely to face considerable headwinds. That could dampen new investment in the industry, especially if it becomes more difficult for novel treatments to get formulary access.

**Funding and investments**

One positive indicator for CDMOs and CROs is the robustness of venture capital investment. Venture capital money has always been more dependable than public equity, even during the years of the global financial crisis. In 2016, even though public equity dropped considerably, venture capital maintained a pace that was close to what it was in 2015 and nearly 60% higher than it was in 2012. Looking ahead,
Outsourcing Review

according to the blog Life Sci VC, life-science venture funds are raising record amounts of new money that can sustain emerging bio/pharma companies for an extended period (2).

Of course, few venture capital or public equity investors place bets on emerging bio/pharma companies with the expectation that they will commercialize their pipeline candidates on their own. Rather, they hope their companies will be acquired, or at least have their candidates licensed by, a global bio/pharma company. Acquired or in-licensed products account for a third to a half of product approvals gained by global bio/pharma companies in recent years, and their reliance on externally-sourced candidates appears to be greater than ever. According to a report published by Deloitte in December 2016, global bio/pharma companies are getting only a 1% return on their investment in internal R&D (3).

So the stars seem to be aligning for a continued healthy environment for CDMOs and CROs. The biggest risks will come from what happens to drug pricing and coverage; and from a system-wide economic shock that negatively impacts the entire economy. The former is likely but over an extended number of years; and the latter can’t be predicted.

References
1. ClinicalTrials.gov.

Figure 1: Ownership of emerging bio/pharma companies sponsoring clinical trials.

Source: clinicaltrials.gov; PharmSource analysis

TASI TEST represents a new force in the packaging leak detection market by combining 3 industry leaders, Bonfiglioli Engineering, Sepha & ALPS.

Our Pharma divisions, Sepha & Bonfig, have developed a range of innovative products designed to optimise packaging quality control processes in a pharmaceutical environment. These product lines include state-of-the-art equipment for:

- Package Integrity Testing
- Headspace Gas Analysis
- Product Recovery
- Packaging Solutions

For more information contact info@sepha.com

Visit us at Pharmapack Paris 2017:
Hall 4 Booths L63 & C70

tasitest.com | info@sepha.com | +44 28 9048 4848
Blister packaging, a common format for solid-dosage forms, continues to evolve. Equipment advances combine flexibility, servo controls, compact size, and integration with upstream and downstream equipment. Material and quality-control innovations focus on protecting product quality and maximizing shelf life. Pouch options wait in the wings to replace cartons.

A new entry in the North American market, the MHI Eagle blister packaging machine from Maruho Hatsujyo Innovations (MHI), is an American version of its parent company’s best-selling machine. Established in 2014, MHI provides US-based installation, maintenance, spare parts, and 24/7 technical support. Parent company, Kyoto-based Maruho Hatsujyo Kogyo, ranks as the second largest pharmaceutical packaging machinery company in Japan and has installed nearly 400 blister packaging machines there. “There is no child-resistant (CR) requirement in Japan, so we had to design sealing for CR lidding (push, peel/push, and peelable),” reports Gregory Zaic, president and CEO of MHI.

The MHI Eagle blister packaging machine (see Figure 1) operates at speeds up to 100 blisters per minute at a maximum index length of 90 mm and maximum index width of 130 mm. Designed for lower volume runs, the compact, servo-driven machine with inline inspection and multi-zone preheating is especially well-suited to copackers and lines with frequent changeovers (1). With hand screws to expedite tooling changes, changeover takes less than 10 minutes and requires no tools. Other quick changeover features include recipe-driven format change and a feeder station on wheels that plugs into the main unit. “We sell two feeder stations for the price of one-and-a-half so feeders can be swapped at changeover,” says Zaic. Swapping units moves feeder cleaning off-line and minimizes downtime for cleaning. The Eagle blister packager accepts feeders from other manufacturers and is easily integrated with a printer or cartoner.

A fully integrated, modular line from Körber Medipak’s Mediseal thermoforms, doses, seals, punches (perforates and embosses), diecuts, and feeds inserts and cartons. Direct product transfer eliminates fault-prone intermediate stacking units and minimizes change parts. Cameras confirm an insert is placed on every other blister before pairs of blister cards are stacked for cartoning. A display at Pharma EXPO (6–9 Nov. 2016) showcased an integrated line on its way to a factory acceptance test. The one-lane CP400 blister packager integrated with a P1600 cartoner featured hot-melt carton sealing but also could accommodate tuck carton closure. Other potential variations include a P3200 cartoner with dual stacking devices, integration of a...
printer from HAPA for online printing of lidstock, various dosing systems (brush box, roller dosing, automatic spiral conveyor, or dedicated feeder) and choice of roller or platen sealing. Maximum speed of the servo-driven line is 400 blisters per minute (2). A sophisticated human/machine interface (HMI) groups functions for ease of use and helps reduce changeover time to less than 30 minutes. “All the information is in the HMI, which provides detailed instructions by system for format changes,” Kai Trepte, area service manager at Mediseal, explains.

Blipack, a company based in Argentina, also supplies integrated blister forming and cartoning lines. The centerpiece, the Blistera 200-240 blister packaging machine, combines heavy-duty construction with user-friendly operation and quick and easy changeover and maintenance. The system can be electromechanical or driven by a programmable logic controller and is compatible with thermoforming or cold-forming and a wide range of accessories including printers and semiautomatic, automatic, dedicated, and universal feeders (3). Blipack’s integrated Estuchadora ACM 150 intermittent-motion cartoner loads cartons horizontally. Carton sizes range from approximately 0.6 x 0.5 x 2.0 in. to 3.5 x 2.8 x 7.9 in. (4).

Another turnkey blister packaging line integrates the TF1e thermoformer and the TC1 cartoner from Pharmaworks. The unified system results in a compact footprint, operates from a single control system, and produces up to 100 blisters/80 cartons per minute. A robotic pick-and-place module transfers blisters from die punch to cartoner flights and eliminates the need for change parts. The number of blisters transferred to the cartoner flights is controlled from the operator interface (5).

Robotics also play an important role in the Integra 520 V integrated blister packaging line from Marchesini Group. The servo-driven system fits in 10 m of floor space and features a balcony design for the thermoforming and cartoning sections. Capable of producing 520 blisters and up to 500 cartons per minute, the Integra 520 V line succeeds the Integra 320 model and incorporates an innovative pusher, a drum-type carton-opening system to manage higher speeds, and a new leaflet pickup and insertion system. Separating product loading from electrical and mechanical zones ensures quick and straightforward cleaning and changeover. An enclosed oil bath system protects mechanicals from wear and tear and extends service life. Maximum forming depth measures 9 mm, although a 12-mm option is available. Carton sizes range from 35 x 16 x 75 mm to 90 x 90 x 150 mm (6).

Uhlmann Packaging Systems, which has offered integrated blister packaging lines for some time, offers three models: the single-lane BEC 300 model for up to 300 blisters/150–300 cartons per minute; the dual-lane BEC 500, rated at 500 blisters/300–500 cartons per minute; and the three-lane BEC 700, capable of outputting 700 blisters/300–500 cartons per minute. Upgraded in 2015, the BEC 300 model features the latest control and drive technology, tool-free format changeover, and smooth surfaces for faster line clearance (7). Existing BEC 300 systems can be retrofitted to shorten the forming
cycle, simplify cleaning, and minimize abrasion marks on forming materials. Uhlmann’s Rebuild Packaging Systems Center performs electrical and mechanical retrofits using genuine Uhlmann parts to extend equipment lifespan and meet the latest GMP requirements and legal regulations. Upgraded equipment comes with detailed rebuild documentation, validation services, and one-year warranty. Rebuilding typically saves 30–70% compared to the cost of a new machine (8).

**Carton alternatives**
Cartons are the traditional secondary package for blisters, but CR pouches provide a lightweight, flexible packaging option. To simplify adoption of a CR pouch, the Child-Guard CR track and slider from Presto Products has a Drug Master File listing. In use, the caregiver moves the Child-Guard slider over a notch, pushes down on a tab and pulls back the slider to open the pouch (9). CR pouches from Impak meet ASTM (American Society for Testing and Materials) D3475 CR standards. Sliding tab or press-to-close CR designs require two-handed dexterity to open, making access difficult for toddlers but not for seniors (10).

**Quality control**
Quality control systems confirm blister packaging equipment is working properly. Systems, such as the camera-based IBIS inline blister inspection system from Pharmaworks, check product and print on sealed blisters. Installed inline or off-line, the vision system identifies flaws such as mis-shaped, damaged, missing, or rogue product, as well as incorrect color and foreign objects (11).

Seal integrity is checked on units such as the AMI 120 leak detector from Pfeiffer Vacuum (see Figure 2). The leak detector requires no tracer gas to nondestructively detect holes as small as five microns, a sensitivity up to 1000 times better than the traditional destructive blue dye dunk test. “Using helium as a tracer gas boosts sensitivity even more,” says Dennis Seibert, head of business development, Leak Detection, at Pfeiffer Vacuum. Time spans for the offline test range from 10–60 seconds. Calibrated orifices quantify the leak rate and provide an alert if seal quality is deteriorating. Compatible with thermoformed or cold-formed blisters, testing a different blister only involves a simple fixture change.

The VeriPac UBV leak detection system from PTI Packaging Technologies and Inspection combines vacuum with volumetric imaging to detect leaks in multi-cavity blister packs. The nondestructive test involves three steps: input the number of blister cavities; place the blister pack on the inspection plate; press start. In seconds, the display shows pass or fail, the volumetric measurement reading, and the location of any defective cavity. The technology provides rapid detection of defects as small as 10 microns in a test cycle that lasts less than 15 seconds (12).

**Innovative materials**
Activ-Blister material from CSP Technologies heat-stakes absorbent material to the interior of blister cavities. Silica gel and molecular sieve technology absorb tailored amounts of water vapour, oxygen, or a combination of the two to control the internal atmosphere of each cavity and protect product shelf life. The active feature can be adopted without changing the footprint of the packaging line (13).

Another option for sensitive products, Pentapharm LiquiGuard film from Klöckner Pentaplast, offers protection from package leaching and moisture gain or loss. The crystal-clear, autoclavable laminate accommodates hot-fill liquids, gummies, and other emerging dosage forms. Features include a customizable moisture barrier, excellent deep-draw properties for complex blister geometries, high heat stability (the glass transition temperature of the contact layer is 120 °C), high slip for quick release and increased productivity, and low leachability and extractability, with excellent odour and flavour retention. Applications include chewables, formulations sensitive to flavour or odour loss, nutraceuticals, pharmaceuticals, unit-dose liquids, and veterinary products (14).

**References**
We have come together to support all your outsourcing needs.

PCI Pharma Services, a market leader for integrated drug development and commercialisation

We have combined the expertise of Penn Pharma, Biotec Services International, AndersonBrecon and Packaging Coordinators to create PCI Pharma Services, an integrated pharmaceuticals provider positioned to support your drug needs from molecule to market. With drug development and manufacturing expertise, laboratory services, global clinical trial services, and commercial services for manufacturing and packaging, PCI supports over 50 product launches per year and medicines destined to over 100 countries around the world.

We invite you to learn more about how partnering with PCI can ensure the success of your next product launch.

Clinical Services
Manufacturing | Packaging & Labeling | Global Storage & Distribution

Commercial Services
Manufacturing | Packaging | Serialisation

© Copyright 2015 Packaging Coordinators, Inc. All Rights Reserved

AndersonBrecon UK Limited trading as Packaging Coordinators, Inc. is a company registered in England and Wales with company number 02543975 and VAT registration number GB 549 7026 19 whose registered office is at Capital Law, Capital Building, Tyndall Street, Cardiff CF10 4AZ, VAT Reg. No. 762 3299 16

Penn Pharma, a PCI company, is a Trading Name of Penn Pharmaceutical Services Limited registered in England & Wales No. 1331447 Registered Office: Capital Law, Capital Building, Tyndall Street, Cardiff CF10 4AZ, VAT Reg. No. 762 3299 16

Biotec Services International is part of Biotec Worldwide Supplies Group of companies, Registered in Wales No. 3483803, VAT Registration No. GB 108216149.
Packaging’s Flexible, Patient-Centred Future

Primary packaging and container design reflects a move to patient-friendly formulations and delivery systems, and more agile manufacturing processes.

Agnes Shanley

Biopharmaceutical packaging is changing. As pharmaceutical manufacturers embrace more flexible processes that limit the risk of product contamination, packaging and containment systems are being designed to facilitate manufacturing of smaller product lots and batches. Some fill/finish operations are moving to fully enclosed, automated operation, requiring the use of not only nested syringes and closures, but also nested vials and caps, and manufacturers are working to standardize these components.

Examples of flexible filling lines may be found at Boehringer Ingelheim’s Fremont, CA facility or Mithra Pharmaceuticals’ line in Belgium. The contract manufacturer, Singota, recently bought contained and fully automated filling technology from Vanrx Pharmasystems.

But agile manufacturing is only part of the picture. As pharmaceutical manufacturers develop more convenient formulations to improve patient compliance, designers of primary packaging and delivery system components have had to change their approach to product development. West Pharmaceutical Services, for example, teamed up with specialists in ergonomics and human factors to develop components for novel packaging and delivery systems (1).

Large molecules, which, in the past, could only be taken via infusion or repeated injection, requiring visits to the hospital or clinic, can now be taken with autoinjectors and new delivery systems, but the move to more patient-centred approaches has presented technical challenges. “The monoclonal antibodies and other biologics that are now being produced are highly concentrated and, therefore, the solutions are more viscous and may require higher dosing volumes,” says Fran DeGrazio, vice-president of scientific affairs and technical services at West.

These changes in dosing have driven recent improvements in packaging components. Earlier this year, for example, West introduced a 1–3mL plunger for use in 2.25-mL syringes, designed to deliver higher volumes of drug product—especially biopharmaceuticals. The new plunger was developed using the same principles that drive quality-by-design (QbD) practices in drug development. This controlled approach wound up revealing the need for a different design and shape, says DeGrazio. “These differences allowed us to optimize functionality and improve control,” she says.

Improved component designs come together in West’s SmartDose platform, which uses a cartridge system made from Daikyo Crystal Zenith (CZ) polymer, a cyclic polyolefin material. When coupled with the Daikyo Flurotec plunger, the system is silicone oil-free. The West SmartDose delivery device adheres to the patient and can deliver more than 3 mL of drug in several minutes.

In July 2016, the United States Food and Drug Administration (FDA) approved Amgen’s monoclonal antibody, Repatha (evolocumab)—not only the drug, but using the SmartDose delivery system and primary container. Five months earlier, Amgen had opted for CZ vials and a closure system based on West’s FluroTec stoppers, to contain its drug Imlygic (talimogene laherparepvec). The vial was designed to minimize extractables from entering product, says DeGrazio.

Benefits of glass substitutes

CZ’s ability to withstand lower cold-chain storage and transport temperatures, even down to the dry nitrogen level required for some gene and cell therapies, has been another benefit, says DeGrazio. In addition, when used as part of a syringe system, it does not contain silicone oil or tungsten, which has led to particulate contamination. This has been found to cause some proteins to aggregate in prefilled syringes (2). A number of companies are working on alternatives to silicone-treated glass containers, including W.L.Gore, which received a patent in 2014 for a silicone-free syringe stopper.

Closure testing

Maintaining system integrity and preventing contamination is crucial for product integrity and
patient safety, says DeGrazio, and manufacturers accomplish this in different ways, through improved facility and workflow design, use of machine vision inspection and continuous monitoring on the plant floor, and the use of higher quality elastomers and barrier systems. Improved integrity testing is also crucial.

In August 2016, the United States Pharmacopeial Convention (USP) released updated its recommendations for container closure integrity testing. The revised United States Pharmacopeia Chapter <1207> outlines the analytical tests that should be performed to show integral product safety, for instance, leak detection for vial and syringe systems, says DeGrazio. Before the chapter was published, she says, methylene blue dye testing was used in vacuum to find leaks. Now, regulators realize that such methods are more probabilistic than deterministic, she says, and subject to error. Among the methods that West uses and offers is helium leak detection, which allows testing and validation down to -120 °C to -140 °C.

**Nested systems**
A small but growing part of the components and packaging business is pre-sterilized and ready-to-use-nested components. This approach was inspired by the semiconductor industry’s Front Opening Unified Pod, a box of silicon disks that could easily be picked up and manipulated by a robot without operator intervention. These tubs of nested containers and closures allowed for a greater level of automation in fill-finish operations, explains Greg Speakman, vice-president of sales and marketing for Vanrx, whose automated approach to fill/finish was inspired by the workcells of the electronics industry.

Becton-Dickinson came out with the first nested systems nearly 30 years ago, he says.

Ompi entered the market in 2007 with EZ-fill nested syringes, introducing vials and cartridges two years later, and nested closures for vials, developed together with Daikyo Seiko, in 2015, says product manager Alessandro Massignani.

Nesting syringes, cartridges, vials and closures in standardized nest or tub packaging allows maximum flexibility from fill/finish equipment, says Gregor Deutschle, business development manager at SCHOTT AG, since fill/finish operations are performed with the containers remaining in the nest. He points to Schott’s adaptiQ vials, which allow all process steps to take place inside the nest, including checkweighing, freeze-drying as well as closure of the vials with press fit caps, as an example.

**Standardization efforts**
The trend to nested systems began with prefilled syringes, so they have been standardized to the highest level so far, says Deutschle. Nested vials and cartridges are just emerging on the market, he says, and are being standardized. Massignani adds that there is a specific work group led by Ompi’s regulatory affairs manager that is entitled to redact the ISO Standard for Ready-To-Use Vials and Ready-To-Use Cartridges.

Vanrx’s system requires that containers and closures be placed in a nest to allow for robotic handling. Packaging component vendors, including Daikyo Seiko, Datwyler, SCHOTT, SCHOTT KAISHA, Ompi, ARaymond, and Vanrx established the Matrix Alliance in 2016, to work on standardization and ensuring interoperability of containers and closures. The key goal is ensuring that a container from one vendor will work with a closure system from another vendor, without requiring extensive retesting and integration by the end-user,” says Speakman.

---

**Fluoropolymers for processing**

Fluoropolymers are being used in systems that hold biopharmaceutical materials during processing and storage. W.L. Gore’s covered Lyoguard lyophilization trays feature a fluoropolymer membrane designed to prevent product contamination and flyout. Storage also poses challenges, since temperatures required for bulk drug product can be as low as -70 °C. Savillex began to sell its containers to pharma in 2011, offering a line of perfluoroalkoxy (PFA) and fluorinated ethylene propylene (FEP) bottles. These are single use, but have a five-year shelf life, says Don Potter, director of marketing, and they can be especially useful for applications that require no trace metals or organics.

Fluoropolymer bottles are traditionally extrusion blow molded, but the company’s current owner developed a stretch blow molding machine that works with the materials, resulting in smoother surfaces that prevent biopharmaceutical materials from interacting with container surface materials. When preforming bottle caps, at the clean bench, the company uses proprietary technology to minimize static electricity buildup, which can attract particles. Savillex has also improved overall factory flow and the inspection training it offers staff and customers for embedded particulates. The company also uses HEPA filters extensively at the plant to prevent contamination, says Potter.

PFA and FEP can be steam sterilized and pyrotreated but they cannot be irradiated. “We can ship unsterilized to end users, or have the containers sterilized by a third party,” says Potter. In the lab, the containers are widely used for analysis with methods such as inductively coupled plasma mass spectroscopy, or wherever trace metals are analyzed.

Contin. on page 31
New Packaging Solutions on Display at Pharmapack 2017

Pharmaceutical manufacturers will display a variety of unique packaging solutions during Pharmapack Europe 2017.

Pharmapack Europe, taking place from 1–2 Feb. 2017 in Paris, France, highlights a variety of pharmaceutical packaging and drug-delivery products. This year marks the 20th anniversary of the conference, which will feature more than 380 exhibitors from more than 70 countries around the world.

The 2017 Pharmapack conference provides opportunities for companies to showcase innovative products and services. The Start-Up Hub, a new addition to Pharmapack Europe 2017, provides a dedicated space on the show floor for start-up companies to showcase their ideas, meet potential customers, partners, and investors, and forge new relationships. During the 2017 conference, Pharmapack Europe will also host the annual Pharmapack Awards, honouring innovation in pharmaceutical packaging products.

To find out more about Pharmapack Europe 2017, visit www.pharmapackeurope.com. You can visit Pharmaceutical Technology Europe during Pharmapack Europe 2017 at Hall 4 Booth M76.

Elastomeric stoppers
Aptar Pharma will display the company’s PremiumCoat range of elastomeric stoppers and the eDose Counter for metered dose inhalers at Pharmapack Europe 2017. PremiumCoat is a novel range of elastomeric stoppers with a thin fluoropolymer film surface coating, which acts as a barrier to extractables and leachables that can be released from the elastomer. Aptar recently expanded the PremiumCoat line to include a 13-mm coated stopper and a 1-mL plunger. The company also offers a 20-mm coated stopper.

Aptar’s eDose Counter is designed to enhance patient compliance. The counter’s sensing technology offers direct detection of inhaler spray, eliminating the risk of miscounting. The technology is also compatible with any metering valve design. The eDose counter includes inhaler priming and medication reminders-to-use and end-of-product-life warnings (1).

Pharmaceutical blister films
Klöckner Pentaplast will introduce LiquiGuard, the latest addition to the company’s Pentapharm line of pharmaceutical blister films and BlisterPro XCEL Services at Pharmapack. LiquiGuard allows hot- and cold-fill liquids and semi-solids to be formed and packaged in a clear, thermostable laminate film that protects sensitive products from package leaching and moisture gain or loss. LiquiGuard provides protection from temperatures ranging from 120 °C filling to -183 °C and lyophilized. The company’s BlisterPro XCEL Services offer pharmaceutical packaging and prototyping capabilities to assist customers in bringing products to market more quickly. Klöckner Pentaplast’s BlisterPro XCEL Services suite located in Charlottesville, VA, aids customers in selecting the appropriate packaging technology for their formulation (2).

Desiccant packaging solutions
Sanner offers multiple desiccant packaging solutions including the Atmo Guard System, AdPack desiccant sachets, and AdCap desiccant capsules. AdPack desiccant sachets are made of Tyvek and ensure protection of moisture-sensitive drugs such as tablets or capsules inside the packaging. AdCap desiccant capsules offer moisture protection. The AdCap’s grid structure eliminates potential confusion with drugs. Both desiccant solutions comply with all regulatory requirements and can be processed on all common dosing and filling lines. Sanner is showcasing its desiccant packaging solutions at Pharmapack Europe 2017 (3).

Tungsten-free syringes
Gerresheimer will showcase the company’s metal-free 1 mL-long Luer Lock Gx RTF syringe at Pharmapack. A common problem with syringes is that traces of tungsten or other metals occasionally remain behind when shaping the syringe cone in the bore. Instead of tungsten, the pin used to shape the cone of the Luerlock Gx RTF syringe is created using a special ceramic. The ceramic material assists in preventing contamination of the syringe. The company will also showcase the Duma Twist-Off Protect, a multilayer product in an injection molding process that offers protection against water vapour and oxygen exposure (4).

References
High-Quality Gx® Glass Vials for Pharmaceuticals and Diagnostics

- High performance design
- High barrier properties
- Superior resistance

1–2 February 2017 | Paris, France

Pharmapack
Drug Delivery & Packaging

Paris expo Porte de Versaille
Booth G1 & H1
The United Kingdom’s ‘Brexit’ vote to separate from the European Union took the world by surprise and has left policymakers, business leaders, and bio/pharma companies with the task of piecing together a way forward for a range of business, political, and social issues, including affordable drugs, research and development funding, and a regulatory approval pathway.

While the business relationships between UK and EU companies and the status of EU nationals working in the UK are top issues for all industries, pharma faces fundamental industry issues, including the potential relocation of the London-based European Medicines Agency (EMA). Other challenges include establishing agreements between the UK and EU on the licensing and approval of new medicines; movement of drugs and active ingredients between countries; continued participation by the UK in the Innovative Medicines Initiative and the Unified Patent Court; funding for academic research; and access to capital for investment in drug development projects (1).

Regulatory experts, however, argue that patients, payers, and drug companies would benefit if the UK remained a part of the European regulatory drug approval process (1). The initiative, however, is part of a trade agreement and may be subject to additional scrutiny under the Trump administration, which campaigned for closer examination of such agreements.

Drug approvals go down as demand shifts
Beyond the Brexit changes, the bio/pharma industry has other crucial productivity, financial, development, and regulatory challenges on its agenda. Drug approvals were down in 2016 in the EU, mirroring a drop of approvals in the US (3). In total, EMA’s Committee for Medicinal Products for Human Use (CHMP) recommended 81 drugs for marketing authorization in 2016, compared with 97 in 2015. Of this total, only 29 new, non-orphan drugs were recommended for marketing authorization in 2016 compared with 41 in 2015. The number of orphan drugs approved declined to 16 from 20 in 2015; and the number of approvals for generic drugs slipped in 2016 to 22 from 25 in 2015. Similar-biologic product...
approvals did increase, from two in 2015 to seven in 2016 (4–5).

While drug approvals were down, the global demand for medicines continued to increase. The QuintilesIMS Institute, in its annual projections for global drug sales (6), estimates that global medicine spending will reach nearly US$1.5 trillion on an invoice price basis by 2021; the total volume of medicines consumed globally will increase 3%. The types of therapies and use of innovator versus generic drugs, however, will vary depending on where patients live.

 Consumption of newer drugs in developed markets, more generic drug use in pharmerging markets, plus patent expiries, discounts, and rebates will result in a 4–7% compound annual growth rate (CAGR) to 2021, slower than the nearly 9% CAGR in 2014 and 2015 when expensive new hepatitis drugs distorted the annual growth rates, but similar to the 5.9% growth during the past five years. Future growth will be generated by autoimmune, oncology, and diabetes treatments.

**Beyond Brexit, the bio/pharma industry has other crucial productivity, financial, development, and regulatory challenges on its agenda.**

The report predicts that specialty drugs to treat chronic, rare, or genetic diseases will be more widely used, particularly in the US and European markets, thanks to the approval of breakthrough medicines and a greater focus by payers on drug value and performance. Spending on such therapies, which was 20% of all medicines spending 10 years ago, will rise to 30% in 2016 and to 35% by 2021 and will represent half of the medicine purchases in the United States, Germany, United Kingdom, Italy, France, and Spain.

The US remains the top spender on drugs (US$461.7 billion), followed by China (US$116.7 billion), Japan (US$90.1 billion), Germany (US$43.1 billion), France (US$32.1 billion), Italy (US$28.8 billion), UK (US$27 billion), Brazil (US$26.9 billion), Spain (US$20.7 billion), and Canada (US$19.3 billion), QuintilesIMS reports.

**Price controls limit EU growth**

Price controls will contribute to limit drug sales growth in Europe to 1–4% to 2021, the report states. Estimated growth rates are 4–7% in the UK, 1–4% in Italy and Spain, 2–5% in Germany, and -1–2% in France. The impact of Brexit on the UK pharma market is expected to be “modest at worst with a 1.5% slower growth rate in the downside scenario” (6). Weak economic growth, unexpectedly high drug costs for innovator drugs in 2014

### Uncertainty across the pond

The election of populist candidate Donald Trump as president of the United States shocked many and created unease in the public and private sectors, but it also boosted the financial outlook for bio/pharma companies, at least in the short term. The investment community initially viewed a Trump administration as more pharma-friendly compared to a potential Clinton administration. Bio/pharma stocks rallied after Election Day; however, ongoing concern about drug pricing, payer pressure, and economic questions still created uncertainty (1). During the presidential campaign, candidate Trump and the Republican Party promised to repeal and replace the Affordable Care Act (ACA) of 2010, which extended healthcare to millions of Americans. Bio/pharma companies benefited from the increased pool of patients requiring medicines, but also paid higher fees and made concessions on drug prices.

**US drug industry performance**

Drug approvals did not live up to expectations in 2016. Only 22 new drugs received US Food and Drug Administration (FDA) approval, compared to 41 in 2014 and 45 in 2015. Fewer submissions and more complete response letters contributed the lower number of approvals, FDA noted. The number of applications received by FDA through 9 Dec., 2016, however, surpassed the average number of new molecular entity filings for the past decade (2) suggesting a steady pipeline of new applications for 2017.

**Regulatory outlook**

Another campaign theme—reducing the number of federal regulations perceived as roadblocks to business—may impact FDA and its efforts to expedite the approval of innovator and generic drugs. The number of warning letters issued by FDA for adulterated APIs or drug products nearly doubled from 2015 to 2016 (3), with many letters addressing data integrity issues and citations at overseas operations. The agency also worked to clear the backlog of generic-drug applications, but has been hindered by ongoing staff shortages. The 21st Century Cures Act, signed into law by President Barack Obama in December 2016, includes support for research on regenerative medicine and development of antibiotics and treatments for rare conditions. Other provisions are designed to streamline the drug approval process using novel clinical trials designs and study modeling and permit drug companies to use real-world evidence to support approval of added indications for marketed medicines.

**References**

and 2015, and a desire to control costs will encourage Europe-based policymakers to be more cautious in adopting new medicines in the future.

**R&D roadblocks**

Amid the clamor about controlling drug prices, drug company executives are examining R&D methods and declining returns. The cost to bring a drug to market, as estimated by the Deloitte Centre for Health Solutions (7), declined slightly from US$1.576 billion in 2015 to US$1.539 billion in 2016, perhaps due to shorter cycle times for breakthrough designations. The study also concluded that companies with less volatility in the therapy-area focus of their late-stage development programmes outperform those that continually change the focus of their drug-development efforts. Company size is also a factor. The study of 12 leading biopharma companies revealed a negative correlation between company size and predicted returns, and indicated that scale is a barrier to creating value in an R&D organization.

Companies have demonstrated greater efficiency in drug development through “nimble decision-making, empowering key decision-makers, accepting greater risk, making quick kills, and embedding a rigorous but dynamic process for funding projects,” the study authors reported (7).

One anticipated source of gaining efficiencies—extensive outsourcing—has not delivered on expectations, the study authors report. Sub-optimal partner management by drug companies and operating models that hinder externalization contribute to less-than-expected results from outsourcing arrangements (7).

**References**


---

### Perspectives from bio/pharma personnel

In the 2016 Pharmaceutical Technology/Pharmaceutical Technology Europe annual employment survey (1)—which was conducted after the Brexit vote, but prior to US presidential elections—respondents from around the globe shared similar perspectives about employment-related prospects, but also expressed varying opinions about business prospects for bio/pharma.

More respondents from Europe worked at generic-drug bio/pharmaceutical companies (28% in Europe vs. 14.5% in North American) than innovator companies (19.5% in Europe vs. 31.1% in North America). The respondents from Europe also worked for smaller companies, were slightly younger, and held more advanced degrees.

Business activity was up slightly 2016, 42.3% of the EU-based respondents reported an increase in business at their company over the previous year, similar to 2015 when 40% of EU-based respondents said business at their company increased (2).

More than one-quarter of the respondents (26.7%) reported that their company had been through a merger or acquisition in the past two years, nearly the same percentage as in 2015 and up from the 19.7% reporting in the 2014 survey. A similar number of respondents reported a company downsizing or restructuring (24.8% in 2016 vs. 28.2% in 2015).

### Optimistic outlook

Respondents based in Europe were more optimistic about the 2017 prospects for their company; more than 60% the respondents predicted that their company’s business will improve this year, up from 50.4% last year. In contrast, only 54.8% of the respondents from North America said business at their companies would improve and 16.6% predicted business would decline.

The EU-based audience also was more positive in their outlook for the bio/pharma industry in general for 2017: 46.4% said business would improve in 2017, up from 39.5% in 2016. While the numbers were up for two consecutive years, the numbers are still down from the 55.3% who expected improvement for 2015.

Predictions for business growth in the bio/pharma industry as a whole over the next five years were more optimistic than for individual companies. Nearly two-thirds (62.9%) of the EU-based respondents predicted that business will improve; however, 14.4% expect business to improve overseas, but not domestically.

### References

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
The potential and anticipation surrounding oligonucleotides as therapeutics has been apparent in the pharmaceutical industry for more than 30 years (1). Until recently, however, the number of success stories has been limited with the actual level of growth failing to meet these initial expectations.

As of September 2016, three antisense drugs have been approved for use in the United States. The development pipeline for these therapies appears to be strong, with ClinicalTrials.gov detailing more than 140 active clinical programmes for oligonucleotides in various stages of development.

This resurgence in oligonucleotide development can be attributed to a combination of factors including improved chemistries, a better understanding of the basic biology of oligonucleotides, more sophisticated delivery systems, and most importantly, increasing success in the clinic (2). Undoubtedly to support these developments, advancement in analytical technology has also been a fundamental aspect, specifically to facilitate characterization and quantitation of the oligonucleotide of interest as well as any synthetic contaminants (3).

Oligonucleotides are generally produced through a synthetic solid-phase chemical synthesis in a manner that likens them directly to traditional small-molecule pharmaceuticals. Oligonucleotides, however, display a diversity in mode of action, which on a cellular level involves interactions more typical of a biological moiety (3). This lack of ready definition as either a large or small molecule has led to many challenges from a regulatory perspective in terms of providing guidance, and subsequently, as yet, neither the US Food and Drug Administration (FDA) or the European Medicines Agency have issued official documentation with respect to expectations surrounding quality control of oligonucleotides.

Despite the lack of formal guidance, FDA has issued papers detailing current thinking in respect to quality control (4). These documents provide an overview of the data required to support product registration in respect to identity, purity, quality, and strength. The actual analytics involved represent a diverse and complex analytical programme. Table I provides an overview of a typical characterization programme.

### Identity testing

Given the complex nature of the molecule, as with many of the quality control analytics, it is recommended that orthogonal approaches be used to verify the identity of the test material.

### Determination of the molecular weight and confirmation of the nucleotide sequence of an oligonucleotide are fundamental criteria for analysis.

### Oligonucleotide structure and sequence

Determination of the molecular weight and confirmation of the nucleotide sequence of an oligonucleotide are fundamental criteria for analysis in terms of confirmation of the identity of the molecule and thus a regulatory expectation. Several methods can be applied to gain this information. Historically, digestion approaches such as enzymatic methods (e.g., Sanger) or chemical methods (e.g., modified Maxam Gilbert) followed by mass spectrometry have been widely used. Methods involving digestion are often complex and relatively time-consuming and the likelihood of success is restricted, in some ways, to the analysis of short chain length species. Mass spectrometric approaches, alternatively, can often be hindered by the polar nature, low thermal stability, complexity, and large molecular weights of oligonucleotides (5), which can hinder the ability to obtain good spectra and thus make clear assignments on mass and sequence.

Advancements in high-resolution mass spectrometry and in particular, tandem methods (MSMS), have provided a viable alternative for the determination of both mass and sequence of oligonucleotides. When
Formulation: Oligonucleotides

Considering intact mass, normal resolution instrumentation can only be used to obtain the average molecular weight; high-resolution mass spectrometry has, however, facilitated the determination of accurate mass. This method is based on obtaining negative ion spectra of the oligonucleotide followed by deconvolution. The accuracy of these measurements is typically less than 5 ppm, and as such, the mass can be used as an aid to establishing the empirical formula of the molecule, which is in turn used to postulate or confirm structure (6).

Such high resolution readily allows discrimination of nucleosides differing by only 1 mass unit, such as Cytidine monophosphate (CMP) (monoisotopic mass 323.05185 Da) and Uridine monophosphate (UMP) (monoisotopic mass 324.03587 Da), including distinguishing between the $^{13}$C isotope of CMP and $^{12}$C isotope of UMP, which effectively have the equivalent mass at a lower resolution (324 Da).

Quinn et al. (7) also detailed how tandem MS can be used to confirm the presence of truly isobaric nucleosides, such as Adenosine monophosphate (AMP) and Deoxyguanosine monophosphate (dGMP), both of empirical formula $C_{10}H_{14}N_5O_7P$ and a monoisotopic mass of 347.06308 Da. In discrimination between species of this type, structural differences are relied upon for definitive identification. In the case of AMP and dGMP, for example, the position of the oxygen atom differs, which can be distinguished by MS analysis and thus allow these isobars to be distinguished. The benefit of these advanced MS-based methods is further demonstrated when considering

### Table I: Characterization of oligonucleotide drug substance.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Analysis</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description and physiochemical characteristics</td>
<td>Molecular weight</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td></td>
<td>Optical rotation (to clarify that stereochemistry is controlled)</td>
<td>Size exclusion chromatography (SEC)</td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moisture content</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pKa</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hygroscopicity</td>
<td></td>
</tr>
<tr>
<td>Assay/impurities</td>
<td>Assay</td>
<td>High-performance liquid chromatography (HPLC)</td>
</tr>
<tr>
<td></td>
<td>Counter ion</td>
<td>Inductive coupled plasma (ICP)</td>
</tr>
<tr>
<td></td>
<td>Duplex content</td>
<td>SEC</td>
</tr>
<tr>
<td>Structure</td>
<td>Sequencing</td>
<td>Enzymatic method (e.g., Sanger)</td>
</tr>
<tr>
<td></td>
<td>Nucleobase composition</td>
<td>Chemical method (e.g., modified Maxam Gilbert)</td>
</tr>
<tr>
<td></td>
<td>Melting temperature ($T_m$)</td>
<td>Enzyme digestion and HPLC of nucleosides. For enzyme-resistant oligonucleotides, transformation may be required; however, in these cases, the process should be shown not to affect other parts of the molecule.</td>
</tr>
<tr>
<td></td>
<td>Chain length</td>
<td>Nuclear magnetic resonance (NMR)</td>
</tr>
<tr>
<td></td>
<td>Melting temperature ($T_m$)</td>
<td>Circular dichroism (CD)</td>
</tr>
<tr>
<td></td>
<td>Internucleoside Linkage</td>
<td>Capillary gel electrophoresis (CGE)</td>
</tr>
<tr>
<td></td>
<td>Molecular backbone composition phosphorothioate to phosphatediester (PS/PO) ratio</td>
<td>Polycrylamide gel electrophoresis (PAGE) analysis</td>
</tr>
<tr>
<td></td>
<td>Chromatographic profile</td>
<td>$^{31}$P NMR for assessment of phosphodiester, phosphorothioate, methylphosphonate, and any other modified phosphate</td>
</tr>
<tr>
<td></td>
<td>UV spectra</td>
<td>$^{31}$P-NMR plus strong anion exchange (SAX)–HPLC</td>
</tr>
<tr>
<td></td>
<td>Spectroscopic profile including stereochemistry</td>
<td>HPLC for phosphorothiates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAX (for phosphorothiates)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lambda max and min for acidic, basic, and aqueous solutions. Determination of extinction coefficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Four transform infrared spectroscopy (FTIR), $^1$H-NMR, other NMR</td>
</tr>
</tbody>
</table>

Pharmaceutical Technology Europe  JANUARY 2017  29
Formulation: Oligonucleotides

In addition to confirmation of core structural and physiochemical features, continued monitoring of the purity and levels of product- and process-related impurities presents a fundamental attribute for oligonucleotides in continued quality control.

The most accepted methodologies for performing this assessment are capillary gel electrophoresis (CGE) and anion exchange–high-performance liquid chromatography (SAX–HPLC), given both methods’ inherent ability to separate truncated species. Each approach offers advantages over the other. CGE methods require little or no development to reach maximum performance and can generally be applied to larger oligonucleotides without loss of resolution over that can be prevalent with the HPLC approach. Alternatively, SAX–HPLC methods are generally more reproducible, the columns last longer, and the response of and amount of loading into the instrument are not affected by species of differing mass to charge ratios (8).

**Internucleoside linkages**

Introducing modification to a nucleoside linkage has been a critical feature in the advancement of oligonucleotide therapeutics. Such alterations help to overcome the two main challenges affecting the efficacy of these molecules, specifically, delivery to the target in vivo and increasing bioavailability. An example of the effect of this engineering is that introduction of phosphorothioate linkages increases resistance to nucleases, but the incorporation of too many bonds can reduce the function of the species.

**Chain length**

Despite improvements in the automation and understanding of the chemistries involved in oligonucleotide synthesis, and despite the most ardent post synthesis clean-up, it is inevitable that there will be some heterogeneity with regards to chain distribution in the final material. Monitoring of this distribution presents a further fundamental aspect of quality control.

**Impurities determination**

In addition to confirmation of core structural and physiochemical features, continued monitoring of the purity and levels of product- and process-related impurities presents a fundamental attribute for oligonucleotides in continued quality control.

Product-related impurities include the following:

- Addition sequences (n+1, n+2, etc.)
- Deletion sequences (n-1, n+2, etc.)
- Phosphodiester analogs
- Depurinated sequences
- Partially deprotected sequences
- Aggregated sequences

When considering impurities involving addition or deletion of sequence, the methods of choice are SAX–HPLC or CGE, when considering chain length. For the other potential product-related species, a combination of chromatographic and spectroscopic methods are applied to cover all relevant components.

Aside from product-related impurities, residual species originating from the process require monitoring, and if necessary, specifications set. Such species include:

- Organic volatile impurities (OVI) or residual solvents, typically quantified by gas chromatography (GC) with flame ionization detection (FID) or mass spectrometry (MS)
- Inorganic molecules metals, inorganic salts, catalysts, cleavage reagents, and counterions typically quantified by inductively coupled plasma (ICP), MS, or OES.
Conclusion

In support of continued quality control of oligonucleotide therapeutics, a vast array of analytics is required to comprehensively control structural, physiochemical composition, as well as the purity and impurities of the test material. Looking forward, some of the challenges facing the resurgence in these therapies and the growing pipeline of oligonucleotides can be effectively addressed through application of these sophisticated analytical approaches and continued advancements in analytical technology.

References

1. A. Aartsma-Rus, Molecular Therapy 24 (2) 193–194 (2016).
4. Rao V.B. Kambhampati, Points to Consider for the Submission of Chemistry, Manufacturing, and Controls (CMC) Information in Oligonucleotide-Based Therapeutic Drug Application, presentation at DIA Industry and Health Authority Conference on: Oligonucleotide-based Therapeutics (Bethesda, MD, April 2007).

Packaging’s Flexible, Patient-Centred Future — contin. from page 21

Alliance members recently shared test results involving vials and press-fit caps with their shared biopharma customers, and plan to release findings publicly during the first quarter of 2017. But the move to nested vials and caps reflects trends that are not going away any time soon: a shift from blockbusters to smaller niches of high-value drugs; more frequent/fast product changeovers in multi-product facilities, and a move from large facilities in developed markets to smaller facilities in more remote parts of the world, says Speakman.

Another important shift is that component packaging suppliers are taking over services once handled by pharma companies, says Deutschle. “In using ready-to-use nested components, our customers want to eliminate the need for preparation of the containers prior to filling. Therefore, we take care of depyrogenation, washing, and packaging as well as sterilization.”

Flexible filling represents a major change from standard fill/finish equipment, which is geared toward high-speed, large production volumes, and often dedicated to a single container type or drug, Deutschle explains. Changeover from one container format to the next can take a long time in a bulk filling plant, because all containers must be handled individually and thus require a large number of spare parts. In addition, he notes, classic bulk lines can be very large and require a lot of expensive clean room space.

Using nested components in a flexible line reduces the need to invest in washing, water for injection, and utilities, and also reduces maintenance and validation costs, says Massignani. “The containers travel in packaging that prevents glass-to-glass contact, reducing rejection rate. This approach adds value, not only by improving product quality but because it shifts responsibility for the sterility and cleanliness of primary packaging from the pharma manufacturer to the packaging components supplier,” he says.

References

A Statistical Decision System for Out-of-Trend Evaluation

Niels Væver Hartvig and Liselotte Kamper

Evaluation of data from stability studies is a central part of the control strategy of pharmaceutical products and is a GMP requirement (1). The purpose is to ensure the safety and efficacy of the product by confirming that the stability is as expected and that it will continue to meet quality specifications until expiry. Stability studies can be part of the development programme for new products or the ongoing stability programme for marketed products. The studies are typically conducted both at long-term storage conditions and at accelerated conditions.

For stability studies on marketed products, the objective is to confirm that the stability profile follows the trend of earlier batches. Unexpected results may either indicate that the batch is out of trend or that the result is out of trend (OOT). A typical approach to evaluate the data is to consider the following three questions (2):

- Is the latest result within the expected range, or is the result substantially different from what is expected? The latter is known as an analytical alert and would usually be related to the analytical procedure or the handling of the stability sample, and more rarely to the actual stability of the product.
- Does the stability of the batch follow the expected trend compared to historical stability data? Or are there indications that the batch degrades in a different manner than observed earlier, which could indicate a special cause event has occurred in the production of the batch? This is known as a process control alert and will often lead to the conclusion that the batch is OOT.
- Will the product comply with specifications throughout the shelf life? In the event of a process control alert, the batch is known to deviate from the historical expectations. The stability should be examined and evaluated to ensure that the batch stays within the specifications. When this stability is questionable, a compliance alert is raised.

The evaluation can be performed subjectively by an analyst, but it requires long experience with the analytical method and the product and its distinct properties. Also, different analysts or different laboratories may conduct the trending; they may have different experience and evaluate the data differently as a result. However, an
RISING TO THE CHALLENGE

Tomorrow’s complex medicines face challenges to overcome low bioavailability and optimize drug delivery. This calls for a partner with the credibility, ingenuity and flexibility to deliver both the product and process design required to make your compound a commercial reality. With a unique range of technology and integrated product development from design to commercial manufacturing, Capsugel is that partner.
An objective evaluation requires data from different sources to be combined, namely the precision of the analytical method and the stability trend of historical batches and their associated uncertainty, and this is a burden both practically and statistically.

Statistical tools can control the risks of false alarms, when the product and result are actually within the expected range, and the risk of overlooking an OOT. The factors of uncertainty that need to be considered are:

- How much historical data are available—how well is the expected slope determined?
- Are there historical batch-to-batch variations in the slope?
- What is the intermediate precision of the analytical method and how well is this determined?
- Is the variation in the current stability study comparable to historical intermediate precision, and if so, what is the combined estimated precision?
- How much data are available in the current study?
- How much confidence is there in the predicted value of the batch when extrapolating to end-of-shelf life?

Unless a system is in place that facilitates the combination and statistical evaluation of data in an automated and standardized manner, the evaluation of stability data will be laborious and may require expert statistical assistance, which is usually not readily available at all the facilities where data are generated and evaluated.

A number of different approaches for evaluating stability data from a statistical perspective have been proposed in recent years (2–5). In this paper, the authors consider only parameters that follow a linear stability trend (or are constant). In this approach, the analysis is based on linear regression models that combine the efficiency of a parametric statistical model with the practical aspect of being relatively simple and intuitive.

From the authors’ experience, the vast majority of parameters that are followed in stability are approximated well by zero or first-order kinetic reactions, which lend themselves to linear regression analyses. Parameters that do not develop linearly must be evaluated, for instance, by tolerance interval methods by time point (3), or by more advanced kinetic models of the stability profile. These methods will not be considered here.

An overview of the system is provided in the following sections. Statistical details are deferred to the appendix.

**System setup**

The system is illustrated in Figure 1. The system supports a work flow where the stability responsible person routinely evaluates and releases results in a stability study as they are available. Stability data are stored in a laboratory information management system (LIMS). To evaluate the trend questions discussed in the previous section, historical data and data on the analytical variability of the method are needed. These data are stored in a database with tables for each product.

The combination of the two data sources and the statistical analysis and presentation of results is implemented in a computer programme (JMP, SAS Institute) (6), but other systems for data analysis and visualization can be used. The evaluation of results and alerts is conducted on a computer screen.

**The parameter table with historical data**

Historical stability data are summarized in a parameter table (see Table I) for each product. The table should be based on batches and results that are representative of the current product and analytical methods.

The parameter table should be established based on statistical analysis of historical stability data that are representative of the current product. For new products, typically data from the new drug application (NDA) stability studies and other development stability studies will be used. For marketed products, the body of historical routine stability data can be used.

The analysis of the historical data should be based on a regression analysis, in which the average stability trend is determined. In the model, each batch should have its own intercept to account for batch-to-batch variation in the starting level. If the stability slope varies slightly from batch-to-batch due to random variations, for instance in raw materials or input factors, a mixed model with random slopes can be used (5).

The intermediate precision of the analytical method should preferably be estimated as the residual variation in historical stability data, because this estimate will cover long-term variation in the method and also any other variation in stability studies, for instance, due to sampling and handling of the samples. Alternatively, method validation data or variation in control samples can be used.

The construction of the parameter table is typically a large task and may require a cross-functional team...
of analytical chemists, product responsible chemists, and statisticians. It is advisable to ensure careful documentation and control of the parameter table because it is the cornerstone of the stability trend evaluation.

Generally, the parameter table need only be established once for each product, but it may be necessary to update the table over time if there are changes to the stability profile of the product or to the analytical methods, or if the initial parameter table is based on a relatively small body of stability data and more precise estimates are obtained over time.

The parameter table summarizes all the historical knowledge of the product and the analytical methods in a single table. Thus, there is a wealth of information in the table, and the creation of the table ensures that the expectation of the stability study is clear across the organization. By using the same parameter table for trending, consistency in the evaluation of the data across persons, departments, and sites is ensured, which is an important benefit of the system.

**Routine trend evaluation**

When conducting routine trending, stability data are retrieved from the LIMS and combined with the parameter table. The system processes the data and presents a graph for each parameter, batch, and storage condition. The graphs illustrate the data and summarize the statistical evaluation of the three trend questions.

**Is the latest result comparable with the results previously seen for the same batch in the study?**

This trend is evaluated by a prediction interval based on the stability results for each batch, excluding the latest result. If the latest result falls within the prediction interval, it can be concluded that it follows the trend seen so far, within the expected uncertainty range.

Typically, a 99% prediction interval will be used to have a reasonably low risk (1%) of a false alarm. This interval corresponds approximately to ±3 standard deviations around the expected value.

The historical stability slope in the parameter table is not used in this evaluation, but the historical intermediate precision of the method is used to calculate the variance of the result.

The result of the analysis is indicated graphically by plotting the data with the regression line, calculated with the latest result excluded, and by overlaying ±3 standard deviation error bars on the latest result. This approach provides a simple visual check for whether the result is within the expected range. The conclusion of the statistical analysis is illustrated visually by plotting the latest

<table>
<thead>
<tr>
<th>Table I: Information on specifications and historical data contained in the parameter table. The information is provided for each parameter and storage condition.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LSL</strong></td>
</tr>
<tr>
<td><strong>USL</strong></td>
</tr>
<tr>
<td><strong>Shelf life</strong></td>
</tr>
<tr>
<td><strong>Expected slope</strong></td>
</tr>
<tr>
<td><strong>Std. err. slope</strong></td>
</tr>
<tr>
<td><strong>Intermediate precision</strong></td>
</tr>
<tr>
<td><strong>D.f.</strong></td>
</tr>
</tbody>
</table>
result with a red symbol, if the result is outside the 99% prediction interval. An example is provided in Figure 2.

Is the development of the parameter comparable to the development of the same parameter in historical studies?

This trend is addressed by a regression analysis, in which the estimated slope of the current batch is compared with the expected slope from the parameter table. Based on a t-test, the statistical significance of any difference can be assessed, accounting for the uncertainty of both the current estimated slope and the expected slope. The uncertainty of the expected slope can express both estimation uncertainty and, if relevant, random batch-to-batch variation in the slope. Typically, a significance level of 1% will be used to avoid too many false alarms, corresponding to the 99% intervals used above.

The result of the analysis is indicated graphically by plotting the regression line for the batch (the green line in Figure 3) as well as a line with the expected slope (dotted line in Figure 3). If a statistically significant difference is observed, all points can be plotted with a separate Colour to provide the stability responsible person with a clear visual indication that this statistically significant difference needs to be evaluated and possibly investigated further.

Can compliance with the specification limits be expected to be maintained until the end of study?

This analysis is conducted following the principles in (7) by evaluating if the 95% confidence interval for the batch intersects the specification limit before the end of shelf life. A one- or two-sided confidence interval is used depending on whether the specification is one- or two-sided, respectively.

If the batch is confirmed to be OOT and there is less than 95% confidence that it will comply with the specification during shelf life, a compliance alert is raised (see Figure 4). The evaluation of criticality is not only a statistical exercise, but the statistical result may be used to evaluate the effect of reducing shelf life or other mitigations.

Practical use of the system

In the practical use of the system, all data for a given time point are evaluated and a graphical overview of the different parameters, batches, and storage conditions presented. The graphical illustrations of alerts make it easy to get an overview of the data. In case one or more alerts are identified, summary tables with estimates and statistical details are available to interpret the findings.

When evaluating alerts, the trend responsible person should be aware of a number of pitfalls and understand the limitations of the methods used:

- **Rounded and truncated results**: The trend analysis requires data with sufficient resolution. In particular, impurity data are often rounded to one decimal and truncated when they are below the limit of quantification. It is important that a database with the unrounded results is available for the trend analysis; if not, the trend system may not analyze impurity data correctly.
- **Non-linear trend**: The system assumes a linear trend over time (or no trend). This approach is typically reasonable, but complex biological reactions or physical parameters are not necessarily linear. In this case, the results of the system should be interpreted with much care, and trending may need to be conducted by other methods, for instance, the by-time-point method (2).
- **Multiplicity**: A number of statistical tests are conducted for each time point. For instance, if three batches are followed at three different storage conditions and five parameters are evaluated for each, a total of 45 tests are conducted. With a significance level of 1% for each test, there is a risk of $1 - 0.99^{45} = 36\%$ of at least one false alert. Because there is no correction for this risk, it is important that the stability responsible person is aware of the risk of a false alert and uses good judgement when evaluating alerts.
- **Independent results**: It is an assumption in the analysis that all results are independent. When this is not the case, for instance, if two determinations are obtained in the same analytical run, there is a risk of over-interpreting findings and getting too many false alarms. The correlation between multiple results can be handled statistically using random effects models, but this method is difficult to automate in a system like this.
Only the latest result is evaluated: Previous OOT results in the same study should be excluded before the analysis; otherwise, these previous OOT results may mask new OOT results. The system supports a workflow where the OOT evaluation is conducted routinely after each result, and, therefore, only the latest result is evaluated.

Patterns across batches: The system analyzes each batch, parameter, and storage condition separately, giving a relatively simple framework, but it means that patterns across similar batches or storage conditions are not discovered. These patterns must be evaluated subjectively or by more advanced statistical analyses in specific cases.

Number of results available. The system can, in principle, estimate the stability slope based on two results, using the historical standard deviation as an estimate of the residual variation in the data. But clearly, the analysis will have low sensitivity until more time points are available.

The computer system should be validated for GMP-use. However, by building the system on existing validated computer systems, the validation effort is relatively smaller than if the system was built from scratch.

Comparison with other methods
As discussed, the methods presented rely on linear trend models with normally distributed errors. They are, therefore, less general than OOT methods that do not rely on these assumptions, such as the “change-from-previous” type methods and by-time-point methods presented in references 2 and 3, but they provide a simpler and more efficient setup when the assumptions are fulfilled.

The methods can be compared with other published regression methods as follows:

Analytical alert: The method presented here is very similar to the regression control chart method (3–5) based on a prediction interval. A difference, however, is that the authors’ method uses a pooled variance based on the historical variance and the variance in the present study. This approach will increase the power of detecting an OOT, provided that the variation in the historical data is comparable to that of the current study. If the historical variance is not entered in the parameter table, the authors’ test simplifies to the regression control chart method.

Process control alert: The method presented compares the slope of the current batch with the average slope of historical batches by a t-test, allowing for uncertainty in the estimated slopes and random batch-to-batch variation in the historical slopes. As such, the interpretation of the test is similar to the slope-control chart method (3), though the statistical framework is slightly different. If the standard error of the historical slope accounts for uncertainty in the slope only, the method is similar to the test for poolability of batches (7), except for the fact that all the historical batches are pooled before comparison with the current batch and the fact that a pooled variance is used in the test. If the standard error of the historical slope includes random variation between batches, the framework is similar to the random coefficient regression (6), where the model is used to set limits for individual results.

Compliance alert: The method presented is the same as used in reference 7, where batches are not pooled and each batch is thus considered individually.

Conclusion and further development
The trend analysis system provides the trend responsible person with exact and reproducible results for evaluating stability data. It makes the evaluation of data objective and standardized, and provides greater flexibility in terms of who does the trending.

The system provides valuable summary measures for each batch, such as the estimated slope with confidence limits, a statistical test for whether the batch is comparable with historical batches, and the expected shelf life based on extrapolation of confidence intervals. The system makes it easy to account for the different sources of uncertainty in the evaluation of the data and thus provides control over the risk of false alarms and the risk of overlooking an OOT.

The system is relatively simple to implement, validate, and maintain, and can be based on a statistical software
package such as JMP and existing database solutions, such as LIMS. The statistical methods strike a reasonable compromise between being relatively simple, based on linear regression model for each batch, yet sufficiently complex to handle, for instance, mixed effect models with random variation in the slope between batches.

Generating the database of parameter tables for all products requires analyses of historical data. Though this effort is a prerequisite for conducting a trend analysis, whether a trend system is used or not, the practical work of establishing, documenting, and maintaining the parameter tables in a system such as this should not be underestimated.

The system is not designed to encompass all parameters, and some level of “manual” trending should, therefore, be expected even with this system. Parameters that do not follow a linear pattern or ordinal responses cannot be analyzed by the system currently. Also, impurity data that are truncated below limit of quantification may need to be trended by other methods. One could extend the system, for instance, by including functionality for transforming responses to linearize the trend, or to include tolerance intervals methods. Still, it is important that the results of the analyses are intuitive and easy to interpret, and this feature should be a cardinal point when extending the system.

Acknowledgement
The system has been developed by a team of stability responsible persons in Novo Nordisk. In particular, the authors acknowledge valuable discussions and input from Marika Ejby Reinau, Jens Krogh Rasmussen, Helle Lindgaard Madsen, Lone Steenholt, Carsten Berth, and Karin Bilde.

References
5. ECA, Laboratory Data Management Guidance; Out of Expectation (OEE) and Out of Trend (OOT) Results (draft, 15 Aug. 2015).
7. ICH, Q1E, Evaluation for Stability Data (Step 4 version, 2003).

Appendix: Statistical details
The following section contains the statistical details.

Consider data from a single parameter, a single batch at a single storage condition. Let $Y_1, \ldots, Y_n$ be the results available for analysis and let $x_1, \ldots, x_n$ denote the corresponding storage time in months. For simplicity, it is first assumed that only a single result is obtained per time-point, and that $x_n$ is the latest time point.

The underlying statistical model is a linear regression model,

$$Y_i = \alpha + \beta x_i + \epsilon_i, \quad \epsilon_i \sim N(0, \sigma^2), \quad i = 1, \ldots, n$$

with all observations independent. Let $\bar{Y}$ and $\bar{x}$ denote the averages,

$$\bar{Y} = \frac{1}{n} \sum_{i=1}^{n} Y_i, \quad \bar{x} = \frac{1}{n} \sum_{i=1}^{n} x_i,$$

and let $SPD_{xy}$ and $SSD_x$ be given by

$$SPD_{xy} = \sum_{i=1}^{n} (Y_i - \bar{Y})(x_i - \bar{x}),$$

$$SSD_x = \sum_{i=1}^{n} (x_i - \bar{x})^2.$$

The maximum likelihood estimates of the parameters $\alpha$ and $\beta$ are then given by

$$\hat{\beta} = \frac{SPD_{xy}}{SSD_x} \sim N\left(\beta, \frac{\sigma^2}{SSD_x}\right),$$

$$\hat{\alpha} = \bar{Y} - \hat{\beta} \bar{x} \sim N\left(\alpha, \frac{\sigma^2}{n + \frac{\bar{x}^2}{SSD_x}}\right),$$

and the residual variance $\sigma^2$ is estimated by

$$\hat{\sigma}^2 = \frac{1}{n-2} \sum_{i=1}^{n} (Y_i - \hat{\alpha} - \hat{\beta} x_i)^2 \sim \chi^2(n-2)/(n-2).$$

Evaluation of shelf life
The (1-$\alpha$)-confidence limit for the regression line at time point $x$ is given by

$$\hat{\alpha} + \hat{\beta} x \pm t_{1-\alpha/2,n-2} \sqrt{\frac{1}{n} + \frac{(x - \bar{x})^2}{SSD_x}},$$

where $t_{\alpha/2}$ is the upper $\alpha$-quantile of the $t$-distribution with $f$ degrees of freedom, and $s$ is the square-root of the estimated residual variance $\sigma^2$.

The estimated shelf-life is established by looping over values of $x$ and determining the largest $x$ where both the upper and the lower 95% confidence limits are within the specification limits.

If the specification is two-sided a two-sided 95% confidence interval is considered by setting $\alpha = 0.05$. If the specification is one-sided, a one-sided 95% confidence interval is calculated by setting $\alpha = 0.1$. 
Pooling of variances
For the OOT-tests a pooled variance is used,

\[ s_{pool}^2 = \frac{(n-2)s_i^2 + f_{ip} s_{ip}^2}{f_{pool}} \]

\[ f_{pool} = n - 2 + f_{ip} \]

Here \( s_{ip}^2 \) is the intermediate precision variance and \( f_{ip} \) is the degrees of freedom, both provided in the parameter table.

For early time points, \( n-2 \) will be small, and the intermediate precision variance provided in the parameter table has to be used to conduct tests for OOT. In this case, \( s_{pool}^2 \) will primarily be given by \( s_{ip}^2 \). On the other hand, for late results, the residual variance contains valuable information on the precision of the analytical method in practice. As \( n \) becomes larger, the residual variance will weigh increasingly more in the pooled variance. A prerequisite for pooling the variances is that the provided intermediate precision represents the current variation in the method.

When \( f_{ip} \) is set to missing in the parameter table, it is interpreted as \( f_{ip} = \infty \) and therefore \( s_{pool}^2 = s_{ip}^2 \). If \( s_{ip}^2 \) is missing in the parameter table, only the residual variance is used, i.e. \( s_{pool}^2 = s_0^2 \).

OOT test for slope
The test for whether the batch is OOT is based on the expected slope \( \hat{\beta} \), and the standard error of this, \( s_0 \), both provided in the parameter table. It is assumed that the expected slope follows a normal distribution, \( \hat{\beta} \sim N(\beta,\sigma^2) \), where the normal distribution expresses the uncertainty of the expected slope and/or an expected batch-to-batch variation in the slope.

In the parameter table, the degrees of freedom \( f_0 \) for the standard error \( s_0 \) could be entered if relevant. It was found that in practice, this parameter was often difficult to obtain, and the degrees of freedom are, therefore, by default set to missing, which is interpreted as \( f_0 = \infty \).

The OOT test for the slope is a t-test for the hypothesis: \( H_0: \beta = \beta_s \). The t-test is given by

\[ t = \frac{\hat{\beta} - \beta_s}{\sqrt{\frac{s_{pool}^2}{SSD_x} + \frac{s_0^2}{SSD_x}} + \frac{(X_n - R_{(n)})^2}{SSD_{x(n)}}} \]

which follows a t-distribution with \( f_{pool(n)} \)-degrees of freedom.

Multiple results at each time point
When multiple results are given for one or more time points, it is assumed that all observations are independent. The analysis is conducted as described above, and an OOT test for the time point is conducted for each individual result. PTE
Validating a Method for Point-of-Use Leak Testing of Single-Use Bag Assemblies

The authors describe the development and validation of a highly sensitive point-of-use pressure decay test.

Single-use technologies have transformed biopharmaceutical manufacturing by providing opportunities to reduce costs, improve flexibility, and shorten cycle times. Manufacturers of biopharmaceuticals want to maximize the benefits they can derive from single-use technologies and are becoming increasingly confident when integrating single-use assemblies into processing steps that have a greater impact on product quality. Today, the expansion of such technologies into more critical applications, such as drug substance and drug product storage, has naturally raised new challenges for the industry to address. Industry surveys show that these challenges include quality assurance, supply chain reliability, supplier change control, raw material transparency, and maintaining the integrity of assemblies (1, 2). “A lack of robustness can lead to contamination of process fluids or drug products and, subsequently, loss of time and materials,” Weibing Ding, PhD, principal scientist, Process Development at Amgen said in a statement. The cost of bag failures could be between $100,000 to $1 million per bag.

To avoid these costs, established suppliers of single-use bags provide assurance of container-closure integrity across the entire product lifecycle. They do this by applying quality-by-design principles, performing process validation, and ensuring process control. Quality control policies ensure the integrity of the film, the welds, and the bag chamber.

As part of their quality risk management strategy and in accordance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Q9, biomanufacturers can reduce the risk of losing high-value product and enhance patient and operator safety by performing a non-destructive point-of-use leak test on all single-use bags used in critical process steps (3). This ensures no damage occurred to the single-use bags during shipping, storage, and handling at the user site.

In this article, a leak test method was validated to detect leaks by means of pressure decay for 2D storage bags (Flexboy 2D, Sartorius Stedim Biotech). This article describes the validation of a pressure decay test method used for the point-of-use leak test at the user site of Flexboy bags from 50 mL to 50 L with the FlexAct BT and the Sartocheck 4 Plus Bag tester. A preliminary parameter study was first performed to pre-determine the test pressure, stabilization time, and test time. A complete validation study was then carried out to validate the parameters, the maximum allowable pressure decay, and the leak detection limit.

Materials and methods
Bag integrity test hardware and instrument. Test method development and validation were performed using the FlexAct BT system with Sartocheck 4 Plus Bag tester. The bag tester was equipped with two bag holders, each consisting of two metal plates with porous spacers. By using porous spacers, the film surface of the bag is not in direct contact with the stainless steel holder during the test. Any potential masking effect is eliminated and environmental heat transfer is reduced. The holders allow performance of the leak test with a small and reproducible inflating bag volume and at a higher test pressure. This is critical for achieving the test sensitivity and reliability required. Furthermore, the holders protect the bag from mechanical stress during the test.

Expansion of technologies into more critical applications has naturally raised new challenges for the industry to address.

2D bags from 50 mL to 50 L. The designs of 50 mL to 50 L Flexboy 2D bags for pre-use have been adapted to meet the specific requirements of critical process applications and pre-use leak testing. This requires the installation of a sterile vent filter line to permit the performance of the test under conditions that maintain the integrity and sterility of the system (Figure 1).

Pressure decay test method. The test method was derived from ASTM F2095-01: Standard Leak Test for Pressure Decay Leak Test for Nonporous Flexible Packages with and without Restraining Plates (4).
Pharma’s dedicated packaging & drug delivery event

INNOVATION
NEW: Pharmapack Start-up Hub
Pharmapack Awards
Innovation Gallery
Innovation Tours

NETWORKING
International Meetings Programme
Exhibitor & Visitor Cocktail Party
Networking Areas

EDUCATION
Conference
Learning Lab
Symposium
Workshops

FREE TO ATTEND
REGISTER NOW!

Follow the link: bit.ly/2cE4k3N

#PharmapackEU

NEWS, WHITEPAPERS & EVENT PROGRAMME ON WWW.PHARMAPACEUROPE.COM
Once the test pressure has been set and allowed to stabilize, the system measures the pressure decay and compares the result to an acceptance criteria determined during the development and validation of the method (Figure 2). The pressure decay test method developed detects defects according to the leak-rate specification on the film, welds, and ports of the bags. Because the validated test method is non-destructive, it is compatible with performing pre-use leak tests on 100% of bags used at a biologics production facility.

**Results**

**Test method development.** The aim of the initial phase of the study was to pre-determine the stabilization time and test time parameters necessary to detect a defect reliably over the volume range of the bag configurations. The range contains bags with 10 different volumes from 50 mL to 50 L. For each of the 10 bag sizes, three non-defective test samples, and three defective test samples were prepared. Defects were introduced into film samples with a laser drill and flow calibrated hole.

All 60 samples were tested at a fixed 300-mbar test pressure. For each test run, four different stabilization times of 60 seconds, 120 seconds, 180 seconds, and 240 seconds were used. The pressure drops were continuously measured and reported every second across the entire test time from 0 to 240 seconds during the four different stabilization time test runs.

The minimum, the mean, the maximum, and the standard deviations ($\sigma$) of the measured pressure drops were calculated for the four different stabilization times separately, with non-defective and defective test samples for each different bag volume. The optimum stabilization time and test time were chosen to provide a selective test method capable of differentiating defective bags from non-defective bags (i.e., the points where the error bars $[\pm 3 \sigma]$ from the defect is distinguished from the error bars $[\pm 3 \sigma]$ from the non-defective measurements). Initial results showed that, for tests performed with a 120-second stabilization time and 90-second test time, a difference between the observed pressure drops of defective and non-defective test samples could be detected with a probability of 99.9%. A safety margin was then applied by doubling the stabilization and test times to avoid false positive and false negative results during normal operations. These timings were selected for the subsequent validation study.

**Test method validation.** The purpose of the validation study was to verify the ability of the pre-established test method and test parameters to detect a defect reproducibly and accurately over the volume range of the bags. The validation study was performed with
a statistically significant number of bags from different routine production lots to provide a robust validation and test method. For each of the 10-bag volumes, 32 non-defective test samples from production with representative raw material and process variability, and 32 test samples with a defect were used. This represented a total of 640 samples tested during the validation study. Every defect film sample was checked for its calibrated hole size before it was used. Tests were performed using the pre-determined test pressure of 300 mbar, stabilization time of 240 seconds, test time of 180 seconds, and a defect size.

This study allowed the validation of the pre-established test parameters and the setting of a maximum allowable pressure decay specification at 3.1 mbar. The validated pressure decay method was capable of reliably detecting defective bags from non-defective bags with a given leak detection limit in less than 10 minutes including installation and testing.

The 3.1 mbar maximum pressure decay specification was established with a 6σ interval of confidence for the full range of bags from 50 mL to 50 L to avoid false positive or false negative results under real testing conditions (Figure 3). The final test parameters established during these studies are provided in Table I.

**Conclusion**

The authors developed and successfully validated a pressure-decay leak test for 2D bags using commercially available equipment and proved that it is a robust and predictive method for the reliable detection of leaks. Using the method, non-defective bags gave results below the maximum pressure drop specification. The bags into which a defect was deliberately introduced gave results above the maximum pressure drop specification and failed the test. The method is, to the authors’ knowledge, the first point-of-use leak test capable of detecting down to 10 μm defects in 2D bags, irrespective of their volume. The sensitivity of the test is independent of 2D bag size.

**References**

For the past few years, to help pharmaceutical manufacturers improve and sustain better product quality, the US Food and Drug Administration (FDA) has been working with industry to define the metrics and key performance indicators that are most critical to product quality (1). This work actually began in 2008, with the release of the International Council for Harmonization of Technical Requirements of Pharmaceuticals for Human Use’s (ICH) Q10 (2), which articulated the need for a systemic approach to quality that would get beyond the case-by-case approach of current good manufacturing practices (cGMPs) and final product testing.

After FDA released initial guidance on quality metrics in 2015 (3), there were complaints about its broad scope. FDA had asked that manufacturers collect data for 10 metrics. In November 2016, FDA released a second version of the guidance (4), which focuses on the following three main metrics:

- Lot acceptance rate, or the number of accepted lots within a timeframe divided by the total number of lots started, for primary and secondary distribution and packaging, during a given timeframe. Included will be number of lots started, released, and rejected.
- Product quality complaint rate, or the number of complaints received divided by the total number of dosage units of that product distributed during that time frame.
- Invalidated out-of-specification (OOS) rate, or the number of OOS batch-release test results and long-term stability test results that were invalidated due to measurement process issues at the facility, divided by the total number of such tests performed at the facility during the time frame. Every OOS result will trigger an investigation, and the guidance specifies best practices.

Long term, the agency’s goal is to furnish metrics that will help process operations and manufacturing teams, quality control departments, and regulators (especially plant inspectors) focus on key principles that determine product quality. These principles should drive, not only day-to-day operations, but also investment in new technology. In addition, they should help regulators prioritize inspections to focus on facilities and companies that are at the highest risk of quality or compliance failure.

In July 2016, FDA began to fund research that aims to analyze existing quality metrics, and to see whether new measurements that incorporate more of the language of the manufacturing plant floor and the principles of operational excellence might help achieve better results in the future (5).

Working on this project is a team at the University of St. Gallen in Switzerland, led by Thomas Friedli, who has spent the past 15 years studying the application of continuous improvement techniques across different industries. Collaborating with Friedli is a team from the Dublin Institute of Technology, led by Nuala Calnan, and, based in the United States, pharmaceutical industry consultant Prabir Basu, who, for more than 10 years, was head of the National Institute for Pharmaceutical Technology and Education (NIPTE).

Some pharmaceutical companies have been reluctant to embrace such universal manufacturing excellence metrics.

Friedli’s team has been analyzing pharmaceutical manufacturing for well over a decade, based on the universal metrics used in automotive, aerospace, and other industries, which include “on-time delivery” and inventory levels. St. Gallen’s surveys of pharmaceutical manufacturing operations look at such things as whether the facility or company uses total predictive maintenance, or how effectively the workforce is engaged in, or how strongly senior management supports, total quality improvement.

Some pharmaceutical companies have been reluctant to embrace such universal manufacturing excellence metrics, with some insisting that “pharma is different,” due to the special requirements for...
product safety and testing. There has been debate over this topic for decades, and, even today, one sees uneven acceptance of such concepts as “process capability analysis” or process analytical technology (PAT) among drug manufacturers.

“The most important question is whether the facility’s or company’s processes are in a state of control.” — Prabir Basu

At this point, FDA wants to see whether the language of operational excellence can further enrich the industry’s understanding of quality. Research is still in a preliminary stage, and could not be discussed for this article, but Prabir Basu shared some of his thoughts on what the industry will need if it is to redefine, and transform, pharmaceutical quality control.

Operational excellence

PTE: Why is operational excellence (OpEx) so important to improving both pharmaceutical manufacturing and quality?

Basu: Quality and operational excellence cannot be separated. Operational excellence metrics show how motivated people within a company are to improve overall performance, and quality with it. FDA has, in the past, taken an approach that has separated the two, as if quality were not a part of operations. The point is, that if a company is not investing in quality, that will show up in the operational excellence parameters, and they will have quality problems too.

A great example is preventive maintenance. If you don’t have a corporate mandate and policy for this activity, you are very likely to have problems with product quality.

PTE: How does all this affect regulators?

Basu: Having links to existing OpEx quality parameters would be very helpful in ensuring that FDA can get pertinent information underlying deviations or batch rejections.

Today, most manufacturing is taking place outside of the US, and FDA has limited ability to inspect all the facilities involved. Having indicators in place that are operations related and that suggest which facilities and companies might pose a higher risk of noncompliance or low quality will allow FDA to prioritize inspections. But it would be ideal if we could get to the stage where quality and operational excellence are considered as one. ICH Q10 gives us indications of how to get there.

So, we are beginning a journey that has much potential, and we can get to this goal of a unified definition of quality, if we continue for the next three to five years.

At this point, we are collecting data using benchmarking questionnaires, correlating between existing operational excellence measurements and quality metrics. We hope to expand the questionnaire to reflect on real quality information.

“We need to come up with metrics that will be attractive for all companies.” — Prabir Basu

PTE: In the past decade, we’ve heard more people in pharma talk about Deming’s approaches to excellence, yet concepts as basic as process capability don’t seem to have been widely embraced. Why is that?

Basu: Some companies are working with the concept of process capability, but they tend to be the larger companies, such as Amgen and Pfizer. And even the larger companies don’t employ this approach for all products.

We need to come up with metrics that will be attractive for all companies.

PTE: How about cost of goods?

Basu: That measure is too variable, because the cost of capital varies so dramatically depending on which country the facility or company is based in.

Quality metrics

PTE: How about the metrics that FDA is focusing on in its latest version of the draft guidance, including out of specification? Are these adequate?

Basu: The metrics are okay but they aren’t yet tied to processes so they won’t necessarily reflect what is going on internally. For example, lot acceptance rate seems okay, but what happens if lots have to be reworked? Will the figure then be a true reflection of the facilities’ processes?

PTE: What are some concepts that might be more helpful?

Basu: I think that Six Sigma value could provide a better indicator.

In the early 2000s, a number of thinkers used to talk about doing this, but it hasn’t yet been fully accepted.

Even if we were to use the lot acceptance rate as a quality metric, ideally some measure of accuracy could be factored in, for example, of the number of batches started, how many came out right the first time, without the need to rework them?

PTE: What role should quality complaints play?

Basu: This is an important metric, but first we need to define very clearly what the complaints are and where they are coming from. Are they coming from the warehouse? From distributors? From patients? From regulators?

Some of the metrics that are currently being discussed may not adequately reflect internal processes. The beauty of operational excellence metrics is that they measure how well processes are performing, so they are much better reflections of the actual situation within a given facility or company.

Some of the important operational excellence metrics to consider are on-time delivery and customer satisfaction. These measurements reflect internal processes.

In addition, I believe that metrics must incorporate more of the spirit of ICH Q10, to determine the company’s quality culture, and such things as whether the firm has a continuous improvement program in place, whether its...
We need metrics to measure these areas, and also to identify facilities and companies that are at the greatest risk of quality and compliance failure.”

— Prabir Basu

The most important question is whether the facility’s or company’s processes are in a state of control. Here, key indicators are measures of variability of the critical process attributes. Even if process capability information is not available, at a minimum, trending of critical process variables and data on process drift such as shifting of the averages or changes in slopes of the trend, degree of implementation of ICH Q9, etc. We need metrics to measure these areas, and also to identify facilities and companies that are at the greatest risk of quality and compliance failure.

In the end, the number of rejected batches may be more important to screen than lot failures. In addition, relative numbers are more important than absolute numbers. For instance, the top 25% should have good systems in place, and the bottom 25% should receive more attention from FDA. It might be most beneficial to use the pillars that St. Gallen has been using to measure performance: total predictive maintenance, total quality management, and just-in-time inventory levels.

Keeping a focus on process operations will ensure that companies and regulators are monitoring operational principles, looking at stabilizing systems, and developing frameworks for knowledge management and risk management. By definition, these efforts can only make any organization more focused on product quality.

References

CORRECTION
The API Synthesis & Manufacturing article, “New Horizons for Cross-Coupling Reactions” in the December 2016 issue incorrectly stated:

Silicon-based cross-coupling reactions have recently been shown to have potential advantages over existing cross-coupling chemistry, particularly with respect to alkyl-alkyl (sp³-sp³) and alkyl-alkenyl (sp³-sp²) cross-couplings.

The correct statement is:

Silicon-based cross-coupling reactions have recently been shown to have potential advantages over existing cross-coupling chemistry, particularly with respect to alkyl-aryl and alkyl-alkenyl (sp³-sp²) cross-couplings, according to Gerald L. Larson, a senior research fellow at Gelest.

A correct version of the article can be found in the digital edition: http://images2.advanstar.com/PixelMags/pharma-tech-na/digitaledition/12-2016.html

Ad Index

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsugel</td>
<td>33</td>
</tr>
<tr>
<td>Catalent Pharma Solutions</td>
<td>47, 52</td>
</tr>
<tr>
<td>Gerresheimer AG</td>
<td>23, 47</td>
</tr>
<tr>
<td>Lonza Clinical Development &amp; Licensing</td>
<td>27</td>
</tr>
<tr>
<td>Penn Pharma, A PCI Company</td>
<td>19, 48</td>
</tr>
<tr>
<td>Rommelag AG</td>
<td>5, 48</td>
</tr>
<tr>
<td>Schott AG</td>
<td>2, 49</td>
</tr>
<tr>
<td>Shimadzu Europe</td>
<td>51</td>
</tr>
<tr>
<td>Starna Scientific</td>
<td>9</td>
</tr>
<tr>
<td>TasiTest</td>
<td>15, 49</td>
</tr>
<tr>
<td>UBMI BV</td>
<td>41</td>
</tr>
<tr>
<td>Unicom International</td>
<td>31</td>
</tr>
<tr>
<td>Vectron Biosolutions AS</td>
<td>11</td>
</tr>
<tr>
<td>Veltek Associates Inc</td>
<td>7</td>
</tr>
</tbody>
</table>
Catalent Pharma Solutions

Company description
Catalent Pharma Solutions is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products. With more than 80 years’ experience across prescription and consumer markets, Catalent has the deepest expertise, the broadest offerings, and the most innovative technologies, to help its customers get more molecules to market faster, enhance product performance, and provide superior, reliable manufacturing and packaging results.

From a single, tailored solution, to multiple answers throughout a product’s lifecycle, Catalent can improve the total value of treatments, and accelerate programs to the clinic and beyond. Catalent. More products. Better treatments. Reliably supplied.™

Major products/services being exhibited
Catalent’s prefilled syringes provide both safety and convenience advantages over multi-dose forms.

From its sites in Europe, Catalent has over 80 years’ experience in providing specialised scientific and manufacturing of complex injectable treatments. As a market leader in sterile manufacturing, Catalent offers an extensively customisable range of prefilled syringe products alongside innovative fill-finish processes, and speciality delivery vehicles such as auto-injectors.

With an annual syringe-filling capacity of more than 200 million units, Catalent provides not only the capacity to support partners, but also access to specialised technologies that ensure extreme precision for safer, more accurate dosing. Its expertise in process design, scale-up, quality assurance, validation and regulatory support provides efficiency and support across virtually any sterile dosage form.

Contact details
Catalent Pharma Solutions
14 Schoolhouse Road
Somerset, NJ 08873 USA
Tel. +800 88 55 6178 (EU)
+1 888 765 8846 (USA)
solutions@catalent.com
www.catalent.com

Booth A80

Gerresheimer

Company description
Gerresheimer is a leading global partner to the pharma and healthcare industries. The company’s special glass and plastic products contribute to health and well-being. Gerresheimer is a global organization with 10,000 employees and manufacturing operations in the local markets, close to customers. It has over 40 production facilities in Europe, North and South America, and Asia generating revenue in excess of EUR 1.4 billion. The comprehensive product portfolio includes pharmaceutical packaging products as well as convenient and safe drug-delivery systems such as insulin pens, inhalers, pre-fillable syringes, vials, ampoules, bottles, and containers for liquid and solid pharmaceuticals with closure and safety systems, plus cosmetic packaging products.

Major products/services being exhibited
Gerresheimer will have a range of new products and solutions for safe, reliable, and convenient pharmaceutical drug packaging and delivery on show at the 20th Pharmapack. A Gerresheimer product expert will also be making a presentation on the production of multilayer plastic containers in an injection blow moulding process for the reliable protection of content against water vapor and oxygen exposure.

Contact details
Gerresheimer
40468 Düsseldorf
Tel. +49 211 6181-0
Fax: +49 211 6181-295
info@gerresheimer.com
www.gerresheimer.com

Hall 4, Booth G1/H1
PCI Pharma Services

Company description
PCI Pharma Services is an integrated full service provider, a proven and trusted partner to leading companies in the global healthcare industry. We offer unparalleled expertise and experience in taking compounds from the earliest stages of development through to successful commercialization, delivering speed-to-market and commercial success for our customers.

Our core services support each stage of the product lifecycle, including drug development, clinical trial supply, commercial launch and ongoing commercial supply. We partner with clients in providing innovative technologies, flexible solutions, and an integrated supply network supporting lifesaving medicines destined to over 100 countries around the world.

With over four decades of commercial pharmaceutical packaging expertise and in excess of 50 successful product launches per year, PCI is a trusted leader and industry expert in the commercialization of new medicines.

Our global capabilities include packaging for large-scale projects requiring sophisticated integrated technologies and automation and the support of more targeted therapies for select patient populations.

PCI partners with clients to develop dynamic and multi-faceted strategies for ensuring product integrity, utilizing the latest technologies in product serialization and cutting edge solutions for incorporating anti-counterfeiting requirements for packaged products.

Evolving legislation within the United States and European Union, along with a patchwork of global requirements, has brought the need for serialization to the forefront of the healthcare packaging market. PCI offers a robust set of serialization services.

Major products/services being exhibited
Commercial pharmaceutical packaging expertise, Serialisation, Anti-counterfeiting and Tamper Evident Solutions, Commercial Launch

Contact details
PCI Pharma Services
Wye Valley Business Park,
Hay-On-Wye, HR3 5PG, UK
Tel. +44 (0)1497 820829
sales@pciservices.com
www.pciservices.com

Booth H79

Rommelag CMO, works Holopack Verpackungstechnik GmbH

Company description
Rommelag CMO provides you with quick and easy access to BFS technology without having to invest in either the mandatory GMP environment that goes with it or the specialists required to operate and maintain the machines. What we offer is the whole spectrum, including the entire infrastructure itself, over 50 years’ experience in bottling using BFS aseptic systems, and the expertise you’d only get from the inventors of bottelpack technology.

With over 50 systems in a whole host of different configurations, Rommelag CMO runs one of the world’s largest, most state-of-the-art bottelpack system ranges. It goes without saying, we’re ideally placed to meet your bottling needs in no time at all and at minimum cost. So whether you’re looking for help with trial batches, the development phase (including feasibility studies, stability tests, and clinical samples) or getting batches ready for market, we’ve got it all covered.

Major products/services being exhibited
We are able to fill the following applications:

Drugs and Medical devices according to GMP
- Eye, ear, and nasal drops
- Homeopathy
- Inhalations
- Infusions and injections
- Rinsing solutions
- Oral
- Cremes, ointments, and gels
- Wound care products
- Vaginal applications
- Rekthal applications
- Disinfectant solutions
- Diagnostika
- Biologicals
- Vaccines
- Biotechnological products

Non-GMP-Products
- Cosmetics
- Food supplements

Technical Products
- Pheromones
- Machine oil and Motor oil
- Detergents

Contact details
Rommelag CMO, works Holopack Verpackungstechnik GmbH
Bahnhofstrasse 18,
74429 Sulzbach-Laufen,
Germany
Tel. +49 7975 960-0
Fax. +49 7975 960-411
sales.hp@rommelag.com
www.rommelag.com

Booth G38
SCHOTT AG

Company description
SCHOTT is one of the world’s leading suppliers of pharmaceutical tubing and parenteral packaging for the pharmaceutical industry. More than 600 production lines in 13 countries worldwide produce more than 10 billion syringes, vials, ampoules, cartridges, and special articles of tubing glass or polymer. Furthermore, the company produces over 150,000 tons of glass tubing each year.

Major products/services being exhibited
SCHOTT has expanded its portfolio of ready-to-use pharma containers to meet growing market demand from drug manufacturers. The latest nest format will be able to hold 20R, 25R, or 30R ISO vials when it’s released in 2017, and will add to the existing 2R to 15R formats. The adaptiQ® concept permits pharma firms to fill different container formats on one production line while minimizing burdensome changeover times in between. SCHOTT developed adaptiQ® to be compatible with the industry’s filling and finishing equipment, and collectively, industry leaders such as Bausch & Stroebel, Bosch Packaging Technology, Groninger, Optima, and Vanrx have tested and verified adaptiQ on a large number of machine types.

SCHOTT is also integrating a specially developed big data solution into its pharmaceutical tubing production, replacing statistical sample-based quality assurance with 100 percent on-line measurement. With the new IT-based process called perfeXion™, process- and product-quality data of each individual glass tube is collected online and in real-time – an innovation that sets new standards in the pharmaceutical glass industry.

Contact details
SCHOTT AG
Hattenbergstrasse 10, 55122 Mainz, Germany
Tel. +49 (0)6131/66-1589
pharmaceutical_packaging@schott.com
www.schott.com/pharma,
www.schott.com/perfeXion

Hall 4, Booth F1 & H89

TASI TEST - Sepha Standard Solutions /ADMC

Company description
Sepha Standard Solutions is a pharmaceutical engineering company specialising in the manufacture of tool-less non-destructive package integrity test equipment for a wide range of products including blister packs, induction-sealed bottles, sachets, pouches and medical device packaging. We also provide a comprehensive range of automatic, semi-automatic and manual deblistering machines suitable for inline, diagonal and offset layouts in addition to small-scale blister packing machines ideal for R&D, product development and clinical trials. We work with the majority of the world’s top pharmaceutical companies and are part of the global Test and Inspection leader, TASI Group.

Major products/services being exhibited
Leak detection services

Specialised pharmaceutical equipment for Package and Closed Container Integrity Testing, Product Recovery and Blister Packaging. Testing services and Blister design services also available.

Contact details
TASI TEST - Sepha Standard Solutions /ADMC
Unit 25 Carrowreagh Business Park, Dundonald, Northern Ireland BT16 1QQ
Tel. 02890 484848
Fax. 02890 480890
info@sepha.com
www.tasitest.com

Booth L63
Siegfried Schmitt, PhD, principal consultant, PAREXEL, discusses how to handle audits and inspections during business expansion.

Q: Our quality unit is responsible for hosting audits and inspections for our manufacturing site. We are a contract manufacturer and due to our expanding client base, we are experiencing a growing number of customer audits and regulatory inspections. Can you provide advice for how to best accommodate this increased workload?

A: First, congratulations on your growing business. In terms of managing this rising number of audits and inspections, we would recommend developing procedures. Formalized processes, in addition to using the right tools, can help make the job more predictable, improve planning, and provide a higher chance of success. You may call this a playbook, or simply “Good Guide to Audits/Inspections.” Being prepared and having a defined process helps reduce uncertainty and drives efficiency.

Being prepared and having a defined process helps reduce uncertainty and drives efficiency.

It is good practice to start putting together this document by getting input from all parties involved. We recommend starting at the moment an audit or inspection is announced, and then structuring it by phase, such as preparation/planning, hosting, follow up/post event, and close out. The guide should include roles, rather than name-specific individuals, when explaining responsibilities involved in the inspection, as this eliminates the need for many updates or changes. For each role, it is beneficial to describe each person’s particular involvement in the inspection (e.g., active or stand by/back up), what and when they are needed, where (e.g., front office or back office “war room”), and any other pertinent information. Note that some roles may only be required occasionally, such as translators.

This playbook can be in any format suitable for your needs, but often it is in the form of a spreadsheet. A spreadsheet allows activities to easily be added into sequence and the ability to select tasks for individual roles or locations. Furthermore, completed tasks can be ticked off, together with any comments or feedback as required.

Information for auditors
A number of documents and data are typically requested by auditors and inspectors; including, but not limited to:

- Number of deviations
- Number of batches manufactured
- Number of out-of-specification (OOS) results
- List of standard operating procedures (SOP)
- Organizational structures
- Annual quality reports
- Number of complaints
- Number of recalls (if applicable).

Having a spreadsheet to refer back to, therefore, is crucial to staying organized and up to date with inspections. Having a running tally readily available in electronic format will greatly reduce the effort with preparations. It can also be beneficial to keep a set of printed copies of all SOPs handy, making these available upon request, which reduces time and effort during the audit or inspection.

Being prepared is key
Ultimately, the key to being prepared for audits and inspections is to follow the old adage: preparation, preparation, preparation. Furthermore, with practice comes experience, and with experience comes perfection. Maintaining procedures and metrics will be helpful for any inspection, especially as you expect to experience more inspections due to a growing client base.

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.
Combined forces

Nexera MX and LCMS-8060: ultra-fast multiplexing UHPLC meets ultra-trace level detection

The Nexera MX ultra-fast multiplexed UHPLC system combined with the LCMS-8060 triple quadrupole mass spectrometer provides routine high performance LC-MS/MS analysis that makes a real difference in increasing laboratory efficiency. Nexera MX features two analytical flow lines in a single UHPLC system; this doubles sample processing capability when compared to the conventional single channel approach. The LCMS-8060 adds ultra-fast polarity switching and scanning speed, highest sensitivity and robustness to push the limits of LC-MS/MS quantitation.

**Unmatched speed**
with fastest sample injection, data acquisition and polarity switching time

**Dedicated software packages**
for automated method and batch creation as well as simplified data evaluation

Boosted operating efficiency through multiplexing technology
Our next generation glass-free injectable platform, with advanced aseptic filling technology, has the potential to reduce foreign particulates by more than 95%, increase sterility assurance through automation, and improve supply reliability.