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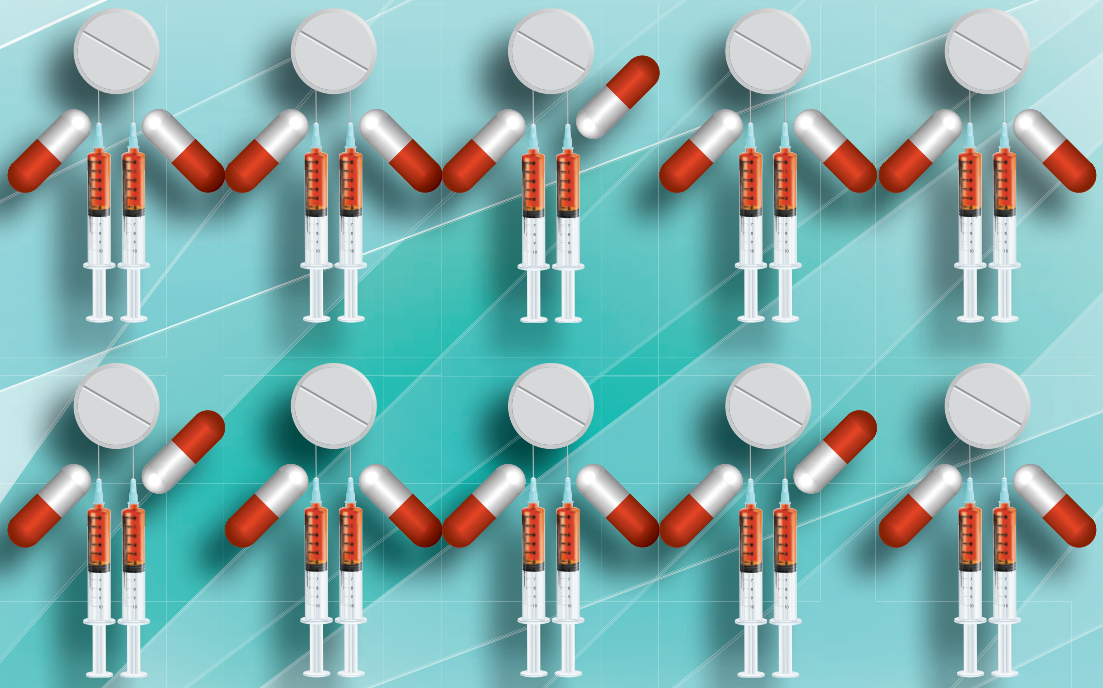

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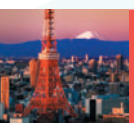

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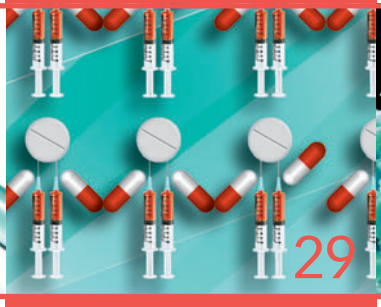

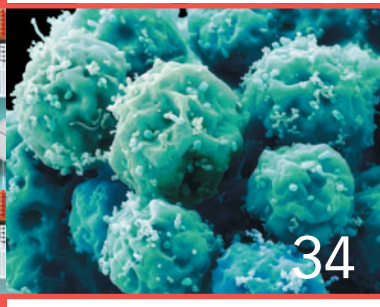

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Mergers, Acquisitions, and the Quest for Value

As 2014 draws to a close, mergers and acquisitions (M&A) appear to be trending in the pharma space. Allergan made recent headlines as the Botox maker accepted a £42 billion offer from Actavis after fending off a hostile joint pursuit by activist investor William Ackman of hedge fund Pershing Square Capital Management and Valeant Pharmaceuticals. Of course, there were dropped deals along the way, for example, AstraZeneca's rejection of Pfizer's £69 billion takeover bid, which would have marked the biggest ever foreign takeover of a British firm in the United Kingdom corporate history had it happened, and the terminated £32 billion merger between AbbVie and Shire in the wake of a US Treasury Department crackdown on tax inversions.

As noted by PwC, the pharmaceutical and life-sciences industry continues to experience a strong wave of M&A activities. The third quarter of 2014 saw 42 deals closed, representing a 27% increase from the 33 deals in Q2 of 2014 and a 68% increase from the 25 deals in Q3 of 2013. In terms of deal value, Q3 of 2014 recorded a total transaction of $61 billion compared with $18 billion in Q3 of the previous year. And with strong assets becoming scarce, we can expect to see a surge in deal values driven by fierce competition among acquirers and reorganisation of product portfolios.

The question, however, is whether or not these M&A transactions translate into real value for the companies involved. How do you maximise the opportunities in a merger or acquisition? According to PwC, the first step involves identifying the synergies in areas such as revenue and market growth, cost reduction and efficiency leverage, and capital optimisation. The next phase is the value driver analysis, this is where prioritisation is key. As the company develops its business cases and project plans, initiatives with the highest financial impact and highest probability of success should be given resource priority. Ultimately, the goal is to deliver real quantifiable results and shareholder value. The final step is the execution of value drivers and tracking of progress as the two companies integrate. As summed up by PwC, a disciplined approach to capturing deal value helps achieve early wins, build momentum, instills confidence among stakeholders, and increases the likelihood of the overall deal success.

Adeline Siew, PhD
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Biosimilar Drug Development and the Importance of Analytical Characterisation

Comparability studies require side-by-side data to demonstrate biosimilarity.

Fiona Greer is global director, BioPharma Services Development, SGS Life Science Services.

Numerous biosimilar drug products have reached the market in Europe since the first, Sandoz's version of the human growth hormone somatropin, gained EU approval back in 2006. Since then, the first two monoclonal antibodies have received the go-ahead in 2013—Celltrion's Remsima and Hospira's Inflectra, which are both versions of Janssen's Remicade (infliximab), a tumour necrosis factor alpha blocker indicated for a range of autoimmune conditions. Despite this progress, no biosimilars are yet approved in the United States, but numerous products are in development. In July 2014, Sandoz was the first to apply for biosimilar approval in the US under the Food and Drug Administration's (FDA) new biosimilars pathway, for the filgrastim biosimilar Zarzio.

The EU took the lead with its first guidance documents for similar biological medicinal products, which were published in 2005, with discussions having commenced a couple of years earlier. Other countries soon followed suit, some adopting the European Medicines Agency (EMA) guidelines, some a modified version of them, and others writing their own. But it was not until 2009 that the Biologics Price Competition and Innovation (BPCI) Act was published in the US, introducing the 351(k) new pathway to market into the Public Health Services Act. This is the new route being taken by Sandoz with Zarzio.

Meanwhile, in Europe, EMA has now produced extensive guidelines, some of which have already been revised. First, there is the overarching biosimilar guideline that contains the general principles, and there is also a set of general guidelines covering quality. These guidelines include the quality comparability exercise, clinical and non-clinical guidance, and immunogenicity requirements. In addition, there are product-specific guidelines.

The new 351(k) pathway in the US requires a comparison to be made between a potential biosimilar, and a single reference product that has been approved under the normal 351(a) route for biologics. The application must include analytical studies that demonstrate the biologic is highly similar to its reference, minor differences in clinically inactive components notwithstanding. It may also include animal studies, including assessments of toxicity, and clinical studies. The BPCI Act provides for the approval of two types of biosimilars—a biosimilar that is highly similar to the original and a so-called interchangeable biosimilar, which requires clinical switching studies to be carried out.

Risk-based approaches

FDA uses a risk-based approach in evaluating biosimilarity. The agency will consider the totality of data submitted, including structural and functional characterisation and non-clinical evaluations, human pharmacokinetic and pharmacodynamic studies, clinical immunogenicity, and clinical safety testing. FDA suggests a meaningful fingerprint-like analysis algorithm should be used, covering a large number of product attributes.

The most recent FDA guideline (1), issued in August 2014, introduces the concept of four categories of assessment outcome following the initial analytical characterisation. The "holy grail" is "highly similar with fingerprint-like similarity," where a product is deemed nearly identical to its reference product, and only minimal studies required to demonstrate biosimilarity. Next is "highly similar," which also meets the standard for biosimilarity but more extensive studies will be required. "Similar" applies where the analysis is inconclusive, and further data or studies will be necessary following consultation with FDA. Finally, there is "not similar," if a product does not measure up to the reference product, so the 351(k) pathway is not appropriate.

Analytical characterisation

So when is analytical characterisation required? The development pathway of a biosimilar is somewhat different from a novel biotherapeutic, certainly in the early stages, with a greatly increased requirement for

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physicochemical analytics compared to a novel biological molecule.

First, the target (reference) molecule must be extensively characterised to determine the variability of quality attributes. Multiple batches of the originator are studied to determine the exact amino-acid sequence and its post-translational modifications. Determining the amino-acid sequence entails tandem mass spectrometry (MS/MS) *de novo* sequencing approaches. These data form the quality target protein profile (QTPP) for the biosimilar.

For the production of the biosimilar, characterisation surveys may help in the selection of an appropriate cell line, allowing biosimilarity to be designed into the molecule from the outset. Once the biosimilar has been expressed, various regulatory guidelines require comparative data for the manufacture of biosimilars side-by-side with the originator molecule. This will require extensive data on both the primary and higher-order structure, which can be determined using a variety of orthogonal analytical methods.

The recently revised EMA quality guideline provides some additional clarification about analytical strategies. State-of-the-art analytical methods must be used to assess composition, physical properties, primary and higher order structure, purity, product-related substances and impurities to be compared between the biosimilar and the originator. The biological activity must also be examined. Quantitative ranges must be established for these quality attributes. It is also important to use material from the final process in the clinical trials if further comparability exercises are to be avoided. While the formulation does not need to be the same as the original product, its suitability does need to be demonstrated.

International Conference on Harmonisation (ICH) Q6B (2), although slightly dated now, can be used as an *aide memoire* to ensure all the molecule's physical attributes are covered. Another rich source of information on appropriate techniques is the updated 2009 EMA monoclonal antibody guideline (3). Experiments will include MS on the intact protein plus the released light and heavy chains, going through the N- and C-terminal sequence, peptide mapping, monosaccharide and sialic acid analysis, the secondary structure and folding, and studying aggregation using appropriate techniques. The complexity and size of the molecule, together with the potential structural variations, present quite a challenge. The potential variations in quality attributes such as deamidation, glycosylation, C-terminal clipping and so on can be extensive, rendering the number of variations to be deduced rather extensive.

The starting point for an antibody, guided by ICH Q6B, is the intact molecular mass measurement, which can be carried out on the whole molecule, or on reduced and released light and heavy chains. Using modern mass spectrometers, well-resolved and accurate data at 150k Da can be obtained, allowing the glycoforms to be assessed. This intact mass is a useful starting point as a comparison tool, allowing various batches of antibodies to be studied.

Peptide mass mapping is a particularly powerful structural confirmational tool. The protein is digested, following reduction and alkylation if necessary, using specific proteases to produce a mixture of peptides that can then be analysed by mass spectrometry to provide a mass fingerprint. Any change in the molecule would result in changes to the mass map, making it an effective identity test. Mapping large molecules, such as an antibody, requires several proteolytic digestions to be performed in parallel and the results combined. The resulting peptides can also be separated by online liquid chromatography–mass spectrometry (LC/MS), and with high energy MS/MS sequencing, the amino acids in the sequence can be confirmed.

A complementary strategy involves the separation of the digested peptides by reverse-phase high-performance liquid chromatography (HPLC) and collection using classical Edman degradation-based sequencing. Once the peptides are identified by mass using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS), they are sequenced, allowing isomeric amino acids, such as leucine and isoleucine, to be differentiated.

A similar mass mapping strategy can be applied to one of the most challenging problems—the characterisation of disulfide bridges. Specific enzymic digestion is used under non-reducing conditions to produce a mixture of peptides, which are identified by mass using MS. Under normal non-reducing conditions, the disulfide bridge will remain intact, giving a signal in the mass map. If the mixture is then reduced and studied by MS once more, the broken disulfide bridge will produce two new peptides, lower in the spectrum, corresponding to the individual masses of the free thiol-containing peptides.

Post-translational modifications

Glycosylation is, arguably, the most important post-translational modification, but it produces a significant challenge to the analytical chemist. The population of sugar units attached to an individual glycosylation site on any protein depends on the host cell type used, and it will also be a mixture of different glycoforms on the same polypeptide. The carbohydrate profile of a biosimilar may not necessarily be the same as that of the originator protein, so further studies will have to be carried out to prove that they have no impact on safety and efficacy.

Guided by ICH Q6B, the carbohydrate content, the structure of the carbohydrate chains and the glycosylation site need to be considered. Mass mapping strategies can be used to give information on monosaccharide composition, glycan populations and antennary profiles, antennae linkages and glycosylation sites. These MS studies can be carried out on both underivatised and derivatised samples to determine glycosylation sites for both N-linked and O-linked structures.

The intact glycoprotein can be studied for example with MALDI and/or electrospray MS, and the monosaccharide composition with LC/MS. Many chromatographic techniques, such as ion exchange can also be used for glycan profiling. The glycoprotein can be digested; N-linked glycans can be removed enzymatically; O-linked glycans can be removed via reductive beta-elimination. The fragments can

be then analysed using MS and LC methods. Linkage analysis is important, particularly the stereospecificity of oligosaccharide antennae linkages, as certain glycotopes such as Galalpha-1,3-Gal can promote antigenic stimulation in humans.

While MS is a powerful and important tool, a host of other non-MS techniques are required for this comparability exercise, looking at the differences in size, shape, and charge of the molecules. Another routine tool, capillary isoelectric focusing, for example, is useful for studying isoform distribution in a comparative manner.

When determining higher-order structure, a battery of orthogonal tests also needs to be employed. Appropriate biophysical techniques include circular dichroism in the far-UV, which enables the number of beta-sheets, alpha-helices, and other turns to be studied, for example. Fourier transform infrared spectroscopy (FT-IR) and fluorescence spectroscopy enable the study of local tertiary structure. And techniques such as analytical ultracentrifugation, dynamic light scattering, and fluorescence resonance energy-transfer methods allow examination of any aggregates that may be formed.

In summary, the development of a biosimilar requires comprehensive physicochemical characterisation at many stages of the development pathway. First, batches of the originator must be examined to determine its exact protein sequence, post-translational modifications, and the variability of quality attributes. These data form the quality target product profile. Advances in MS instrumentation and proteomic/glycomics strategies enable rapid identification of these structural data. The extensive comparability studies that must then be carried out require side-by-side data to demonstrate biosimilarity, and there is an increasing importance being placed on higher-order structure to link with the biological activity. Clearly, if the regulators are to be convinced that the potential biosimilar and the originator are sufficiently similar for approval to be granted, these comparability studies must be carried out comprehensively and effectively.

This material was originally presented by the author as commentary during a webinar in June 2014 (4).

References

1. FDA, *Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (Rockville, MD, May 2014).
2. ICH, Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products,* Step 4 version (1999).
3. EMA, *Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products* (London, Dec. 2008).
4. A. Kudrin and F. Greer, "Analytical & Clinical Development of Biosimilar mAbs: from Vision to Reality," webinar, June 2014. **PTE**

Year in Review: Key Outsourcing Trends in Biopharmaceutical Manufacturing

Outsourcing is taking on a greater role in the biopharmaceutical manufacturing industry.

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According to BioPlan's *11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (1), which identifies various industry trends, almost all areas of R&D and manufacturing are at least in contention for some degree of outsourcing. CMOs are becoming sought-after partners as a result of their use of innovative technologies, single-use bioreactors, and other novel bioprocessing services.

Trend one: Popular outsourcing activities continue to expand

This past year BioPlan's study noted a year-over-year increase in the use of many of the most popular outsourcing activities, such as:

- Toxicity testing (87% outsourcing to some degree, up from 75% last year)
- Fill/finish operations (80% vs. 70%)
- Validation services (77% vs. 72%).

There was a general pullback, however, in the less commonly outsourced activities. These activities included downstream production operations, downstream process development, and design of experiments. Some of these downstream activities may have declined as facilities resolved problems and bottlenecks in purification steps. Despite these declines, current outsourcing levels for even those activities represented growth over levels in 2010.

These data indicate that the most common outsourcing activities are becoming cemented in place as mainstream contract manufacturing activities. BioPlan expects that to continue, as the study also shows an increased willingness to outsource them to a greater extent in the years to come.

Trend two: Outsourcing is no longer about cost cutting

In years past, outsourcing was used as a way to cut costs and more efficiently allocate in-house capacity; BioPlan's recent studies indicate that cost control is no longer a top priority when outsourcing. Indeed, when respondents were asked about the cost-cutting actions they undertook during the past 12 months, only 9% had outsourced manufacturing to domestic service providers for this purpose, down from 14% last year, and the proportion that outsourced manufacturing to non-domestic service providers (off-shoring) to control costs was essentially flat at 13%, after rising from 6% since 2011 (see **Figure 1**).

Similarly, the share of respondents outsourcing jobs in manufacturing, process development, and R&D to cut costs remained either flat or slightly below last year's levels.

In a related development, the BioPlan study revealed that, this year, cost-effectiveness was not the big priority it was last year when developers were considering contract manufacturing partners. Only 22% reported that it was "very important" to them that the CMO demonstrate the cost-effectiveness of their services, roughly half the proportion (42%) from last year's survey.

Further, outsourcing budgets are expanding at a rapid rate, compared with other segments. And because outsourcing is a long-term and strategic decision, facilities don't easily make changes in their outsourcing budgets, as they might for equipment purchases. This year, respondents reported having increased their budgets for outsourced biopharmaceutical manufacturing by nearly 4%, up significantly from each of the prior five years. Outsourcing is taking on a more strategic role, moving away from a simple cost calculus and toward a partnership based on quality and value.

Trend three: Outsourcing relationships evaluated on managerial factors

While contract manufacturers should of course be able to display their technical proficiency (particularly as they bid for high-value activities previously considered too "core" to outsource), data from the BioPlan study indicate that clients are increasingly basing their partner evaluations on a host of managerial and "people" factors.

When biopharma decision-makers were asked about the issues they find important when considering outsourcing manufacturing to a CMO, of

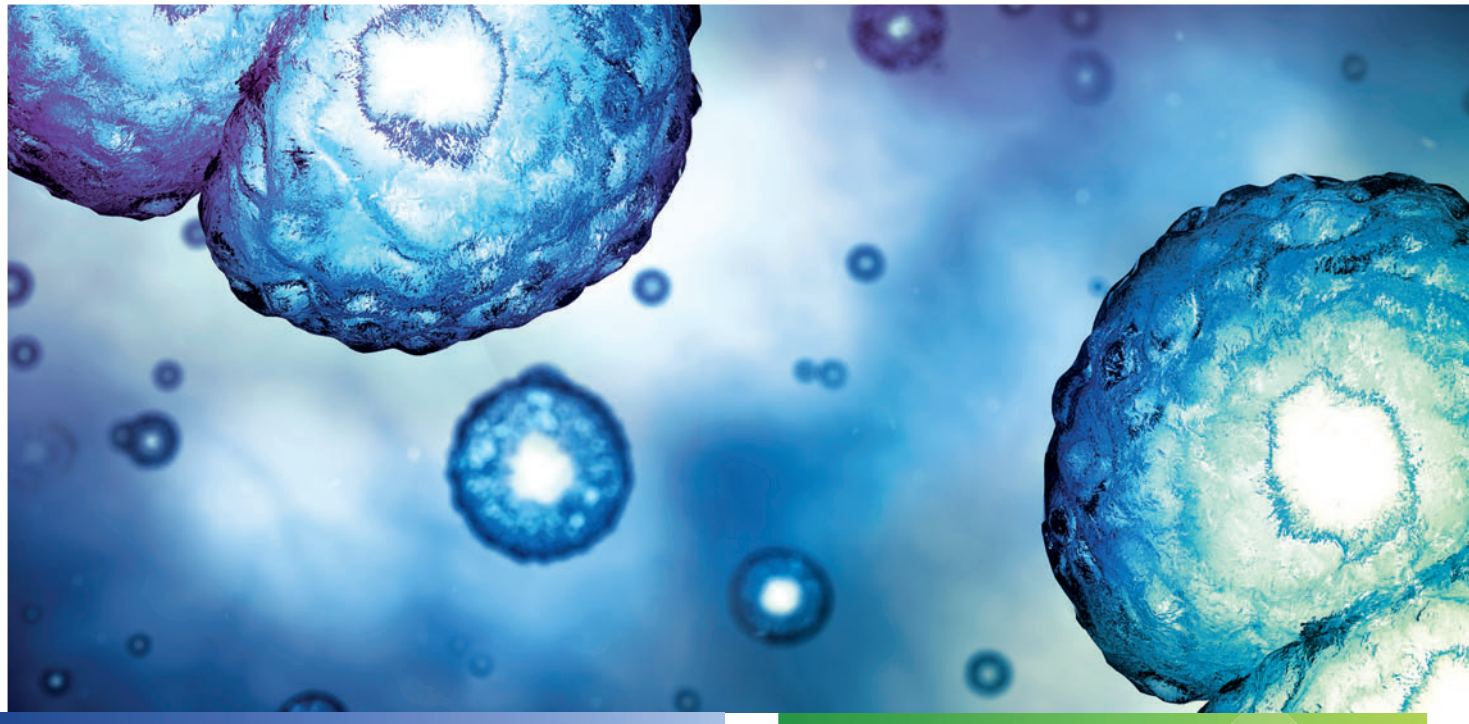

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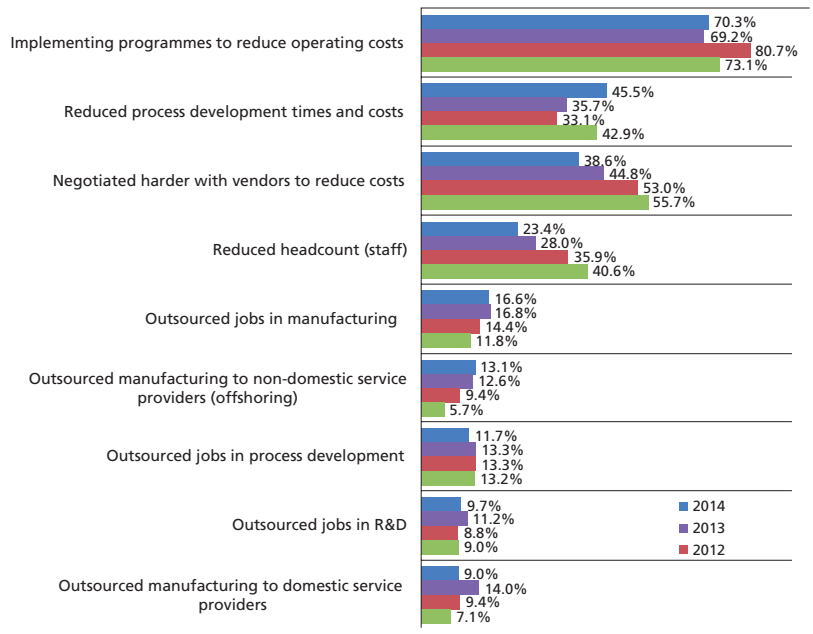
Figure 1: Selected cost-cutting actions, "Past 12 Months" comparing 2011–2014.



Source: Selected data: 11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, BioPlan Associates, Inc. (Rockville, MD, April 2014).

the 18 most critical areas indicated, the most important were:

- Establish a good working relationship ("very important" or "important" to 98.2% of client respondents)
- Stick to a schedule (94.5%).

To put this in context, when evaluating only critical ("very important") attributes, more decision-makers pointed to establishing a good working relationship (70.9%) than did compliance with the client's quality standards, protection of intellectual property, or effective handling of cross-contamination issues.

In other words, while technical competency is important, clients are recognising that they are not enough on their own, and that effective partnerships are built on strong relationships.

Trend four: It doesn't matter where the CMO is located

Assuming that the relationship is solid, the CMO's location remains relatively unimportant to clients today—only 7.3% considered a CMO being local a "very important" attribute. This runs contrary to what many CMOs have said they experience—they feel clients appreciate the opportunity to meet in person, often, and locally to watch the processes. Such in-person meetings, however, may have more to do with clients' need to keep projects on track (a major concern), than with wanting to personally watch the CMO's process development and manufacture.

Although location remains at the bottom of the decision-factor list, respondents from different regions do display different preferences when it comes to potential outsourcing destinations. Western Europeans, for example, are becoming increasingly interested in China as a potential outsourcing destination: 47% of respondents from that region named China a potential destination in the next five years, representing a large increase from just 6% a few years earlier. Indeed, China drew level with the United States as a potential destination (one that is at least in the consideration set).

Among US respondents, however, India may be the emerging market with more potential activity, while Singapore tops among Asian markets overall. In fact, Singapore topped the list of potential destinations for US respondents, 39% of whom cited it as a "possible" destination in the next five years (up from 28% in 2011). Singapore was followed in the rankings by Germany.

Trend five: Biosimilars will expand the global CMO market

The growth of interest in biosimilars, with more than 800 follow-on products in the pipeline, will provide a significant upswing in business for CMOs who are primed to be the biggest beneficiaries of this emerging trend.

Biomanufacturers, who have cut back on their in-house capabilities in recent years, may not use their remaining capacity for biosimilars manufacturing, given that these drugs will be lower cost and lower margin relative to innovator products. As a result, larger players may be expected to outsource the manufacture of these products to CMOs. Additionally, newer entrants to the market may well follow a business model in which they license-in follow-on products from smaller players and then outsource the manufacture of those products. Indeed, CMOs are anecdotally already reporting business increases of up to 15% from biosimilars services.

Conclusion

Many of the trends identified in this year's annual report will likely continue apace next year. Outsourcing will take on a higher-value dimension that puts cost behind other considerations, and the outsourcing market will increasingly globalise, a trend that will be fueled further by the advent of biosimilars. All in all, it's a time of growth for biopharmaceutical outsourcing.

Reference

1. BioPlan Associates, *11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production* (Rockville, MD, April 2014), www.bioplanassociates.com/11th. **PTE**

Figure 1 courtesy of the author

An Update on Regulatory and Application Developments in Pharmaceutical Excipients

The authors review key takeaways from the the APV/IPEC Europe Excipient Conference 2014.

As the pharmaceutical regulatory landscape continues to evolve, for example with the implementation of the EU Falsified Medicines Directive, excipients manufacturers, suppliers and users are increasingly under pressure to ensure the quality and safety of their supply chain. The APV/IPEC Europe Excipient Conference 2014, held in Dusseldorf, Germany on 23–24 Sept., gathered together industry experts to discuss recent developments in the regulation of excipients and its impact on pharmaceutical business activities.

Regulations on excipients

The excipients regulatory landscape has evidently evolved over the years from no regulation prior to 2005 to the provisions introduced in 2004/27/EC directive (1), in which GMP was a requirement for certain excipients on an EU list that was never published, noted Richard Andrews, unit manager, inspectorate operations GMP/GPvP, from the Medicines and Healthcare products Regulatory Agency (MHRA). The current European directive 2011/62/EU (2) requires appropriate GMPs for all excipients based on a risk assessment conducted by pharmaceutical companies, and enforcement of these GMPs is an obligation. Final risk assessment guidelines by the European Commission describing this process are expected at the end of 2014. The newly revised chapter 5 of EU GMP Guidelines Part 1 specify in further detail supplier qualification requirements, supply-chain traceability and the conditions for the use of suppliers test results (3). This new regulation will result in more supervisions and auditing of suppliers.

Steven Wolfgang, customer safety office at the US Food and Drug Administration, provided an update on the US regulation, requiring GMP for excipients in the same way it does for active substances and finished pharmaceuticals, according to section 501 in the Food, Drug, and Cosmetic Act. In the past, FDA used to only focus on finished pharmaceuticals. However, due to globalisation, FDA is now paying more attention to compliance and supply-chain security of excipients. FDA is getting more involved in the development of standards such as ANSI/NSF 363 and *United States Pharmacopeia* (USP) general chapters to support quality and safety. Also, Title VI of the Food and Drug Administration Safety and Innovation Act (FDASIA) (4) has put increasing emphasis on excipient quality and authenticity. Supply-chain controls should ensure traceability and safety. FDA will, therefore, be looking out for deficient supplier qualification systems and will strengthen cooperation and shared responsibility between suppliers and users of excipients. As pointed out by Wolfgang, "managing excipient quality is a multifaceted approach."

Emerging markets perspectives

Dave Schoneker, director of global regulatory affairs at Colorcon and vice chair for maker and distributor relations at IPEC-Americas, shared perspectives on the regulations of excipients in Brazil, China and India.

Frank Milek is chair of the International Pharmaceutical Excipients Council (IPEC) Europe.

Hubertus Folttmann was a board member of the International Association for Pharmaceutical Technology (APV) until September 2014.

Brazil published draft guidelines on GMP for excipients in 2012 and IPEC has been involved in discussions concerning this new regulation with ANVISA, the responsible agency in Brazil. It is likely that these draft GMPs would be revised before coming into force, according to Schoneker.

China has increased its regulatory focus on excipients tremendously over the past years. GMPs for excipients have existed in China since 2006, but with so many incidents of substandard excipients being reported, the Chinese FDA published in 2012, guidelines for strengthening the supervision on excipients. While this move demonstrates the country's concern for excipient safety, enforcement is yet unclear. Schoneker also outlined the import license procedure for excipients entering China and the burden it places on exporters to China. Furthermore, it is expected that the *Chinese Pharmacopoeia* will be implementing more than 200 new excipients monographs into its next revision in 2015. India, on the other hand, has no distinct GMP regulations for excipients yet. However, India requires a licensing process for excipients that is claimed to be compliant with the Indian pharmacopeia.

Qualifying excipient suppliers

One of the most important responsibilities of pharmaceutical companies today is to manage their suppliers. Harald Scheidecker, head of qualification and validation within systems QA at Boehringer Ingelheim, presented an example of the supplier qualification system used in his company and made it clear that a risk-based approach is essential given that risk management is part of most GMP guidelines. "It is an approach needed to manage the huge number of excipients and suppliers that a pharmaceutical company usually sources from," said Scheidecker. "This [approach] also requires more understanding of pharmaceutical requirements by the suppliers and a better communication relating to processes, product properties and changes." Supplier management requires more involvement of the suppliers and different departments within pharmaceutical companies, such as the quality assurance, quality control and purchasing divisions. "Understanding of risk and the supply chain is key in this context," emphasised Scheidecker.

Wolf-Ruediger Schlag, regulatory affairs manager, Pharma Ingredients & Services at BASF, described the information on excipients required in a marketing authorisation dossier, citing the common technical document (CTD) format as the general standard applicable in Europe. All information on excipients has to be provided in section 3.2.P.1 of the dossier. All details relating to the properties of the excipient, their controls and justification of the specifications have to be provided as well. This way, the suppliers can understand what excipient users are asking for and how the excipients are going to be used.

Excipient quality system standards

With excipient quality system standards being the focus of the first day, Helen Stubbs, product regulatory manager at Dow, summarised available standards such as IPEC PQG GMP Guidelines, EXCiPACT, ISO 9001, ISO 22000, ANSI/NSF 363, and European Federation for Cosmetic Ingredients (EFfCI) GMP. "There is a lot of overlap between these standards," said Stubbs. "Therefore, it is evident that a look to the left and to the right makes sense when working on compliance of a quality system to one or more of these standards."

Iain Moore, head of global quality assurance at Croda and president of the EXCiPACT asbl introduced the association's standard for supplier qualification and certification. EXCiPACT provides GMP and GDP evaluation of excipient suppliers through approved third-party certification bodies using auditors especially trained on this standard. This system fits the new expectation of EU regulation for tighter supply-chain controls and the opportunity to use third parties for this process. To date, 10 GMP/GDP certificates and audit reports have been granted to excipient suppliers, according to Moore. "This makes EXCiPACT a future oriented system for supplier qualification." The pre-conference workshop on the first day, which was led by Moore, provided participants the opportunity to learn about the interpretation of the new risk assessment requirements for excipients and excipient supplier qualification in the EU. Participants could also find out more about the details of the draft risk assessment guidelines of the EU and see how the different processes outlined in the draft EU guide may be applied in practice.

Excipients for paediatric and parenteral products

Jörg Breitkreutz, professor for pharmaceutics and biopharmaceutics at the University of Düsseldorf, Germany and president of APV, kicked off the second day by giving an overview on incidences where the use of excipients had caused fatal outcomes or severe adverse events in children. He explained the specific physiological conditions in children of different age groups and highlighted the need for revision of excipient guidelines in relation to the labels and package leaflets of medicinal products for human use. "It is important to note that the safety of excipients can affect children differently from adults due to the ongoing organ development and incomplete maturation depending on their age," said Breitkreutz. After covering the Paediatric Investigation Plan (PIP) and the guideline on pharmaceutical development of medicines for paediatric use, Breitkreutz concluded that pharmaceutical excipients are required and useful for paediatric medicines; however, there is still lacking the much needed data on age-related safety and evidence-based regulatory guidance.

In terms of critical raw materials used in biopharmaceutical manufacturing, Mathieu Ballie, quality assurance lead biologics, External Supply Operations, Novartis, pointed out that biologics are complex molecules that are characterised by their manufacturing processes. "Slight changes to critical raw materials and

consumables can impact quality, safety and purity of the product," he said. "It's all about supply-chain control, specification setting and controls, quality oversight and supplier relationship."

Speaking from a CMO's viewpoint, Thomas Froneck, head of quality control at Vetter-Pharma GmbH & Co. KG, discussed excipients for use in parenteral products, including their various functions and the associated risks and challenges. "In an ideal world, full GMP standard for excipients in parenterals should be a given," said Froneck. However, he pointed out that, for example, there is currently no castor oil, an excipient used as solvent in injectables, available that is produced according to GMP. In addition, not all excipient suppliers agree to be audited by pharmaceutical manufacturers. In reviewing supplier management as well as the roles and responsibilities of the marketing authorisation holder (MAH), the CMO and excipient supplier, Froneck emphasised the necessity of knowledge transfer between excipient suppliers and users and the importance of a partnership between the two parties.

Quality by design

The application of quality-by-design (QbD) principles in the development of pharmaceutical dosage forms is widely recognised among suppliers and regulators in the pharmaceutical industry. "Excipients are used in virtually all drug products and are essential for product manufacturing and performance," commented Amina Faham, senior pharmaceutical development application manager at Dow. "The successful manufacture of a robust product requires the use of well-defined excipients and manufacturing processes that consistently yield a quality product. QbD is a systematic approach that relates a mechanistic understanding of material attributes and process parameters to the drug product's critical quality attributes (CQAs)." Faham explained that multivariate experimentation is required to fully understand the drug product and process. It is, therefore, important that multivariate experimentation is incorporated into the experimental design as an evaluation of material variability, which includes both the API and excipients used in the formulation.

Novel excipients

The conference ended with an R&D case study presented by Doris Gabriel, R&D head of the laboratories, Apidel, on creating value with novel excipients. Gabriel shared about two promising, chemically new, early-stage excipients under development—a polymer for a sustained-release injection that is liquid at room temperature and a nanocarrier for drug transport into the cornea and skin following topical application. To overcome the financial burden of such development projects and to avoid the risk of a slow market introduction usually associated with novel excipients, the developing company, Apidel, signed agreements with seven pharmaceutical companies at an early stage.

References

1. Directive 2004/27/EC of the European Parliament and the Council of 31 March 2007, *Official Journal of the European Union,* L 136/34–57, 30 April 2004.
2. Directive 2011/62/EU of the European Parliament and the Council of 8 June 2011, *Official Journal of the European Union,* L 174/74–87, 1 July 2011.
3. EudraLex Volume 4—*EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use,* http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm, accessed 10 Nov. 2014.
4. Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112–144, 9 July 2012, 126 STAT. 993), www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf, accessed 10 Nov. 2014. **PTE**

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FDA Realigns Drug Inspection and Manufacturing Oversight

Operational changes at the US Food and Drug Administration aim to improve global market monitoring.

A greatly expanded range of regulated food and drug products, now produced all over the world, has prompted the United States Food and Drug Administration commissioner Margaret Hamburg to seek new ways for FDA to handle its more complex and far-flung regulatory responsibilities. Hamburg formed a high-level agency-wide group in 2013 to assess and make recommendations for improving alignment of FDA centres with its inspection field force. The result is a new Programme Alignment Group (PAG) plan to integrate more closely centre and field oversight functions through "commodity-based and vertically-integrated regulatory programmes."

At the same time, the Centre for Drug Evaluation and Research (CDER) is implementing a major reorganisation designed to bolster programmes and policies to ensure drug quality. After two years of planning, CDER director Janet Woodcock is establishing a new "super" Office of Pharmaceutical Quality (OPQ), a move that reflects Woodcock's "one voice for quality" approach that coordinates review, inspection, and research activities related to drug quality.

Field and centre integration

FDA's programme alignment process will revise inspection functions carried out by the Office of Regional Affairs (ORA), which manages operations for inspecting and overseeing compliance for all FDA-regulated products and companies in the US and abroad. For drugs, a main initiative is to form an ORA pharmaceutical inspectorate, a cadre with specialised expertise to inspect and evaluate manufacturing facilities for both human and animal drugs throughout the world. CDER staff may participate in certain inspections and will provide more input into inspection scheduling, operations, and enforcement actions. Field force specialisation will involve more training, and ORA laboratories will become more specialised (1).

These operational changes will be spelled out in a five-year Pharmaceuticals Action Plan that will be developed in 2015 by ORA, CDER, and the Centre for Veterinary Medicine (CVM). These parties will calculate future resource levels needed to shift from a regional oversight structure to a dedicated drug surveillance programme, a process that will involve assessing the number of field investigators, compliance officers, and managers for the new programme. The programme will develop enforcement standards, policy guides, and guidance and clarify field and centre responsibilities for issuing warning letters, enforcement actions, and decisions related to compounding, clinical disqualifications, and recalls.

Key to formulating a multi-year, risk-based process for scheduling plant inspections and monitoring imports for ORA, CDER, and CVM is to overhaul and update manufacturer registration and inventory databases. This involves "harmonising" centre and ORA data systems, using common facility identifiers, product codes, and software platforms that permit all parties to access information on field inventory, applications, facilities, adverse events, and risk information. To this end, FDA issued guidance in October 2014 advising manufacturers to use DUNS numbers (Dun and Bradstreet's Data Universal Numbering System) for a unique facility identifier (UFI) system (2).

Once the programme is established, CDER will supply ORA with an annual surveillance priority list that provides a basis for an ORA work plan for the coming year. A pilot for team-based domestic and foreign drug quality inspections has been launched to ensure that these changes enhance field and centre agreement on where regulatory action is required.

FDA's Centre for Biologics Evaluation and Research (CBER) should experience less disruption from this initiative to integrate field and centre inspection activities, as an ORA Team Biologics has been in place since 1997 for cellular therapies and blood products, with CBER reviewers regularly participating in field inspections. Still, a Biological Products Action Plan will be developed to improve CBER's plant registration data system and support a risk-based approach for setting priorities on facility inspections. In 2015, CBER and ORA will update existing Team Biologics procedures and identify gaps in training and policies.

Another important PAG change is to establish a central Bioresearch Specialisation Action Plan for agency bioresearch monitoring (BIMO) activities. A dedicated corps of ORA investigators will conduct BIMO inspections for drugs and biologics, as well as other regulated products.

Changes at CDER

CDER's reorganisation will go live on 5 Jan. 2016, shifting to OPQ most functions of its Office of Pharmaceutical Science (OPS). OPQ will evaluate the CMC (chemistry, manufacturing, and controls) submissions for drugs, biotech therapies, and generic drugs and conduct research on drug formulation and manufacturing issues (3). OPQ will also oversee the process for scheduling and conducting preapproval and surveillance inspections now carried out by CDER's Office of Compliance (OC). OPQ will become responsible for certain functions related to risk analysis and informatics in planning inspections now handled by OC's Office of Manufacturing and Product Quality, and oversight of bioequivalence testing and non-clinical studies will move from OC to CDER's Office of Translational Sciences. These changes will enable OC to focus on compliance and enforcement activities, including recalls, supply chain security, and unapproved drugs.

GLOBE: ZOONAR RF/GETTY IMAGES

Woodcock will head OPQ on an acting basis, assisted by deputy director Lawrence Yu, who has been serving as acting director of OPS for the past year. Steve Kozlowski will continue as director of OPQ's Office of Biotechnology Products, and Cindy Buhse remains acting director of the Office of Testing and Research. New offices will process CMC applications for new drugs (acting director Sarah Pope Miksinski) and for lifecycle drug products (acting director Susan Rosencrance). Other new OPQ operations include an Office of Programme and Regulatory Operations, an Office of Policy for Pharmaceutical Quality, and an Office of Process and Facilities. An OPQ Office of Surveillance will develop written standards and inspectional procedures, led on an acting basis by Theresa Mullin, currently director of CDER's Office of Strategic Programmes where she has headed up the development of quality metrics for assessing manufacturing operations and products.

These changes aim to achieve uniform quality oversight for new drugs, generic drugs, and over-the-counter products by providing a single drug quality assessment "that captures the overall OPQ recommendation on approvability," Woodcock stated. Manufacturers will benefit from feedback on quality deficiencies earlier in the review cycle, and FDA will be able to provide a more uniform quality programme across domestic and foreign manufacturing sites, as well as for all drug product areas. The result, Woodcock believes, will be "consistent approaches, a transparent process, and clear standards to which the regulated industry must conform."

Woodcock has voiced these goals repeatedly in the past two years, emphasising the need to instill a "culture of quality" as opposed to compliance, throughout the bio/pharmaceutical industry. She emphasised at the FDA/PQRI conference in September the importance of moving from a "rule-based" to a "risk-based" approach based on common understanding of what constitutes real risk in pharmaceutical products. Field inspections will shift from "writing traffic tickets" to full product assessment—not just negative observations but what the manufacturer is doing well. This intelligence will support a "pharmaceutical platform" with a complete inventory of regulated facilities around the world (e.g., location, ownership, products, surveillance information). CDER has been piloting its team-based review approach this past year, and Woodcock anticipates "rapid evolution" of these initiatives over the next few years.

References

1. FDA, PAG action plans, www.fda.gov/aboutfda/CentersOffices/ucm392733.htm, accessed 11 Nov. 2014.
2. FDA, *Specification of the Unique Facility Identifier System For Drug Establishment Registration, Guidance for Industry* (Nov. 2014).
3. CDER, CDER reorganisation, www.fda.gov/AboutFDA/CentersOffice/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm, accessed 11 Nov. 2014. **PTE**

EMERGING MARKET REPORT

Drug Scandals Impact Industry in: Japan

Jane Wan

The spate of drug scandals may alter the relationship between manufacturers and research institutions, and reshape Japan's clinical research industry.

Japan's pharmaceutical industry has been littered by a spate of drug scandals in recent years. In April 2014, Takeda Pharmaceutical was questioned for a clinical research Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) for its hypotensive drug Blopress (candesartan cilexetil) regarding possible data manipulation, conflict of interest, and appropriateness of the use of study results in promotions. Investigation by a third-party organisation confirmed several instances of involvement by the company in statistical analysis of this "doctor-initiated research." Furthermore, inappropriate promotions of the study results were pointed out.

In another case, a former Novartis employee embroiled in the Diovan (valsartan) scandal has been arrested. Japan's Ministry of Health, Labour, and Welfare (MHLW) has also filed a criminal complaint against the company. A fine of $18,710 for exaggerated advertising is also highly likely to be levied against Novartis. Furthermore, the company's recent scandal involving a failure to report the side effects of its leukaemia drugs Tasigna (nilotinib) and Gleevec (imatinib) could earn more than a rebuke by the MHLW to clean up its act.

Refining clinical trials

Clinical trials have been decreasing in Japan over the past few years, falling from a peak of 375 in 2011 to 337 in 2013 according to ClinicalTrials.gov (1). This decline, however, is set to change as the country liberalises its clinical research regulations in three key ways, according to Ang Wei Zheng, a pharmaceuticals and healthcare analyst at Business Monitor International (BMI).

Firstly, Japan is looking to relax rules that require new drug applications from outside the country to have clinical trials that use a sufficiently large number of Japanese citizens. Secondly, Japan has created new tracks for clinical research in a bid to accelerate the development of its pharmaceutical industry especially in stem cell research as echoed in its Act on Pharmaceuticals and Medical Devices (PMD), which was passed in 2013. This legislation creates a separate expedited approval system for regenerative medicines where a provisional approval can be obtained after a single clinical trial as long as there is confirmed evidence of effectiveness. Thirdly, Japan has been a step ahead of the United States by delineating a biosimilars regulatory pathway in 2007.

In reforming this system, Japan is following the example of European countries that face similar challenges. France, for example, requires companies to declare their links with students, associations, establishments, and the specialist press. In addition, companies have to declare all benefits provided to doctors and others. To control aggressive advertising, France also requires promotional materials to gain approval before use.

Changing relationship

The string of drug scandals in Japan may change the relationship between drug manufacturers, doctors, and research institutions. Ang says, "We expect more scrutiny that will result in a more cautious relationship between parties involved. Eventually, this one-to-one relationship will involve more parties, including regulators, who are keen to avoid

a repeat of the scandals. However, we do not expect this relationship to cease due to its symbiotic nature as research institutions require funding and drug manufacturers stand to benefit from an accelerated drug development process with these links."

The government has adopted a proactive role to deal with the situation. On 8 Jan. 2014, MHLW sent a "Notice to comply with ethical guidelines for clinical research and epidemiologic research" to all research institutions in Japan. The Ministry of Education, Culture, Sports, Science, and Technology, which has governance over national universities, revised its guidelines for research activity misconduct measurement and reinforced the measures against research institutions.

The Japan Pharmaceutical Manufacturers Association (JPMA) issued a transparency guideline which required its members to disclose the following: fees for research and development, fees for grants for academic research, fees for writing manuscripts, fees for provision of information (e.g., speaker fee, honorarium), and other fees (e.g., entertainment). By February 2014, all 70 member companies of JPMA disclosed their own transparency policies.

Naoya Takuma, healthcare, pharmaceuticals, and life sciences lead of PricewaterhouseCoopers (PwC) Japan says, "An effective reform needs to have two components. New regulations, incentives/penalties, and government oversight over the conduct of clinical research have to be put in place. Another is to have pharmaceutical companies put in place a more robust risk and compliance governance system."

Increasing transparency of work practices

When discussing transparency, Takuma adds, "All pharmaceutical companies, both domestic and foreign, realise now that the transparency of clinical research sponsored by pharmaceutical companies will be under close scrutiny, and that they will be required more than before to disclose not only the outcome of the research but also other factors such as planning and process of research."

Internal measures to prevent recurrences include strengthening of the compliance system, adding new members to review materials from both a legal and medical perspective, strengthening the system for the screening and evaluation of donations and implementing information technology support for hardwiring, and monitoring payment approvals and payments to healthcare professionals. In recent years, some companies have also introduced the Medical Affairs function with Medical Science Liaisons to manage Key Opinion Leaders and to support their clinical research activities independently of the sales and marketing function.

Moving forward

Japan will continue to remain a key player in the pharmaceutical industry despite the drug scandals. Ang says, "The government will not impose overly onerous regulations that will derail the promotion of Japanese clinical research. From a domestic standpoint, the pharmaceutical industry remains a cornerstone for future growth in the country with regenerative medicine showing strong promise to drive the economy and meet the needs of its ageing population. It is thus unlikely that the government will risk stifling this industry and measures will always be weighed against the goal of making Japan a pharmaceutical research and development hub."

Globally, Japan remains the second largest market in the world with pharmaceutical sales at $112.6 billion in 2013 (2). The country also ranks highly on BMI's Risk/Reward Index for strong patent respect and political stability (3). This ranking maintains Japan as a highly attractive market for pharmaceutical companies that are looking to launch innovative drugs in the market. Moreover, the bold steps taken by the country in the field of regenerative medicine will help Japan maintain its premier position regionally against rivals like South Korea.

References

1. Clinicaltrials.gov, www.clinicaltrials.gov/, accessed 14 Oct. 2014.
2. BMI, Pharmaceutical Sales 2014.
3. BMI, Risk/Reward Index 2014. **PTE**

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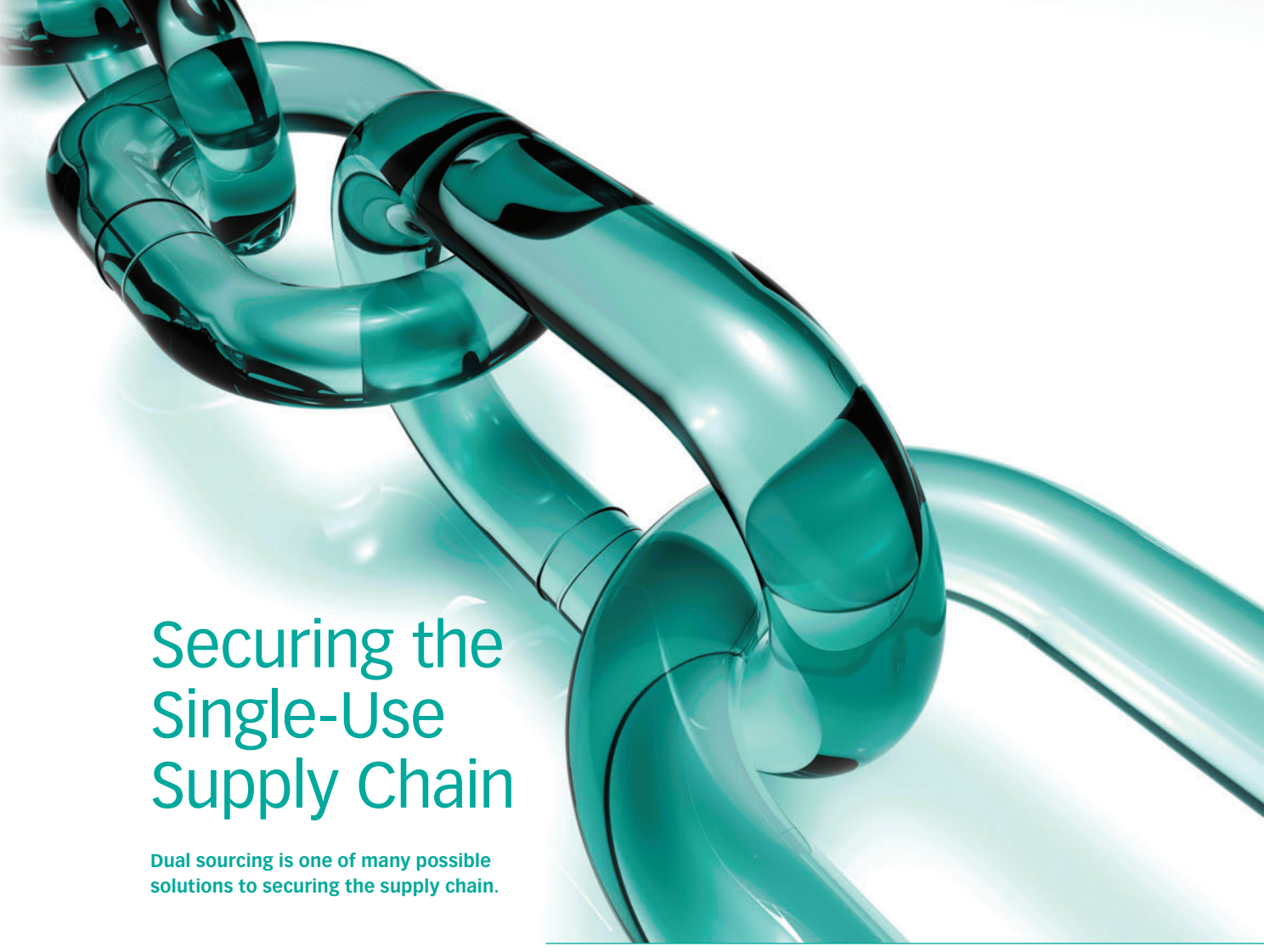

Securing the Single-Use Supply Chain

Dual sourcing is one of many possible solutions to securing the supply chain.

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

Single-use systems (SUS) have become established in biopharmaceutical drug development. As confidence in the technology has increased, the adoption of disposable equipment for commercial manufacturing has begun to take place. With this shift has come a dependence on suppliers that is related to production capabilities, a situation that did not previously exist. This reliance on suppliers translates to increased risk, and consequently biopharmaceutical manufacturers are focused on managing this risk and ensuring security of supply. Dual sourcing of single-use systems and components was initially proposed as the key solution. After further consideration of the issues surrounding the supply of single-use systems, however, many in the industry believe that dual sourcing presents many challenges that can often be avoided by taking alternative approaches.

Large-scale impact

Today, single-use systems are used throughout the entire process chain from upstream to downstream and from bench scale to production scale. In the past, when drugs were manufactured in stainless steel, the manufacturer was in control of the infrastructure once its facility was in place, sourcing only critical disposable components such as filters and chromatography sorbents. Although disposable systems do provide numerous advantages, such as reduced contamination risks, shorter set-up times, and lower capital costs, biopharmaceutical manufacturers do not have that same level of control over the disposable systems as they did with traditional stainless-steel equipment because the systems and components must be purchased from a supplier, according to John Briggs, director of quality, regulatory, and compliance at ASI-Life Sciences. As a result, adds Mario Philips, vice-president of single-use technologies at Pall Life Sciences, there is a greater dependence on the single-use supplier, which increases the risk for the manufacturer and thus requires greater vendor transparency and supply-chain security.

"Unlike with traditional equipment, where almost everything is physically located at the facility, single-use systems are delivered to the site from a supplier. If the user operates on a just-in-time basis with no inventory, any delay in delivery could put the manufacturing schedule at risk. Consequently, an SUS is a critical part of drug substance manufacturing, and there is a greater need to understand and secure the sourcing of these systems," says Roman Rodriguez, global market development manager for single-use technologies with EMD Millipore. As such,

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it is logical to consider qualifying a back-up supplier as part of the SUS risk-management system, and dual sourcing is a response to a need for anticipating unforeseen issues and scenarios.

The implementation of single-use systems in commercial manufacturing has had the additional consequence of shifting the purchasing of these systems from those in development to sourcing professionals. As a result, according to Tony White, a founding director of the BioPhorum Operations Group (BPOG), some biopharmaceutical manufacturers are now starting to consider single-use technologies as a strategic commodity and managing their purchases across their manufacturing network, which often leads to the identification of risks that were not previously perceived. "In addition," says White, "they are realising that they have been single-sourcing key components by default—a position they do not find very comfortable."

Past experience with SUS sourcing problems is also a driver for the increasing focus on multisourcing, according to Terry Hudson, director of process development engineering with Genentech. "At any conference with single-use as a topic, you can find a case study or conversation about a single-use component being changed with either no prior notification or inadequate notification to the end user, and in several cases that has been tied to a negative impact on production," he explains. In addition, Hudson notes that companies are also learning that occasionally a given process may be more sensitive to a leachable or film type than other processes, and it is beneficial to have an alternative film that can be used with that process.

There are regulatory drivers as well. Regulatory authorities have had a clear and simple message with respect to single-use products, according to Ross Acucena, product strategy manager–ReadyToProcess with GE Healthcare Life Sciences, which is that their use is analogous to outsourcing crucial elements of GMP operations, such as presterilisation. "The role of the supplier is therefore now more critical, and regulators expect drug manufacturers to mitigate any risk with close partnerships and thorough knowledge of their suppliers' quality systems and supply chains," he says. Furthermore, the increased focus on suppliers has highlighted the fact that SUS supply chains are both broad and deep because of the integration of many components into the end products. "Single-use customers recognise that it is difficult to fully control the supply chain, which presents a potential risk to their operations and subsequent supply of needed drugs to patients," Acucena asserts. The industry response has been to increase its focus on mitigating such risk through multisourcing.

Different views of dual sourcing

The ultimate goal of multisourcing is to have the ability to seamlessly transfer from one single-use product source to another without risk to patient safety, according to Acucena. "There is a strong need to characterise and understand this issue for all parties in the complex supply chains that exist within the industry. Upon investigation, it may materialise that some parties have a robust supply chain where risk is small. The converse is that unacceptably high levels of risk are detected, requiring either dual-source or multisource strategies, or even exiting a specific relationship," he observes.

In an ideal state, according to Hudson, the multisourced component would be supplied by two different companies with different supply chains to minimise the potential for a single change impacting both components. At a minimum, multisourcing needs to provide assurance that a change or disruption to one source will not also occur at the second source. Thus, risk mitigation can be achieved by using one vendor that has two plants or by using two separate vendors. "The latter option also provides some commercial leverage and tends to be the preferred approach for end users," Philips says, "but a lack of industry standards for single-use systems makes it more difficult, if not impossible." Not surprisingly, suppliers prefer the dual site or manufacturing redundancy concept, according to Spencer Parkinson, senior product manager for bioproduction with Thermo Fisher Scientific. "If it is truly assurance of supply that is of interest, then more than one production site addresses this need, while allowing a supplier to provide 'best-in-class' products," he notes.

For Rodriguez, multisourcing is the basic view, and the real issue relates to supply chain understanding, assurance, and control, as well as taking action to reduce inherent risks. "Doing so is not as easy as it seems due to supply chain complexity down to the resin suppliers and the varying approaches that can be taken. It really starts with a close interaction with SUS integrators on a whole supply chain view. An alternative supplier's products must be assessed with the same science-based qualification process, and if different suppliers adopt slightly different approaches, the end-user must determine what is acceptable," he says. As an example, Rodriguez points to bioburden levels, which can be tested on every single lot or using a statistical approach. Both methods may be acceptable depending on the end-user's specifications.

The challenges of complexity and cost

There are numerous challenges when considering true dual sourcing, and many relate to the complexity of the single-use supply chain. The SUS business is highly customised, and there are thousands of single-use components, many of which only work with other components made by the same supplier. Of course, not all those components need the same scrutiny depending on their criticality and demand, according to Rodriguez, but due to the huge number of components and suppliers, it is a complex task to track and understand the supply chain to secure and control it. As an integrator, EMD Millipore has prioritised and ranked SUSs based on criteria (i.e., criticality, volume used, lead time, reliability of the suppliers) and customer interaction.

Qualification and validation are, in fact, the critical criteria that must be met to achieve dual sourcing,

according to Acucena. "To achieve dual sourcing, one must have documented evidence that a change in input (product contact materials) will not affect the output (product quality, efficacy, safety), and it is ultimately through qualification and validation that such assurance is achieved," he notes.

ASI-Life Sciences is taking a close look at how to demonstrate functional equivalency of materials obtained from different suppliers. "At this point there is no standard or definition for functional equivalency, but it is necessary to define what constitutes functionally equivalent materials in order to ensure change control," Briggs observes. "The challenge lies in the fact that proprietary plastics/elastomers are used by different suppliers, and thus composition alone cannot be used to determine equivalency, and other characteristics, such as the physical and chemical properties of the single-use product and its performance under process conditions must be evaluated. In addition, the ability to integrate the product into an end-user process and the quality system of the supplier must also be considered," he comments.

Standardisation is frequently raised as another issue for dual sourcing of single-use systems. Philips notes that with limited standards in place, variation in SUS design continues to be significant, and it is much harder to have contingency in supply. Hudson agrees that the main challenge to dual sourcing is the current business model used by most single-use companies, which involves the development of hardware for a SUS that will only work with their single-use components. "This approach for end users is a significant impediment to deploying such systems into a GMP environment. Until companies are willing to standardise enough on their design that they fit more than one single-use assembly, including an assembly from another company, it will be difficult to achieve true dual sourcing," says Hudson.

Parkinson, on the other hand, argues that standardisation would lead to a halt in innovation. "Single-use products are not commodities and will not be in the foreseeable future; innovation is critical to improving the technology. While it also leads to the development of different designs and materials by each vendor, improvements would not occur otherwise" he states.

Standardisation is frequently raised as another issue for dual sourcing of single-use systems.

The continued advancement of single-use technology adds to the complexity, however, with new products constantly introduced that require change management. "We are aiming at full process integration by adding supply chain considerations from the lead times associated with single-use items, which requires discussions with the end-user because it is an integral part of technology transfers into manufacturing operations," Rodriguez says.

"Obviously the primary action is to communicate and build a basis of understanding about the supply chain itself and the potential associated risks, which naturally leads to actions to minimise those risks at every level of the supply chain, starting with the single-use integrator. Focusing on the product attributes, quality, and specifications may not be enough, however, as there are other steps involved such as sterilisation and transportation (sometimes international) that may impact the product and lead time. Ultimately, therefore, the first challenge is to get a clear understanding of the supply chain, to communicate about it, and then establish an action plan on a case-by-case basis," he continues.

Thoroughly understanding the supply chain is, however, an intense endeavor that requires significant resources, according to Acucena. He in particular points to the case where two SUS suppliers purchase equipment from the same precursor company, and thus qualifying the two SUS suppliers does not achieve dual sourcing. He also notes that there are significant costs associated with qualifying dual-source suppliers, and the value of such an investment is an important consideration. "In essence," says Acucena, "dual-sourcing or multisourcing can be likened to an 'insurance policy' that is relatively expensive to buy."

Not the only option

While the initial reaction of many biopharmaceutical manufacturers to concerns over single-use supply chain security was to look at dual-sourcing solutions, the focus has since shifted to the broader issue of security of supply and how best to manage it, according to Acucena. "The need is security of supply," agrees Kevin Ott, executive director of the Bio-Process Systems Alliance (BPSA). He adds that dual sourcing is one possible solution, but there are others with fewer validation challenges, including redundant supply sources from a single vendor and inventory plans, for example. "The question," he continues, "also becomes complicated by how far back in the supply chain one needs to go. That depends on volume versus demand, structure of the supply chain, etc."

For example, Ott notes that suppliers of biocontainers that can assemble containers in two locations and carry sufficient inventory of finished units and film to cover film supply disruptions do not necessarily need to be dual sourced to ensure continuity of supply, just perhaps be "dual located."

"The justification for dual sourcing should depend on the risk and the level of simplicity, and single sourcing is in many cases appropriate as long as the relationship between the supplier and the end user is a partnership," asserts White. He notes that many automotive manufacturers only single source strategically important materials because the investment in establishing a reliable supplier is significant and not worth doubling.

One alternative to dual sourcing is, according to Philips, to limit the number of contact materials in single-use systems and aim to create interchangeability for any layer (e.g., films, filters, valves, and tubes) that comes in contact with a drug product. Pall Life Sciences

has taken a step forward in this direction by vertically integrating its own production processes one step back in the supply chain. The company uses its own in-house extruded film to make the supply chain more robust and is working to mitigate any potential changes from resin suppliers. "While we can't prevent change, we are prepared to manage that change, and if we fully understand our supply chain, we have the power to support customers through any change that may occur through our supply strategy, which adds up to an increased ability to offer a greater level of supply-chain security and continuity to users," remarks Philips.

Business continuity planning and inventory management are additional mechanisms for reducing risk, according to Acucena. He notes that suppliers are now engaged in an increased focus on these aspects, and thus the crucial first step of increasing industry awareness is already taking place. He also notes that the experience with reducing the risk associated with the single-sourcing of critical chromatography media, such as protein A, can be translated to single-use systems. "GE Healthcare sought to satisfy the industry's need to mitigate this risk through a strong focus on business continuity planning (in accordance with ISO 22301 and achieving conformance to this standard), including qualifying dual sources for critical raw materials and a significant investment in safety stock. These efforts have delivered supply-chain security improvements that should help to eliminate end-user dual sourcing. Similar approaches should be applicable to single-use technology," he explains.

Both White and Ott also note that focusing on dual sourcing at this stage in the industry's development may not be appropriate. "Many biopharmaceutical manufacturers are not yet in a good position to dual source, as they are just starting to understand the extent of their complete single-use portfolios across their networks," White says. Ott adds that it may be premature or counterproductive to imagine risks. "It is better to actually study, evaluate, and understand your own supply chain and the real risks. Once that is done, the need to establish truly independent dual sources and the difficulty that such an approach represents with respect to validation and regulatory filing begins to look like much less of an issue than might be imagined," he comments.

Business continuity planning and inventory management are additional mechanisms for reducing risk.

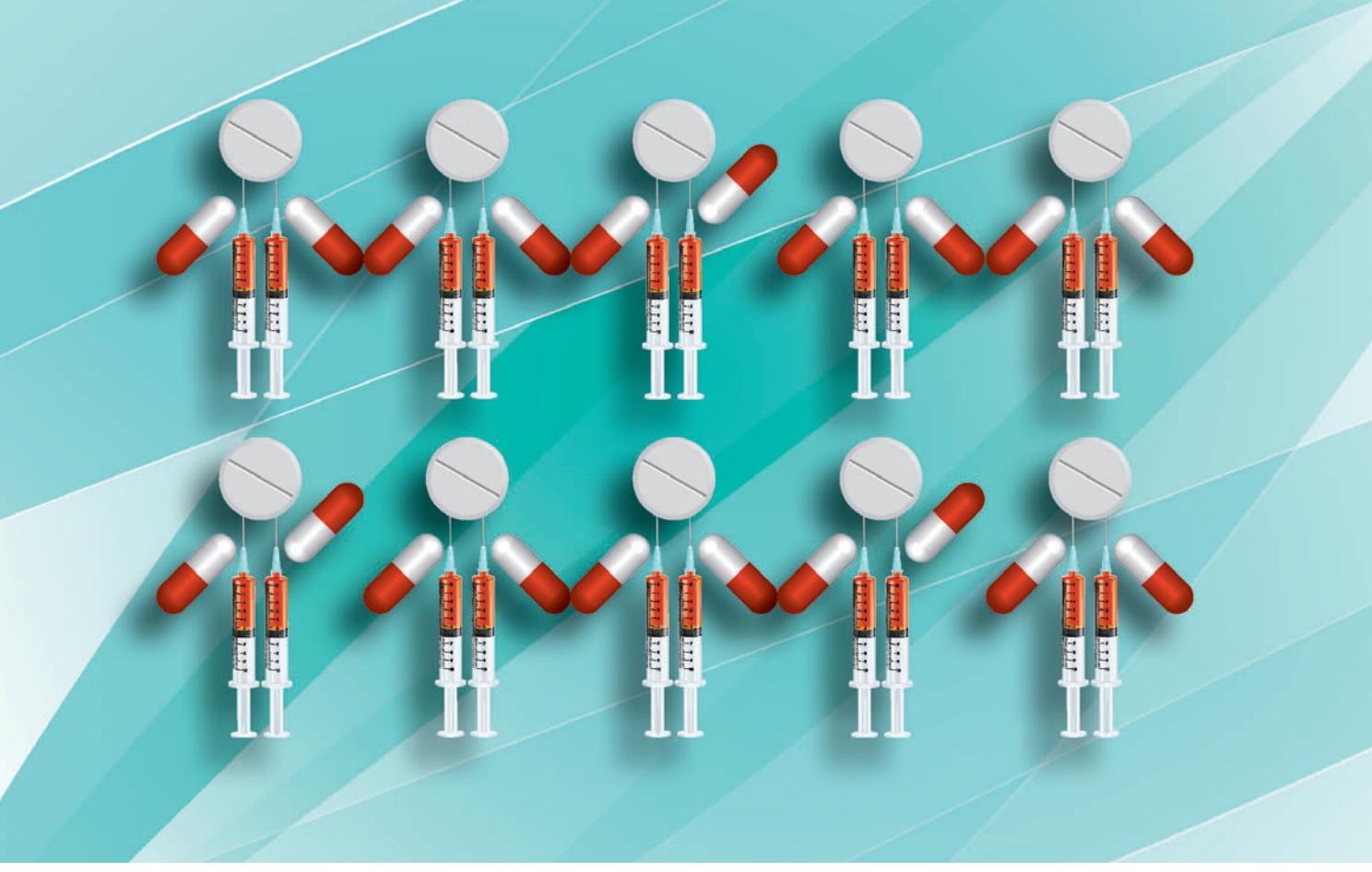
Industry commitment

Supply-chain security is a top challenge for both BPSA and BPOG moving forward into 2015. The Parenteral Drug Association (PDA) is also working on concepts to facilitate multisourcing. While these initiatives are important, Philips would prefer to see vendors, users, and regulators working together to bring one set of standards forward, rather than multiple associations working on multiple standards. "The biopharmaceutical industry is still a relatively immature industry, and substantial changes can be expected over the coming decade. Standardisation is going to be a key element of true multisourcing, and having one body regulating the industry will make supply chains more transparent and keep user expectations realistic," he says.

Many of the industry-wide initiatives already underway to provide standardisation and guidance on change notification, leachable/extractable testing, and other end-user needs for increased adoption of single-use systems, and particularly for components and systems that already allow some interchangeability such as buffer bags and tubing connectors, will help speed up multisourcing, according to Hudson. On the other hand, where the supplier's business model is to design a system that only works with its components, education is the key. "Genentech recently presented a proof-of-concept design for a single-use bioreactor that could work with top- and bottom-mounted bags from two different suppliers. The next step is convincing management at suppliers that designs such as this one will lead to higher future sales because they help open the doors to more GMP applications and greater adoption of single-use technology in general," he states. Genentech is also partnering with several single-use supplier companies to gain greater visibility into their supply chains, to provide recommendations on what it considers "multisourced", and to communicate what applications of single-use simply will not occur until they can be multisourced.

EMD Millipore, meanwhile, in addition to implementing a business continuity plan and supply risk management and emergency management programmes focusing on products, suppliers, and its sites, respectively, has teamed with a third party (Resilinc Corporation) to map its supply chain for key products and suppliers to identify and mitigate risks with suppliers, according to Rodriguez.

In its quest to identify a practical approach for determining the functional equivalency of unassembled components, ASI-Life Sciences submitted platinum-cured silicone tubing with similar specifications, mechanical properties, and performance profiles under typical use conditions obtained from two suppliers to Chemic Laboratories for comparative analysis of their extractable/leachable profiles. "Tubing was selected for this exercise because it is a common component of single-use systems and can be evaluated in a fairly straightforward manner," Briggs observes. Importantly, no significant differences in the extraction profiles were observed for the two tubing samples. "These results indicated that the materials were comparable within the variability of the analytical techniques used," Briggs says. He also recognises that tubing is a universal single-use component, and establishing the functional equivalency of other, more proprietary single-use systems and components will be more challenging. "Our goal is to initiate a dialogue around the practical considerations for achieving dual sourcing of single-use systems." **PTE**



The Ups and Downs of the Bio/Pharma Job Market

Bio/pharma employees in Europe report greater job security and satisfaction but limited salary gains.

Randi Hernandez

While bio/pharma employees feel more secure in their jobs than in previous years, stagnated salary increases and growing confidence in finding new job opportunities with other employers could result in more people seeking new roles with other companies in the next year.

Responses to *Pharmaceutical Technology Europe*'s 2014 Employment Survey (1) indicated that only 41.3% of European-based bio/pharma professionals surveyed reported salary increases in 2014 versus 2013, a slight increase from the 39.3% who reported increases in 2013. In comparison, 61.4% of all respondents in the global survey sample reported salary increases in 2014 versus 2013 (2).

A breakdown of respondents

The respondents to this year's survey represent a range of roles, including research, development, and formulation; analytical studies; quality control and assurance; process development; manufacturing, and regulatory affairs. The respondents work for bio/pharmaceutical manufacturers, academic institutions, contract service providers, or other companies supporting the industry. Almost 43% of the respondents work for companies that produce both small- and large-molecule drugs; 16.7% work for companies that develop or produce small molecule drugs only; and 25% develop or manufacture biologics drugs, cell therapies, or regenerative medicines.

More than two-thirds of the respondents have more than 11 years of professional experience in the industry, and respondents overwhelmingly rated new hires as "adequately trained, but not exceptional."

In Europe, 20% of the respondents worked at small companies with 1–50 employees. In contrast, respondents from the United States worked primarily for larger corporations.

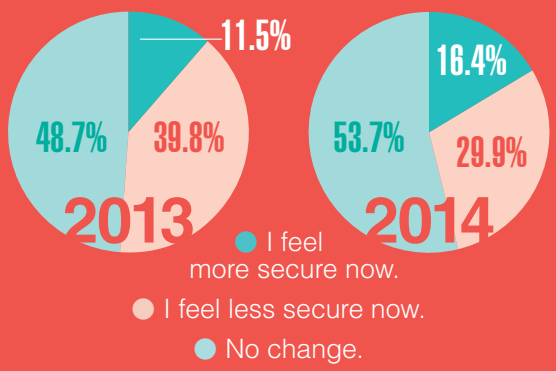
Cont. on page 32

In your view, what is the general outlook for the bio/pharmaceutical industry in the short and long term?

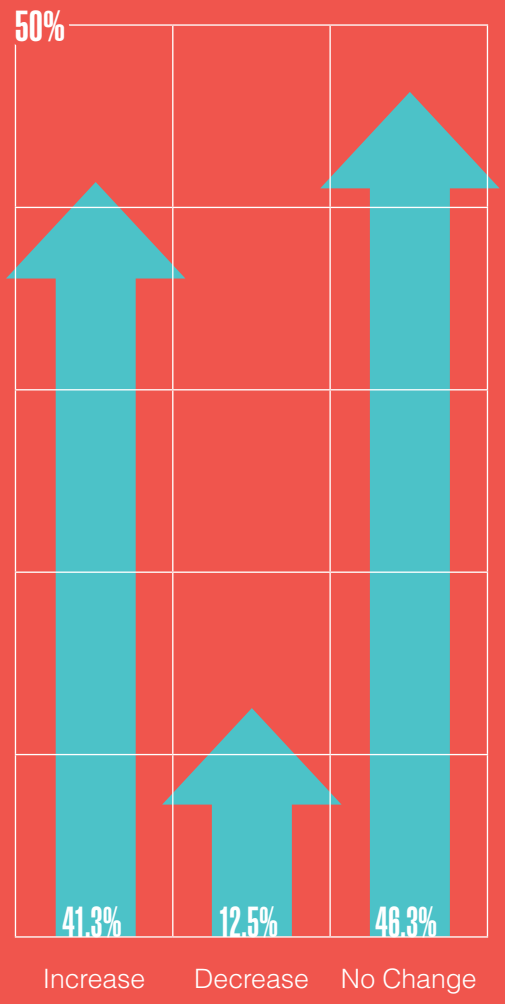
	2013	2014
Business will improve.	37.2%	55.2%
Business will decline.	14%	7.5%
Business will improve overseas, but not domestically.	37.2%	22.4%
Business will decline domestically, but not overseas.	7%	3%
No significant change expected.	4.7%	11.9%

Please rate your satisfaction with your current salary.

How secure do you feel in your job compared with last year?



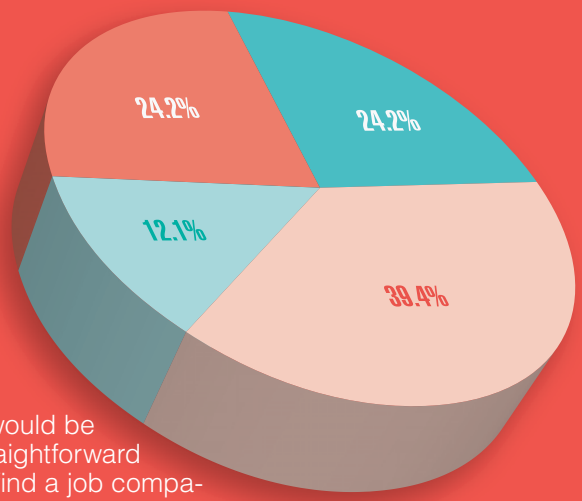
Does your current salary reflect a change over last year's salary?



Please indicate the extent to which you agree with the following statement:

	Agree strongly	Agree somewhat	Disagree somewhat	Strongly disagree
MY GENDER IS NOT A FACTOR IN DETERMINING OR LIMITING MY PROFESSIONAL ADVANCEMENT AT MY CURRENT COMPANY.	67.6%	19.7%	9.9%	2.8%

If it was necessary for you to change jobs this year, how would you assess the job market?



- It would be straightforward to find a job comparable to the one I have now.
- It would take a while, but I would be able to find a job comparable to the one I have now.
- It would be straightforward to find a job, but it probably wouldn't be as good as the one I have now.
- I would have to search hard, and be prepared to take what I could get.

In the past two years, has your organisation been through merger, acquisition, or restructuring?

	YES	NO
2013	52.7%	47.3%
2014	45.1%	54.9%

Due to rounding, some percentages may not add up to 100%.
Some questions allowed multiple answers.

Results based on 2014 *Pharmaceutical Technology Europe* employment survey.

Cont. from page 29

Among all business sizes, respondents rated knowledge of ICH guidelines (59.7%), good manufacturing practices (58.2%), analytical techniques (46.8%), chemistry (45.5%), and general principles of management (43.4%) as very important.

Workload: more of the same

Workloads remained relatively stable compared with 2013. In 2014, 26.2% of respondents reported that they worked more hours than two years ago. In 2013, the number was 28.1%.

The workload increase has also remained fairly level; 61.8% of the respondents said their workload has increased this year, compared with 65.5% who reported an increase in 2013. By comparison, 76.1% reported an increased workload in 2011. While 50.6% of the respondents said they are contracted to work a 40-hour work week, 20% said they work more than 40 to 50 hours per week.

Of those who reported an increase in workload, 88.1% attributed it to the expansion of business without corresponding staff increases.

Limited wage growth

More than half (55.2%) of participants say that business at their company will continue to expand and improve in the future, a number that is slightly less optimistic than last year's projection, in which 58.1% said business would improve.

Compared to last year, there was less corporate ownership disruption: approximately 45% of participants said their company had been through a merger, acquisition, or restructuring in the past two years, a lower percentage than what was reported in 2013 (approximately 53%).

In light of limited salary increases, satisfaction with wages appears to be suffering; many industry representatives captured in the survey (60%) say that they are either paid below market value or in the low end of their salary range, slightly less than what was reported in 2013, when 64.6% of respondents said the same. Salary matters, but not as much as professional advancement: advancement was cited as the top reason for quitting a job.

Many industry representatives captured in the survey (60%) say that they are either paid below market value or in the low end of their salary range.

The increased dissatisfaction with employment conditions may drive people to seek better opportunities. This year, 61.4% of participants agree or somewhat agree that they will not leave their jobs within the year. However, 43.5% expressed that they would like to leave their present job, if given the opportunity. Although industry personnel may be looking for employment elsewhere, a higher percentage of respondents this year say they feel more secure in their jobs than in 2013 (16.4% and 11.5%, respectively).

Last year, almost half (48.8%) of survey participants said they were confident they could find a job comparable to the one they currently hold; in 2014, 63.6% said they could find a similar job now if they were to look.

Gender considerations

When broken down by gender, 25.3% of survey respondents were female. This percentage represents a decrease from last year, where 31.6% of those surveyed were female. While 87.3% of all respondents agree that gender is not a factor in determining or limiting professional advancement, only 75% of females agree that gender does not play a significant role in limiting professional advancement. A lower percentage of females reported a salary increase this year when compared with the entire population (38.1% compared with 41.3%, respectively). Two-thirds of women felt they were paid in the low range or below market value, a higher percentage than the number reported for the entire study population (57%). This salary discrepancy may be explained by a lower percentage of women in managerial roles: only 47.6% of all female respondents managed other people, compared with 52.4% of all male respondents.

Contract manufacturing concerns

In candid comments, survey participants commented negatively about the impact that downsizing internal operations and the use of contract manufacturing organisations have on employment conditions at bio/pharmaceutical companies.

References

1. 2014 *Pharmaceutical Technology/ BioPharm International* Employment Survey.
2. 2013 *Pharmaceutical Technology/ BioPharm International* Employment Survey. **PTE**

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Maintaining an Efficient and Safe Cell-Therapy Supply Chain during Scale-Up and Scale-Out

For cellular therapies to become a viable treatment for large-sized patient groups, steps need to be taken to develop an efficient manufacturing and supply system to minimise the cost of goods.

Matthew Lakelin
is chief scientific officer at TrakCel.

At the time of writing this article, more than 40 cell-therapy products are commercially available and more than 500 are undergoing clinical evaluation (1). Unlike traditional pharmaceutical products that have linear supply chains, autologous therapies have circular supply chains where the first step is to obtain cellular starting material from the patient (2). Should an error occur in an autologous therapy supply chain, resulting in a patient receiving a therapy manufactured from another individual's cellular starting material, there is a significant risk of graft versus host disease (GvHD) and other unwanted responses (3). Supply-chain complexity is exacerbated when considering the time and temperature-sensitive nature of these products. Furthermore, some autologous cell therapies require invasive procedures to obtain cellular starting material (4). Supply chain errors could, therefore, result in patients having to repeat these uncomfortable procedures.

The manufacture of allogeneic products does not require harvesting of tissue or cells for processing from the therapy's recipient; however, regulations state that it must be possible to trace the therapy to the original donor of the cellular starting material (5). Allogeneic therapies present their own challenges for scale up. Take a dimethyl sulfoxide (DMSO) cryopreserved product as an example, scaling up to larger batches will increase the time between addition of DMSO to the cells and completion of fill finish and subsequent chilling to sub-zero storage temperatures. Although a tried and trusted cyropreservative, the deleterious effects of DMSO when exposed to cells at room temperature (6) are documented, and prolonged exposure due to scale-up led process modifications may affect cell viability.

Scale-up and scale-out

Typically, manufacturing of cell-therapy products is labour-intensive and requires continuous communication between treatment centres and manufacturers to coordinate manufacturing and treatment. Products tend to be separated so that only one patient's therapy is contained within a cleanroom to prevent cross contamination. To efficiently scale up and scale out cell-therapy products, clear strategies need to be developed for scheduling management, logistics management, product stability and closed systems manufacturing. To commercialise Provenge (sipuleucel-T), an autologous treatment for prostate cancer, Dendreon had to develop an IT system (Intellivenge) to assist with coordinating treatments and logistics management (7). Once a prescription of Provenge is issued, Intellivenge examines manufacturing assets to identify the next available manufacturing slot and schedules a manufacturing exercise for the patient's therapy. It then schedules collection of cellular starting material at an apheresis centre close the patient's home as well as arranging the transportation of cellular starting material to and the final therapy from Dendreon's manufacturing facility.

Not all cell-therapy developers will have the luxury of stabilising cellular starting material and the final therapy by cryogenic preservation; however, any opportunity to increase a product's or an intermediate's shelf life should be examined during the early stages of development to improve the product's chance of obtaining a marketing authorisation and also to reduce the unit cost of manufacture. There are clear guidelines available on the requirements and testing required for a cell therapy to gain approval (8).

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A therapy with a limited shelf life will either require localised manufacturing assets or the movement of patients over long distances to colocated treatment and manufacturing centres. There are some therapies currently undergoing clinical assessment when stability data allow transatlantic transportation of cellular starting material from EU treatment centres. In these cases, the study sponsors avoided the need to build EU manufacturing assets or outsource manufacture to European CMOs, driving down the cost of generating clinical data in the EU. Although this strategy may not be wise for commercialisation, it demonstrates that increased stability data can permit a more flexible manufacturing strategy. Furthermore, a patient missing a treatment appointment may not require the manufacture of a new batch if a new treatment date can be scheduled within the product's shelf life. A simplified view is that the longer an autologous therapy's shelf life, the fewer manufacturing assets will be required for meeting post-approval market demand.

For cryopreserved products, there is a conundrum for the manufacturer—ship a cryopreserved product to treatment centres, or thaw the product and then dispatch. Some treatment centres may be reluctant to thaw samples prior to treatment and in some cases may not have the capability. However, thawing at the site of manufacture may require supplementary analytical steps in addition to the original lot release but will negate the need for shipping in dry nitrogen shippers. Both strategies have advantages and pitfalls and full final user engagement is required when developing a strategy. Pluristem Therapeutics developed a thawing device (9) to enable uniform thawing of its PLX cell product at the point of care. Fibrocell Technologies, on the other hand, preferred to thaw, wash, formulate and then ship Azficel-T (10) at 2–8 °C to prescribing physicians because of concerns that the treatment centres may not be willing to undertake these steps.

Scheduling management is a key consideration for maintaining an efficient supply chain during scale up. Depending on the manufacturing process, after standardisation, some flexibility in the proposed duration of manufacture may be required to allow for patient-specific cellular dynamics. An active scheduling system should be considered so that at the point of treatment approval, the treatment centres and manufacturing asset's resources can be assessed so that cellular starting material will not arrive for processing when manufacturing slots or resources are unavailable. The scheduling system must also be able to respond to unforeseen changes or delays, and then automatically notify all the parties involved. It is worth considering linking inventory control with scheduling management to ensure that stocks of raw materials are available to meet demand.

Logistics management

A robust transport procedure needs to be in place to enable cell therapies to be delivered efficiently to treatment centres for clinical programmes and post-approval. The World Health Organisation outlines that every activity in the distribution of pharmaceutical products should be carried out according to the principles of GMP, good storage practice (GSP) and good distribution practice (GDP) as applicable (11).

Anecdotal evidence suggests that one company was prepared to charter aeroplanes to guarantee patients' treatment, although a redoubtable sentiment, such shipping strategies will erode product profitability. Risk-based management needs to be applied when evaluating shipping strategies. Tools such as failure modes effects analysis should be employed to identify weak points in logistical systems and mitigation plans should be developed, which may need revising as product demand increases.

The most efficient method for moving temperature-sensitive products is to use validated shipping systems; robust validation negates the need to monitor all shipments. However, it is questionable if this approach will work for all aspects of the supply chain. Complications arising from a temperature excursion of a cellular starting material shipment to a manufacturing facility may be identified by the facility's own quality-control analysis but treatment centres may not have the facilities to analyse incoming shipments and this should be considered when assessing logistics options.

For the movement of susceptible products, using temperature monitors in shipments is the most effective way to monitor the product in transit and to record the product's temperature during shipment. However, even with robust mitigation strategies, temperature excursions do occur. Using conventional temperature monitors the recipient will only discover a temperature excursion once the shipment has been received. Temperature monitors are available that can supply real-time data and issue warnings should shipping temperatures exceed pre-set parameters. To effectively use real time data, strategies need to be formed for addressing temperature warnings during shipments. To effectively use real-time data the following needs to be considered:

- If access to the shipment is possible, how will the current custodian be notified should a temperature warning be issued?
- What can be done, or what equipment is required to return the shipment to the desired temperature at each step of the journey?
- What resources are required to continuously monitor the shipment?

Employing such strategies is difficult and resource intensive but may be the only way to protect patients from having to be subjected to additional invasive procedures following temperature excursions.

Release testing and manufacturing batch records

As scale up and scale out progresses, release testing and batch recording will need to be assessed and new strategies developed. Some autologous treatments that are currently undergoing clinical assessment have the potential to treat thousands of patients per annum in North America alone (12). Technically, each treatment will be a separate batch requiring its own record of manufacture (5), and paper-based batch records will not be suitable for such a high number of recorded treatments. Considering that

harvesting cellular starting material and movement of cells between treatment centres and manufacturing sites will have to be recorded to produce a full custody record as part of the batch document, it seems unlikely that using paper-based document control will be an option.

Integrating automated data capture at treatment centres, logistics providers and manufacturers in a regulatory compliant manner will not be simple. Such a system, however, will drive down the unit cost of a cell therapy significantly, reducing the resources expended to document the manufacture of each batch. Batch release can be a resource hungry beast for autologous therapies and as patient populations increase reviewing each set of batch records will strain even the most efficient of quality departments. Consideration should be given towards batch approval, which follows a release-by-exception strategy. Using automated data capture during manufacture, attention should only be directed to events that are observed outside specified limits for the process (13). All batches manufactured that meet these specified limits required limited quality-assurance review. Validating release by exception is a complex and challenging process but has a long-term payoff when batch volumes increase to justify the expense and the complexity.

References

1. Alliance for Regenerative Medicine, "Regenerative Medicine Annual Report," http://alliancerm.org/sites/default/files/ARM_Annual_Report_2013_Website.pdf, accessed 15 Oct. 2014.
2. T. Monesmith, *BioProcess Int.,* 9 (S1) 38–41 (2011).
3. J.L. Ferrara et al., *Lancet,* 9674 (373) 1550–1561 (2009).
4. L. Mazzini et al., *Amyotroph Lateral Scler. Other Motor Neuron Disord.,* 4 (3) 158–161 (2003).
5. EC Directive 2006/17/EC, European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, Official Journal L 38 of 9 Feb. 2006.
6. Z.W. Yu and P.J. Quinn, *Biosci. Rep.,* 14 (6) 259–281 (1994).
7. D. Miller, "Dendreon's Biggest Provenge Problem? Managing Demand," www.minyanville.com/businessmarkets/articles/DNDN-Provenge-Prostate-Cancer-dendreon-jpmorgan/2/12/2010/id/26833?page=full, accessed 15 Oct. 2014.
8. ICH, Q5C, *Stability Testing of Biotechnological/Biological Products,* Step 4 version (1995).
9. Pluristem, "Pluristem Develops Point-of-Care Thawing Device for PLX Cells," Press Release, 4 Oct. 2012.
10. Fibrocellscience, www.fibrocellscience.com/wp-content/uploads/2014/03/Fibrocell-Science-Form-10-K-December-31-2013.pdf, accessed 15 Oct. 2014.
11. WHO good distribution practices for pharmaceutical products, WHO Technical Report Series, No. 957, 2010.
12. N.K. Gupta et al., *Curr. Cardiol. Rep.,* 16 (2) 447 (2014).
13. T.M. Monesmith, *BioProcess Int.,* 9 (3) 40–44 (2011). **PTE**

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A Next Generation of Quality Management

The author proposes a quality management system that uses the power of executive management to promote a positive quality culture.

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When a bio/pharmaceutical and life-sciences (PLS) company encounters a quality issue, United States Food and Drug Administration warning letters and consent decrees are usually addressed directly to the chief executive officer (CEO), explicitly placing the responsibility for quality with the head of the organisation. The typical PLS CEO, however, has neither the background nor the tools available to sufficiently address quality—especially at the level of regulatory oversight. Responsibility in the absence of tools or background is a precarious position that the PLS industry needs to meet head on.

At its core, this situation stems from the historical fact that the life-sciences industry often perceives quality management systems (QMS) as compliance-driven rather than as an effective process to realise continuous improvement in product and process quality. This was the case dating back to 1987, when the International Organisation for Standardisation (ISO) developed the original QMS framework—ISO 9000. While the PLS industry never fully embraced ISO 9000, over time different regulatory agencies in the PLS space created various QMS frameworks to fit their own purposes.

In this environment, current QMS standards have not kept pace with a growing variety of products and technological complexity. In many instances, the high cost of change and the associated regulatory approvals deter companies from implementing quality improvements. Further complicating matters, companies typically have separate quality management systems across the GxP lifecycle spectrum and, because of acquisitions, across divisions as well. As a result, current QMS frameworks are complex and not scalable.

Companies that have been hit by regulatory action are often keenly aware of the technical issues at hand, and, in many cases, they have tried to implement solutions. Those solutions, however, often fall victim to organisational resistance, lack of resources or funding, or management's insufficient understanding of the importance of establishing a "quality first" culture. At the end of the day, the C-suite must own quality issues and take appropriate action when problems arise.

A new QMS framework is needed to inject heightened effectiveness and efficiency into the industry quality processes. To meet this challenge, PricewaterhouseCoopers (PwC) proposes QMS 3.0, a holistic solution that provides the tools CEOs need to take control of quality matters and significantly reduce the corporate risk associated with noncompliance.

Leading from the top

Forward-looking members of the C-suite know that QMS is ultimately a culture rather than a regulation. QMS 3.0 recognises the power of executive management to promote a positive quality culture. It elevates technical regulations from the realm of scientists, clinicians, regulators, engineers, and production operators to the C-suite and board level. Because it is driven by executive management, QMS 3.0 promotes accountability throughout the entire company. Ultimately, it is about driving culture change to achieve quality excellence. Linking compliance with product quality, operational performance, business results, and patient safety is the first step toward achieving a strong corporate quality culture.

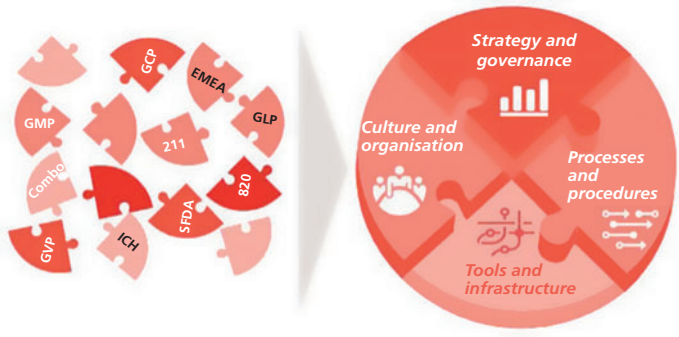
At its core, QMS 3.0 aims to simplify the quality management process by promoting executive responsibility and leadership and ensuring a mutual understanding of quality measures and goals across the industry. From this perspective, QMS 3.0 is similar to the financial budgeting process, which allows executive management to "own" the financials without getting into the specifics. This new approach to PLS quality control encourages executive management to align its business interests and quality objectives. Doing so helps companies reap the most from their quality-control investments by reducing compliance risks and avoiding potentially costly fines and remediation efforts—all to the benefit of patients and stakeholders alike.

A next-generation, industry-wide QMS framework holds the potential to help standardise quality in an industry that has become too complex for the patchwork systems that currently attempt to govern it. This new framework (see **Figure 1**) should, at a minimum, accomplish four objectives:

- Emphasise the alignment between compliance, product quality, business performance, and, ultimately, patient safety
- Focus on end-to-end process improvements rather than just having procedures in place
- Become a tool for executive management to drive quality
- Create a single, integrated QMS framework across GxP that becomes the standard for all industry segments and regulatory agencies.

To realise such a goal, regulators and the industry need to work together. But companies' executive management must lead by example and promote quality as part of the

Figure 1: QMS 3.0 framework.



corporate culture that governs individual organisations.

The benefits of QMS 3.0 include the following:

- It creates a culture of driving improved patient outcomes as well as business benefits by aligning quality, compliance, and operational improvements.
- It emphasises controlling end-to-end processes and measuring a balanced set of metrics, rather than focusing on individual standard operating procedures (SOPs).
- It provides the tools for executive management and the business to "own" quality and drive continuous improvement, just as budgets are a tool to manage financial performance.
- It is a next-generation framework that integrates various quality management systems across GxP and industry segments to create a single, simplified quality structure without replacing current regulations.

The four elements of QMS 3.0

The QMS 3.0 framework that PwC proposes has four elements: strategy and governance, culture and organisation, processes and procedures, and tools and infrastructure (see **Figure 2**). As companies grow in maturity in their approach to QMS, these elements build upon one another. The strategy and governance and culture and organisation elements are cultural in nature, while the processes and procedures and tools and infrastructure elements are more technical. While the four elements are not unique by themselves, QMS 3.0 emphasises the integrated nature of the elements required to ensure a patient-centric approach.

Strategy and governance. The approach that QMS 3.0 takes toward strategy and governance represents the biggest difference between QMS 3.0 and the earlier generations of quality management. Strategy and governance is the most important link between executive management and a company's quality organisation. While clinicians, scientists, and operators affect quality on a day-to-day basis, QMS 3.0 elevates quality and translates it into a language that management can understand and apply. When a company is struggling with quality management, this element is typically the weakest one.

Culture and organisation. One of the main factors resulting in poor quality control is an overemphasis on business performance without the counter-balance of stressing quality. Management may communicate and reward the achievement of quarterly financial numbers and yet be silent on quality matters, for example. Employees may interpret that silence as a justification to cut corners on quality issues. Instead, management must regularly demonstrate its willingness to make difficult decisions to ensure a positive quality culture (and, ultimately, patient safety) by prioritising quality over financial performance.

Processes and procedures. Traditionally, companies have focused on SOPs to anchor their quality initiatives. QMS 3.0 focuses instead on end-to-end processes (see **Figure 3**). Only end-to-end processes can be analysed for critical control points to drive measurable improvements in both quality and operational performance. A focus on end-to-end processes also allows companies to establish business process owners who can drive continuous improvement across a company's various functions and divisions. With solid processes in place, companies can reduce and simplify their number of SOPs while also improving quality. Well-vetted processes can align business interests with quality objectives.

From the process and procedure perspective, QMS 3.0 articulates three subsystems to integrate the various quality system frameworks in existence (see **Figure 3**). Rather than having six or seven subsystems at various levels of detail, the QMS 3.0 framework has three subsystems of equal magnitude: management controls, lifecycle controls, and operations controls. These subsystems do not introduce any new regulations; rather, they logically restructure regulations that already exist. Not incidentally, this framework is easier to communicate to (and is better understood by) executive management.

Tools and infrastructure. It is in this foundational element that all of an organisation's actual work is conducted. Whether it is a scientist in a lab, an engineer using computer-aided design (CAD) systems, a physician evaluating a patient, or an operator turning valves on a bioreactor, everyone needs tools and infrastructure. The facilities, equipment, and IT systems that make up a company's tools and infrastructure work together to design, manufacture, test, document, and evaluate the output of their work processes. In the process, employees collect, approve, store, and manage objective evidence.

QMS 3.0— analogous to financial planning

Although QMS 3.0 does not introduce any new regulatory requirements, it does introduce the necessary processes that enable a company's executive management to own its quality systems. In this way, it is analogous to a company's financial planning and budgeting process. The planning and budgeting performed by a company's financial department enable executive management to plan for the future, establish financial targets, manage revenue, and control spending without having to monitor every financial transaction.

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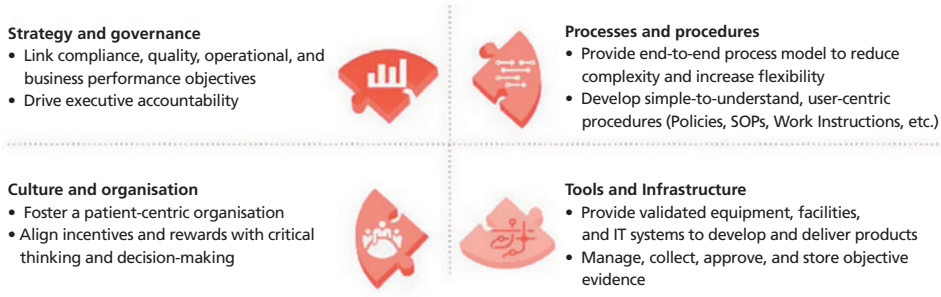
Figure 2: QMS elements–descriptions.



Financial regulations and accounting rules can vary significantly from country to country and industry to industry, but financial planning and budgeting can easily adapt to those differences. Similarly, QMS 3.0 allows management to oversee quality without getting mired in variations among regulations for different technologies and countries. While the finance department "owns" the budgetary process, management owns the budget itself, making it ultimately responsible for a company's financial performance. Similarly, while a company's quality unit facilitates the quality control process, executive management assumes ultimate responsibility for quality itself. Yet not many managers understand what that means to them.

Figure 3: QMS 3.0 framework.

Operations Controls
- Qualify Facilities, Equipment and Computers
- Train and Qualify Staff
- Qualify Suppliers and Release Materials
- Produce and Release Manufacturing Lots
- Control Product Distribution and Logistics

Life Cycle Controls
- Manage (Pre-)Clinical Programmes
- Define Product, Specifications and Mfg. Processes
- Optimise Label Claims and Risk Profiles
- Manage regulatory submissions
- Manage Post-Market Surveillance

Management Controls
- Define quality strategy and objectives
- Manage Document and Change Control
- Investigate and Disposition NCRs, CAPAs, SCARs, etc.
- Manage Recalls, Field Actions, etc.
- Improve Ongoing Quality and Compliance

Management can use QMS 3.0 as a means to drive compliance and quality objectives without needing to be involved in the details of quality control. Just as a company typically has a three- to five-year financial plan and an annual budget, it should also have a three- to five-year quality plan with annual quality objectives. And just as a company's management reviews its budget plan on a quarterly basis, it should review its quality objectives just as frequently. Budget reviews drive managers to adjust their financial decisions regularly to increase revenue or cut costs. Similarly, quarterly quality reviews can drive management to implement and adjust continuous improvement efforts as necessary.

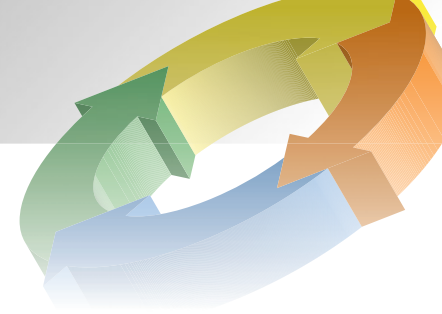
Benefits of QMS 3.0

The introduction of a new quality system can often spur a wave of batch rejects and recalls. Over time, however, the new controls are likely to cause the number of adverse events, recalls, batch rejects, and overdue medical device reportables to decrease. It can also require a significant investment as companies revalidate their products and processes and implement new organisational capabilities, cultural changes, procedures, and IT systems. Ultimately, these efforts likely pay for themselves in the form of reduced compliance risks, decreased quality costs, and improved efficiencies.

While risk reduction is a major benefit of QMS 3.0, once implementation efforts have had a chance to "mature," the new system can drive improved efficiency, higher-quality products and processes, and additional business benefits. The operational improvements catalysed by QMS 3.0, for example, can be measured in terms of improved product yields, reduced batch release cycle time, reduced last-patient-out to database lock cycle time, and reduced number of complaints and recalls. Businesses can quantify these operational improvements, which in some cases produce a competitive advantage and increased market share.

This next generation QMS 3.0 is a framework that incorporates the legacy of QMS while also moving ahead to meet the marketplace's new challenges. QMS 3.0 builds on the industry's major improvements in quality and compliance over the years to define the next generation of quality management. It provides a common management framework across all the components of GxP throughout an entire company. It allows for technical differences across regulations while also recognising that it is possible to standardise the management of quality. When it is fully implemented, management can use the QMS 3.0 framework to establish quality objectives, set targets, and monitor progress over time.

QMS 3.0 also has intangible benefits. Because it is driven by executive management, it promotes accountability at the C-suite level as well as throughout the entire business. It creates a common language within and among regulatory agencies, quality experts, and functional managers, simplifying communications among them and ensuring common objectives are understood and met. **PTE**



Effects of 100% Ethylene Oxide Test Gas on the Resistance of Ethylene Oxide Biological Indicators

Garrett Krushefski, Anthony M. Piotrkowski, Craig A. Wallace, and Kellie A. Matzinger

As of 31 Dec. 2014, the United States Environmental Protection Agency Clean Air Act will prohibit the sale and use of HCFC-based (hydrochlorofluorocarbon) products in the US, including Oxyfume ethylene oxide (EtO) sterilant blends such as Oxyfume 2000, which consists of 8.6% EtO and 91.4% HCFC-124. Biological indicators (BIs) manufacturers will, therefore, have to move to 100% EtO as the test gas for determining the resistance performance of EtO BIs by the end of 2014. In anticipation of this mandatory switch from Oxyfume 2000 to 100% EtO for BI testing, comparison studies were performed to determine if the switch from Oxyfume 2000 to 100% EtO would have any impact on BI resistance label claims.

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Biological indicators (BIs) are used during cycle development, validation, requalification, and routine monitoring of sterilisation processes. Published standards provide appropriate resistance performance characteristics (e.g., D-value) and thus govern the efforts of the manufacturers of biological indicators (1–3). Similarly, BI user guidance documents also reference appropriate selection and use of BIs, and the information provided in such documents will often guide end-user purchase specifications (4). In turn, information about appropriate resistance capabilities of the BIs are sometimes written into regulatory submissions when medical device or pharmaceutical manufacturers seek regulatory clearance for their products.

As of 31 Dec. 2014, the United States Environmental Protection Agency Clean Air Act will prohibit the sale and use of HCFC-based (hydrochlorofluorocarbon) products in the US, and that will include Oxyfume ethylene oxide (EtO) sterilant blends such as Oxyfume 2000, which consists of 8.6% EtO and 91.4% HCFC-124. (Oxyfume is a registered trademark owned by Honeywell International.) This requirement means that all BI manufacturers will have to move to 100% EtO as the test gas for determining the resistance performance of EtO BIs by the end of 2014. Currently, Oxyfume 2000 is often used by BI manufacturers for assessing BI EtO D-value label claims, so it is in the best interest of the BI community (manufacturers and end users) to assess the potential effects of this change.

There have been previous changes to the EtO gas used for BI testing. A previous version of an HCFC mixture, Oxyfume 2002, which consists of 10% EtO, 63% HCFC-124, and 27% HCFC-22, was eliminated by the Clean Air Act in December of 2009. At the time, many BI manufacturers were using Oxyfume 2002 as the source gas in their resistometers when performing BI EtO D-value resistance assessments. As the elimination of Oxyfume 2002 approached, comparative studies were performed to determine if the switch from Oxyfume 2002 to Oxyfume 2000 would have any impact on measured resistance performance. The results of these studies indicated that the change in gas had no significant effect on the measured resistance of the BIs. As an example, MesaLabs EZTest lot G-162 displayed a D-value of 3.60 minutes when tested in Oxyfume 2002 or 3.58 minutes when tested in Oxyfume 2000. STERIS indicators showed similar results. STERIS VERIFY tested

Table I: Results from biological indicators manufactured by STERIS Corp, 3M, and Mesa Laboratories, tested for D-value at each facility. SCBI is self-contained biological indicator.

Product tested	Manufacturer label claims		Re-tested by facility:	D-value results (minutes)		Percent difference
	Population	D-value (minutes)		Oxyfume 2000	100% EtO	
Company A strip	1.2×10^6	3.2	A	3.2	2.5	-21.9%
			B	3.6	2.9	-19.4%
			C	2.7	2.7	0.0%
Company A disc	2.3×10^6	3.2	A	3.2	3.1	-3.1%
			B	3.3	2.9	-12.1%
			C	2.7	2.7	0.0%
Company B SCBI	2.7×10^6	3.7	A	3.6	2.6	-27.8%
			B	3.7	2.4	-35.1%
			C	3.2	2.2	-31.3%
Company B strip	2.2×10^6	4.1	A	3.6	2.9	-19.4%
			B	4.1	3.3	-19.5%
			C	2.9	2.2	-24.1%
Company C SCBI	2.7×10^6	3.6	A	3.7	3.2	-13.5%
			B	4.3	2.6	-39.5%
			C	3.5	2.6	-25.7%

Table II: Requirements for BI D-value when tested in EtO.

Reference	When tested at 600mg/L, 54 °C, 60% relative humidity
USP, Table I in Chapter <1035>	"Range of D-values for Selecting a Suitable Biological Indicator" Minimum 2.5 min, maximum 5.8 min.
ANSI/AAMI/ISO 11138-2:2006/(R)2010, paragraph 9.5	"…shall have a D value of not less than 2.5 min at 54 °C…"
EP 7.0, Section 5.1.2	"The D-value is not less than 2.5 min…"

USP = *United States Pharmacopeia*
ANSI = American National Standards Institute
AAMI = Association for the Advancement of Medical Instrumentation
ISO = International Organisation for Standardisation
EP = *European Pharmacopoeia*

at 4.0 and 3.9 minutes, Spordex strips at 4.2 and 4.7 minutes, and Spordex discs at 3.4 and 3.5 minutes, when exposed in Oxyfume 2002 and Oxyfume 2000, respectively.

Comparability studies

In anticipation of this mandatory switch from Oxyfume 2000 to 100% EtO for BI testing, additional comparison studies were performed to determine if the switch from Oxyfume 2000 to 100% EtO would have any impact on BI resistance label claims. The test results for this change were markedly different than the change between mixed gasses. Despite programming both resistometers for identical exposure parameters (600 mg/L EtO, 54 °C, 60% relative humidity [RH]), Mesa BIs (both paper strip and self-contained versions) were showing a 26% to 39% reduction in measured D-value when tested in a resistometer using 100% EtO as the source gas. Having obtained these results, Mesa obtained strip and self-contained BIs (SCBIs) from other manufacturers, and when tested in Mesa resistometers, the same trend was observed. Specifically, the D-values when tested with 100% EtO were 29% to 51% lower than the results from the Oxyfume tests. (These data were the subject of a whitepaper [5] previously posted on the MesaLabs website).

Results and discussion

Based on these results and other preliminary tests performed by other BI manufacturers, this issue was brought up for discussion at the Association for Advancement of Medical Instrumentation, AAMI ST/WG 4, Biological indicators working group meeting in Alexandria, Virginia on 15 Oct. 2012. The result of that discussion was the decision to launch a collaborative effort amongst the three BI manufacturers that possessed the ability to perform both Oxyfume 2000 and 100% EtO exposures. Each manufacturer (STERIS Corporation, 3M, and Mesa Laboratories) agreed to exchange BIs to be tested by the other parties and share results. Exchanged BIs included spore disc, spore strip, and self-contained BI configurations.

The results in **Table I** are presented in a manner that protects the identity of the manufacturer. Of the 15 results, 13 showed a decrease in resistance when tested using 100% EtO as the source gas and two instances showed no change in measured resistance. There were no observations of a higher measured resistance for BIs tested in 100% EtO. Specifically, the D-values in this round of testing are 0% to 39.5% lower when tested in 100% EtO as compared to the Oxyfume results, with an average reduction in measured D-value of 19.5%.

It is unknown what causes the lowered resistance measurement when 100% EtO is used as the resistometer source gas. The authors speculate that when using an Oxyfume blend gas, the HCFC competes with the EtO molecules for access to critical binding sites on the spores. Such competition would not exist when 100% EtO is the source gas for the resistometer cycles. With HCFC present in the exposure chamber and blocking EtO molecule access to the critical binding sites, the result is fewer alkylation reactions and thus a decreased lethal insult to the spore, despite both chambers providing 600 mg/L EtO, 54 °C, 60% RH conditions.

Recommended standards

The differences in measured D-value are cause for concern when considering the resistance recommendations that appear in current published standards. **Table II** shows the recommendations that appear in *United States Pharmacopeia (USP)*, International Organisation for Standardisation (ISO), and *European Pharmacopoeia (EP)*. When use of Oxyfume 2000 becomes prohibited and BI manufacturers switch to 100% EtO, the labeled D-value claims will likely show a pronounced downward shift consistent with the test results reported here, compared to historical values. The authors stress the fact that the BIs are not changing; the spores have not become less resistant to the sterilisation process. Rather, the "measuring stick" has changed with the changeover from Oxyfume 2000 to 100% EtO as the source gas used in resistometers. Because the measuring stick is changing, published standards will need to follow suit and adjust the verbiage in the relevant documents.

The data from this study indicate a decrease in measured value of up to 39.5% solely due to the use of 100% EtO as the supply gas. As such, the authors would recommend a change in published ranges to match. Whereas 2.5 minutes to 5.8 minutes were a suitable range of D-value for BIs tested in an HCFC blend gas, ISO and *EP* should consider lowering the "not less than 2.5-minutes" specification to "not less than 1.5-minutes" to accommodate the observed percent differences in the test data. *USP* provides a lower and upper range of resistance that is typical for EtO BIs. As such, the current *USP* citation of 2.5 to 5.8 minutes should be adjusted to perhaps 1.5 to 5.8 minutes (i.e., 2.5 – 40% = 1.5) for BIs that are tested using 100% EtO as the resistometer source gas.

Given that making changes to published standards can takes months, or even years to complete, the industry will likely experience a gap in time where available BIs (tested in 100% EtO) may not have a resistance label claim that meets the minimum values that currently appear in *USP, EP,* and American National Standards Institute (ANSI)/Association for the Advancement of Medical Instrumentation (AAMI)/ISO documents. Furthermore, end user purchase specifications and/or the information in the end user's regulatory submissions may also conflict with what is available from BI manufacturers, as the end user's stated values were based upon BIs that were resistance tested with an EtO/HCFC blend gas, rather than 100% EtO.

References

1. ANSI/AAMI/ISO 11138-1:2006/(R) 2010 (AAMI, Arlington, VA, 2006).
2. *USP* General Chapter <1035>, "Biological Indicators for Sterilisation" (US Pharmacopeial Convention, Rockville, MD 2014).
3. *European Pharmacopoeia* General Chapter – 5.1.2, "Biological Indicators of Sterilisation" (Ph. Eur. Commission, Strasbourg, France, 2013).
4. ANSI/AAMI/ISO 14161:2009 (AAMI, Arlington, VA, 2006).
5. K. Matzinger, "Oxyfume Blends vs. 100% EtO," *Mesa Labs Spore News* 9 (1) Jan. 2012, http://biologicalindicators.mesalabs.com/wp-content/uploads/sites/31/2014/07/Spore-News-Vol-9-No1.pdf, accessed 10 Nov. 2014. **PTE**

Pinpointing the Source of Tablet Spots and Specks

Solving the problem of tablet spots or specks involves prevention and thorough investigation.

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Manufacturers of tablets have long battled a host of occasional but common issues that can be alternately irritating and serious. Tablet defects can be purely cosmetic or they can be related to problems such as incorrect dosages, resulting in a potentially dangerous situation for consumers (too much or too little active ingredient in the finished tablet), loss of revenue due to excessive rejects and waste, and/or issues with downstream equipment. A few of the more common issues well-known for causing headaches for experienced compression personnel include:

- Capping: a splitting of the tablet and its "cap," occurring at the top of the perimetre band
- Picking: product sticking to the punch tip within an embossed area
- Laminating: a lateral fracture within the tablet
- Sticking: product adhering to the face of the punch tip
- Spots or specks: undesirable visual flaws that can be superficial and/or embedded within a tablet.

This article addresses the problem of spots or specks. Commonly referred to by the over-generalising term "black spots," these unsightly blemishes or foreign substances should more appropriately be categorised as any spots or specks that are not supposed to appear in the first place, but that in most cases are easily (and visually) detectable. Spots are generally those imperfections that reside on the surface of the tablet only, while specks can be present throughout a tablet. Specks are sometimes visible on the surface, sometimes hidden inside, or both. It is important to note that undesirable spots or specks can be gray, black, or almost any other colour, even white.

Manufacturers battling a spot or speck issue can occasionally find themselves with a simple, easy-to-find solution. Conversely, they can also bang their heads against the proverbial wall in their effort to unmask a source. Unless it is by design that spots or specks are on or in a tablet, their presence clearly calls for swift remedial action. The aim of this article is not to try and provide an exhaustive list of all possible sources for the intruders, but rather to point out that said sources are not always obvious and, in some instances, will warrant an investigative effort Sherlock Holmes would envy. Regardless, a reputable manufacturer will attempt to rapidly pinpoint the source of the issue and eradicate it.

Case study

A reputable pharmaceutical manufacturer discovered spots in one of their products—a tablet—prompting an immediate and exhaustive investigation. At the outset, optimism reigned for quickly determining the root cause of the spots because they were, in fact, blue. Despite a methodical, intensive process of elimination, however, the manufacturer could not locate any material within the manufacturing line or raw material that matched the colour of the spots appearing in the finished tablets. The ultimate resolution of this atypical issue will be discussed after first examining some of the more common sources of spots and specks.

Possible causes of spots and specks

Although it often proves true that an oil-based issue on the tablet press is the culprit, the following are other potential sources:

- Over-lubricated upper punches
- Worn, faulty, or missing dust cups
- Sloppy, worn upper-punch bores
- Reactions between incompatible material combinations (e.g., certain active ingredients will turn darker when subjected to high heat or when mixed with particular tooling lubricants)
- A "slinging" effect at excessively high turret speeds, where an accumulated product–lubricant mix is thrown from the punch barrel
- Poor or inadequate cleaning procedures, especially between product changes
- Upstream origins (e.g., contaminated raw materials, blending issues, dislodging of grease and lubricants on mixers or granulators)

- Improper product-specific gaps between feeder base plates and the turret surface; too-tight gaps can cause some particle sizes to "roll" and ultimately change colour
- Poor punch quality and/or maintenance.

Potential solutions

The best possible solution for an issue with spots on tablets is to consistently employ methods for avoiding them in the first place. This may appear obvious, but in reality, tablet press operators often deviate from GMP methodology, especially in terms of following recommended guidelines for cleaning and set-up as provided by original equipment manufacturers (OEMs). If not already in possession of such procedures, every company should poll their suppliers for them and implement their contents into a cohesive and all-encompassing set of standard operating procedures (SOPs).

Having stated the above as a best line of first defense, strict adherence to good SOPs cannot supersede all potential issues. Some suggested guidelines for eliminating spots when they do appear, or for helping to prevent their occurrence at all, include:

- Optimising lubrication settings, including dose rate, interval, and duration, especially for upper punches; documents and suggestions from the OEM should help here
- Regular use and replacement of quality dust cups; they are easy to install and are disposable
- Regular use and replacement of upper punch seals (on presses that offer them as an option)
- Use of punch bellows, especially for particularly dirty products or those necessitating the use of maximum upper lubrication; bellows can actually prevent the mixing of lubricant and dust in the first place, greatly reducing the likelihood of eventual spots
- Strict adherence to SOPs for cleaning and set-up
- The use of equipment manufacturer-recommended vacuum settings
- Judicious inspection and replacement of "contact" parts, such as feeder base plate seals and "tail-over-die" scrapers
- Regular inspection of seals and/or gaskets located within mechanical feeders
- A systematic inspection of all product-contact areas within the entire manufacturing line where an oil or other lubricant may be used.

If, indeed, raw material issues are ruled out and a press manufacturer is asked to recommend a first place to look, most will generally suggest the bottom of the barrels on the upper punches, where the punches protrude from the upper punch ring. A quick visual inspection can detect any unusual build-up of material and excessive lubricant that may be contributing to a problem. If present, it should then prove easier to put a stop to the offense.

The presence of spots or specks calls for swift remedial action.

Depending on the severity of the issue and the company experiencing it, some will seek independent analysis from a third-party laboratory in an effort to determine the source and composition of the spots. It is, however, important to note that the success of such an investigation can vary considerably. Certainly there are times where the lab can shine the brightest light on a shadowy issue, while just as frequently, the offending contaminant is identified and confirmed locally, at the floor level.

Case of the blue spots resolved

Having turned over virtually every imaginable rock in their quest to locate the source of the blue spots referenced earlier in this article, the manufacturer had come up with no cause, only effect—no means, only ends. Not until the completion of a blending campaign that spanned multiple days did they, quite by accident, finally uncover causality. While cleaning the flange on a V-blender, a maintenance technician noticed blue material resembling that which plagued the final tablets. It was ultimately determined that airborne particles of the active material were sticking to a white anti-seizing compound used on the flange bolts, agglomerating there and ultimately falling through the flange and into the blend destined for compression. There it remained undetected, even throughout the compression cycle (it was still white at the time) until after approximately 48 hours, a chemical reaction would occur, turning the spots blue.

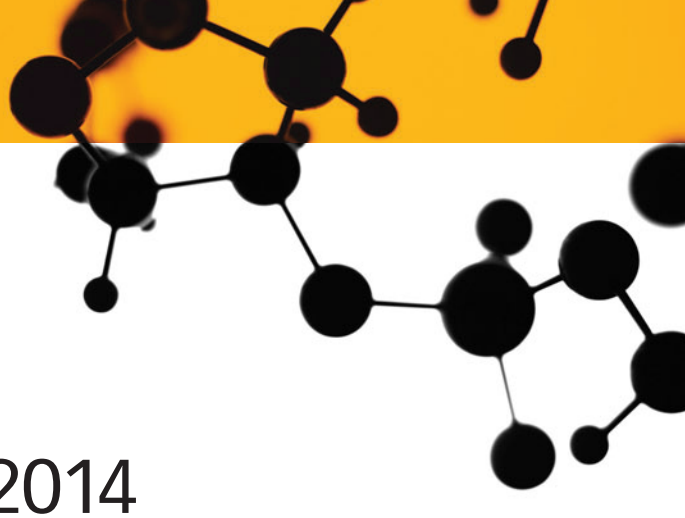
Keep an open mind

As is the case with so many undesirable equipment issues, regular and judicious training (and retraining) can have a positive effect on the prevention and elimination of spots. One item to mention of paramount importance is that tablet manufacturers must keep an open, inquiring mind when seeking to identify those factors contributing to such an issue. Although problems may often have their genesis with something local to the tablet press, this is most definitely not always the case, as shown with the case study example. If raw material contamination can be ruled out early on, then the investigator must bear in mind that the source of spots can originate at any location where product makes contact with another surface or substance, be it prior to, during, or following compression, even if said contact does not immediately result in the undesirable defect. Be prepared to grab an oar and row against the current, as the solution to your problem might just be upstream. PTE

Join the discussion

Have you experienced tablet spots or specks? What did you find as the root cause?

Post your comments on www.pharmtech.com/linkedin.



FDA Approves Novel Treatments in 2014

FDA approves treatments for new diseases and drugs that operate by new mechanisms.

With respect to the United States Food and Drug Administration approval of new medicines, 2014 has been another strong year for the pharmaceutical industry. The agency's Center for Drug Evaluation and Research (CDER) approved a total of 34 new medicines (as of the end of October 2014): 22 new molecular entities (NMEs) (see **Table I**) and 12 biologic license applications (BLAs) (see **Table II**) (1). In 2013, the total number of approvals for the entire year was 27, while in 2012 the number reached 39, which was unusually high compared to the numbers of approvals over the previous 10 years (2). Not only were a high number of new medicines approved in 2014, there were numerous examples of first-ever approvals for the treatment of certain diseases and new classes of drugs that treat diseases *via* new routes. Treatments were also approved under new designations.

First treatments

Hetlioz (tasimelteon, Vanda Pharmaceuticals), a melatonin receptor agonist, was the first treatment approved by FDA for non-24-hour sleep-wake disorder, a chronic circadian rhythm (body clock) disorder that causes problems with the timing of sleep that occurs almost exclusively in people who suffer complete blindness (3). Vimizim (elosulfase alfa) from BioMarin Pharmaceutical is the first FDA-approved treatment for mucopolysaccharidosis type IVA (Morquio A syndrome), a rare, autosomal recessive lysosomal storage disease caused by a deficiency in *N*-acetylgalactosamine-6-sulfate sulfatase (GALNS). Vimizim is intended to replace the missing GALNS enzyme involved in an important metabolic pathway. Absence of this enzyme leads to problems with bone development, growth, and mobility (4). Myalept (metreleptin for injection) developed by Amylin Pharmaceuticals, which was acquired by AstraZeneca, is an orphan drug and the first treatment approved by FDA for patients with congenital or acquired generalised lipodystrophy (5). Sylvant (siltuximab, Janssen Biotech) is another drug approved as a first treatment for a rare disease—multicentric Castleman's disease, a rare disorder that causes an abnormal overgrowth of immune cells in lymph nodes and related tissues in the body. Administered as an injection, Sylvant works by blocking a protein that stimulates abnormal growth of immune cells (6).

Novel mechanisms of action

Several of the drugs approved by FDA also fall into new classes of drugs. Three of the most noteworthy are manufactured by Merck & Co. Zontivity (vorapaxar) tablets reduce the risk of heart attack, stroke, cardiovascular death, and need for procedures to restore the blood flow to the heart in patients with a previous heart attack or blockages in the arteries to the legs. It is the first protease-activated receptor-1 antagonist and is designed to decrease the tendency of platelets clumping together to form a blood clot (7). Belsomra (suvorexant) for insomnia is the first FDA-approved orexin receptor antagonist, which alters the signaling of orexin in the brain. Orexins are involved in regulating the sleep-wake cycle (8). Keytruda (pembrolizumab) was approved for the treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. It is the first approved drug that blocks the programmed death-1 (PD-1) cellular pathway, which restricts the body's immune system from attacking melanoma cells. Keytruda was also designated a breakthrough therapy and an orphan product and received priority review (9).

Harvoni (ledipasvir and sofosbuvir) from Gilead Sciences is the first combination treatment (pill) for chronic hepatitis C virus (HCV) genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin, two FDA-approved drugs also used to treat HCV infection. Both drugs in Harvoni interfere with the enzymes needed by HCV to multiply. Harvoni was designated a breakthrough therapy (10).

New designations

In addition, 2014 saw the first approved antibiotic drugs—Dalvance (dalbavancin, Durata Therapeutics), Sivextro (tedizolid, Cubist Pharmaceuticals), and Orbactiv (oritavancin, The Medicines Company)—designated as qualified infectious disease products (QIDPs) under the Generating Antibiotic Incentives Now title of the FDA Safety and Innovation Act

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Table I: New molecular entities (NMEs) approved by FDA Center for Drug Evaluation and Research (CDER) in calendar year 2014 through 29 October 2014.*.

Date	Drug Name	Active Ingredient	Company
15/10/2014	Esbriet	pirfenidone	**InterMune**
15/10/2014	Ofev	nintedanib	**Boehringer Ingelheim**
10/10/2014	Lumason	sulfur hexafluoride lipid microsphere	**Bracco Diagnostics**
10/10/2014	Akynzeo	netupitant and palonosetron	**Helsinn Healthcare**
10/10/2014	Harvoni	ledipasvir/sofosbuvir	**Gilead Sciences**
16/9/2014	Movantik	naloxegol	**AstraZeneca**
13/8/2014	Belsomra	suvorexant	**Merck Sharp Dohme**
6/8/2014	Orbactiv	oritavancin	**Medicines Co**
1/8/2104	Jardiance	empagliflozin	**Boehringer Ingelheim**
7/7/2014	Kerydin	tavaborole	**Anacor**
3/7/2014	Beleodaq	belinostat	**Spectrum Pharmaceuticals**
20/6/2014	Sivextro	tedizolid phosphate	**Cubist**
6/6/2014	Jublia	efinaconazole	**Valeant**
23/5/2014	Dalvance	dalbavancin	**Durata Therapeutics**
8/5/2014	Zontivity	vorapaxar	**Merck Sharp Dohme**
29/4/2014	Zykadia	ceritinib	**Novartis**
21/3/2014	Otezla	apremilast	**Celgene**
19/3/2014	Impavido	miltefosine	**Knight Therapeutics**
19/3/2014	Neuraceq	florbetaben F 18 injection	**Piramal Imaging**
18/2/2014	Northera	droxidopa	**Lundbeck**
31/1/2014	Hetlioz	tasimelteon	**Vanda Pharmaceuticals**
8/1/2014	Farxiga	dapaglifozin	**AstraZeneca**

*Source: FDA's Center for Drug Evaluation and Research (1).

(FDASIA) (11). Vimizin was also the first drug to receive the Rare Paediatric Disease Priority Review Voucher, a provision that aims to encourage the development of new drugs and biologics for the prevention and treatment of rare paediatric diseases (4).

For only the second year, FDA was able to classify new NMEs and BLAs as breakthrough therapies, which are drugs with preliminary clinical evidence demonstrating that they may have substantial improvement on at least one clinically significant endpoint over available therapies. While in 2013 just three approved drugs were designated as breakthrough therapies, to date in 2014, six have already been approved: Zykadia (ceritinib, Novartis), Zydelig (idelalisib, Gilead Sciences), Keytruda, Harvoni, Ofev (nintedanib, Boehringer Ingelheim Pharmaceuticals), and Esbriet (pirfenidone, InterMune). Zykadia was approved for patients with a certain type of late-stage (metastatic) non-small cell lung cancer (12), and Zydelig was approved for patients with relapsed chronic lymphocytic leukaemia, elapsed follicular B-cell non-Hodgkin lymphoma, and relapsed small lymphocytic lymphoma (13). Both Ofev and Esbriet were approved for the treatment of idiopathic pulmonary fibrosis, which is a serious, chronic condition in which the lungs become progressively scarred over time (14). Four additional supplemental submissions also received breakthrough therapy designations (15).

In addition to the breakthrough designation, FDA also has several other designations designed to expedite the review of NMEs and BLAs. These include fast track, orphan product (for rare diseases), and priority review designations. Drugs can receive multiple designations. Up to 29 Oct. 2014, seven approved drugs had fast-track status, nine were designated as orphan products, and 12 underwent priority review (1).

Biggest winners

Looking at companies that received the most approvals, two have come out on top as of 29 Oct. 2014. Boehringer Ingelheim and Merck & Co. each received approvals for two NMEs and one BLA. Boehringer Ingelheim received approvals for Ofev, Jardiance (empagliflozin) for improvement of glycaemic control in adults with type 2 diabetes, and Striverdi Respimat (olodaterol), a biologic drug for the treatment of chronic obstructive pulmonary disease (1). Merck's winners included Zontivity, Belsomra, and Keytruda as

Table II: Biological license applications (BLAs) approved by FDA Center for Drug Evaluation and Research (CDER) in calendar year 2014 through 29 October 2014.*

Date	Drug Name	Active Ingredient	Company
18/9/2014	Trulicity	dulaglutide	**Eli Lilly And Co**
4/9/2014	Keytruda	pembrolizumab	**Merck Sharp Dohme**
19/8/2014	Cerdelga	eliglustat	**Genzyme**
15/8/2014	Plegridy	peginterferon beta-1a	**Biogen Idec**
31/7/2014	Striverdi Respimat	olodaterol	**Boehringer Ingelheim**
23/7/2014	Zydelig	idelalisib	**Gilead Sciences**
20/5/2014	Entyvio	vedolizumab	**Takeda Pharmaceuticals**
23/4/2014	Sylvant	siltuximab	**Janssen Biotech**
21/4/2014	Cyramza	ramucirumab	**Eli Lilly And Co**
15/4/2014	Tanzeum	albiglutide	**GlaxoSmithKline**
24/2/2014	Myalept	metreleptin for injection	**Amylin**
14/2/2014	Vimizim	elosulfase alfa	**BioMarin Pharmaceutical**

*Source: FDA's Center for Drug Evaluation and Research (1).

described above. AstraZeneca, Eli Lilly, and Gilead Sciences were also successful with two approvals each: Gilead for one BLA and one NME (Harvoni and Zydelig, respectively); Eli Lilly for two BLAs, Cyramza (ramucirumab) for the treatment of stomach cancer and Trulicity (dulaglutide) for the treatment of adults with type 2 diabetes; and AstraZeneca for two NMEs, Farxiga (dapaglifozin) to improve glycaemic control, along with diet and exercise, in adults with type 2 diabetes and Movantik (naloxegol) to treat opioid-induced constipation in adults with chronic non-cancer pain (1). Through its acquisition of the diabetes alliance assets of Bristol Myers Squibb, including Amylin Pharmaceuticals, AstraZeneca also acquired Myalept.

References

1. FDA, "New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products of 2014," www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm20025676.htm, accessed 29 Oct. 2014.
2. FDA, "Novel New Drugs 2013 Summary," www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM381803.pdf, accessed 29 Oct. 2014.
3. FDA, "FDA Approves Hetlioz: first treatment for non-24 hour sleep-wake disorder," Press Release, 31 Jan. 2014.
4. FDA, "FDA approves Vimizim to treat rare congenital enzyme disorder," Press Release, 14 Feb. 2014.
5. AstraZeneca, "US FDA approves orphan drug Myalept (metrleptin for injection),"
6. FDA, "FDA approves Sylvant for rare Castleman's disease," Press Release, 23 Apr. 2014.
7. FDA, "FDA approves Zontivity to reduce the risk of heart attacks and stroke in high-risk patients," Press Release, 8 May 2014
8. FDA, "FDA approves new type of sleep drug, Belsomra," Press Release, 13 Aug. 2014.
9. FDA, "FDA approves Keytruda for advanced melanoma," Press Release, 4 Sept. 2014.
10. FDA, "FDA approves first combination pill to treat hepatitis C," Press Release, 10 Oct. 2014.
11. FDA, "FDA approves Orbactiv to treat skin infections," Press Release, 5 Aug. 2014.
12. FDA, "FDA approves Zykadia for late-stage lung cancer," Press Release, 29 Apr. 2014.
13. FDA, "FDA approves Zydelig for three types of blood cancers," Press Release, 23 July 2014.
14. FDA, "FDA approves Esbriet to treat idiopathic pulmonary fibrosis," Press release, 15 Oct. 2014.
15. FDA, "CY 2014 Breakthrough Therapy Calendar Year Approvals," www.fda.gov/downloads/RegulatoryInformation/Legislation/ederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM380724.pdf, accessed 29 Oct. 2014. PTE

Novel technologies win CPhI Pharma Awards

On 7 Oct. 2014 at CPhI Worldwide in Paris, France, UBM Live announced the winners of the 11th annual CPhI Pharma Awards. Winners were recognised for their innovative solutions in formulation, process development, packaging, and partnering. The first three category winners were selected by a panel of judges representing industry and academia, while the latter, which was a new category this year, was determined by voting on the CPhI Pharma Awards website. The winners included MJR PharmJet in the formulation category, ACIB (Austrian Research Center of Industrial Biotechnology) for process development, Locked4Kids for packaging, and Catalent for partnering. For more information, visit PharmTech.com/CPhI_Pharma_Awards_2014.

AirBridgeCargo Airlines

AirBridgeCargo Airlines (ABC) is one of the key international cargo market players that links the world's largest manufacturers with consumers and business partners worldwide.

The AirBridgeCargo Airlines (ABC) network in Europe covers all major markets, including Basel, Switzerland; Amsterdam, the Netherlands; Frankfurt am Main, Munich, Leipzig in Germany; Milan, Italy; Paris, France; Zaragoza, Spain; Malmo, Sweden. The airline's network in Russia includes Khabarovsk, Krasnoyarsk, Novosibirsk, Moscow and Yekaterinburg. The company operates scheduled flights from Europe to Asia's largest gateways, such as Beijing, Hong Kong, Shanghai, Chengdu, and Zhengzhou in China; Seoul in South Korea and Tokyo in Japan. It also operates scheduled flights from Moscow to Chicago and Dallas in the US.

ABC's fleet of 13 Boeing 747 freighters is one of the youngest in the industry and offers the capacity to carry up to 130t on a single flight.

Being an all-cargo carrier, ABC has an opportunity to adjust each of the four Boeing's 747 cargo compartments between 4-29 degrees Celsius, therefore ensuring safe and reliable transportation for the high-value pharma goods. Trained to handle temperature-controlled products, its knowledgeable and highly skilled staff allows ABC to successfully transport temperature-sensitive cargo, including pharmaceutical products.

The airline's high on time performance and fast handling through Moscow hub will enable AirBridgeCargo's customers to achieve shorter than 48-hour connections on O&D within the airline's route network.

Today, ABC is an internationally recognised cargo airline with high-quality service levels and a range of competitive products including chartering and trucking services covering Europe, the USA, Asia and Russia.

In 2014 AirBirdgeCargo has been voted as 'The Best All cargo Carrier' in 28th Asian Freight&Supply Chain Awards and as 'The Best Cargo Airline' by Golden Chariot award that is known as 'the Oscars of the transport industry'.

ABC is a member of IATA, Cool Chain Association, TAPA and Cargo 2000.

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Anton Paar GmbH

Company description

Anton Paar GmbH produces high-end measuring and laboratory instruments for industry and research. The internationally active high-tech company specializes in measurements of optical rotation, refractive index, density and viscosity as well as rheometry and material characterization. Established by Anton Paar in 1922 as a one-man locksmith's workshop in Graz, Austria, over the years the company has become a global enterprise with a record turnover of 202 million Euros in 2013. Currently Anton Paar employs 2000 people worldwide, 900 of which work at Anton Paar GmbH, the company's headquarters in Graz, Austria. Anton Paar has strong links with universities and research laboratories worldwide. The company is owned by the Santner Foundation, which invests in research in the field of science and technology as well as in the rehabilitation of drug addicts.

Markets served

Pharmaceutical Industry, Hospitals, Pharmacies, Food companies, Calibration companies, Standard institutes

Major products/services

To identify, analyze, control, characterize or check your raw materials, intermediates, APIs and final formulations, benefit from Anton Paar's portfolio of instruments covering polarimeters, refractometers, density meters, viscometers, rheometers, synthesis instruments, sample preparation instruments, X-ray analysis systems and zeta potential instruments.

Facilities

Anton Paar has built up a strong sales network and is active in over 110 countries around the world—from the US to Japan. With 100 sales partners and 21 subsidiaries around the globe, Anton Paar is close to its customers, speaking their language and reacting quickly to requests for application support and service. Anton Paar presently has 21 subsidiaries and cooperates with 70 sales partners in 110 countries.

Anton Paar

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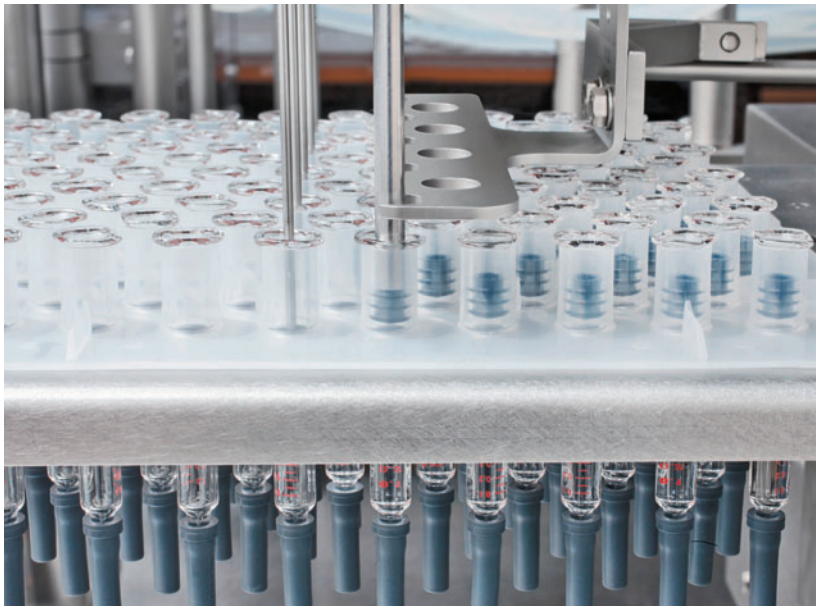
Bausch+Ströbel Maschinenfabrik Ilshofen

Company description

The BAUSCH + STROEBEL product range specializes in machines for pharmaceutical primary packaging, including equipment for washing, sterilizing / depyrogenating, filling, closing and labeling containers such as ampoules, cartridges, disposable syringes, vials and bottles of all kinds. The systems are designed to comply with the latest FDA and GMP requirements and are available for all capacity ranges, starting from laboratory testing and clinical batches to fully integrated commercial production. With more than 45 years of experience and over 10,000 machines delivered BAUSCH + STROEBEL is a leading manufacturer of high-quality equipment for the pharmaceutical industry.



Markets served

Bausch+Ströbel customers include notable pharmaceutical companies all over the world.

Major products/services

The manufacturing program covers a wide range of machines for the pharmaceutical, cosmetic and allied industries.

Facilities

The company grows with the number and size of the orders. From approximately 770 employees ten years ago the staff has increased to 1200 now (1400 worldwide). In Spring 2011 the biggest new building project in over 45 years of company history was started: under construction at the headquarters in Ilshofen is not a simple industrial structure but an architect-designed building. It includes a modern assembly building, a spacious warehouse, meeting rooms for seminars or discussions with customers, offices and a company restaurant seating about 200 employees, guests or participants in training sessions. About 5,000 sq. m. floor space are now available for the final machine assembly.

Since 2012 the Swiss company Wilco, an unparalleled expert for leak testing and quality control technologies, is part of the Bausch+Ströbel-Group.

Further manufacturing plants are located in Büchen in North Germany and in Connecticut, USA.

In step with the increasing globalization of the pharmaceutical industry resulting, among other things, from the mergers of major manufacturers, Bausch + Ströbel puts great emphasis on the international market. The development of a market-oriented, worldwide group of companies has brought Bausch + Ströbel increased market presence, proximity to its customers and faster communication between customers and staff. Representatives and agents serving our local market areas are active on every continent on our behalf.

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Baxter BioPharma Solutions

Company description

Baxter's BioPharma Solutions business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. As a parenterals specialist with over 80 years of expertise, BioPharma Solutions offers contract manufacturing form/fill/finish services and solutions for injectables designed to meet complex and traditional sterile manufacturing challenges. As a global injectables specialist, we can help solve unique challenges with confidence of delivery, service and integrity.

Markets served

Baxter's expansive network offers more than 50 manufacturing facilities across six continents and our global presence provides opportunities for unique sterile contract manufacturing collaborations. The power of an extensive global network lies in the coordination of, and efficiencies resulting from, a systemic approach to cGMP manufacturing. Our manufacturing network provides the possibilities of tailor-made solutions. Baxter has manufacturing sites across the globe in support of a diverse portfolio of delivery systems and manufacturing solutions.

Major products/services

Our Parenteral Delivery Systems include: prefilled syringes, liquid/lyophilized vials, cartridges, frozen premix systems, liquid premix systems, BIO-SET luer system, diluents for reconstitution, ampoules, powder-filled vials, and sterile crystallization.

Our Drug Categories include: small molecules, biologics, vaccines, cytotoxics, highly potent compounds, ADCs (antibody-drug conjugates), and cephalosporins/pencillins.

Facilities

Baxter has manufacturing sites across the globe in support of a diverse portfolio of delivery systems and manufacturing solutions. Our state-of-the-art facilities specialize in sterile contract manufacturing services and have primary locations in:

Bloomington, Indiana USA—The Bloomington facility is one of the largest contract manufacturers of sterile products in North America and offers form/fill/finish services and solutions for injectables designed to meet complex and traditional sterile manufacturing challenges. As a full service contract manufacturer, this facility serves client needs with clinical through commercial launch. These include: manufacturing, packaging, quality systems, experience with worldwide regulatory agencies, and our *Lyophilization Center of Excellence*, an industry-leading resource center focused on the development of high-quality freeze drying.

Halle/Westfalen, Germany—Recognized as a world-class manufacturer of highly potent and cytotoxic drugs with almost 60 years of experience, the Halle/Westfalen facility offers dedicated clinical through commercialization production with integrated services and technologies. Our recent collaboration with **SAFC®** will enable us to offer our clients a high quality, streamlined, comprehensive and collaborative solution for the production of their antibody drug conjugates; from development of conjugate, linkers, payloads, formulations via clinical supplies to commercial drug product by industry leading CMOs in the ADC field who are committed to success.

Round Lake, Illinois USA—Baxter is the world's leading provider of manufacturer-prepared IV solutions and our Round Lake facility is a best-in-class aseptic solution manufacturer. Baxter's portfolio of premixed drugs is the broadest in the industry and we are the only CMO to offer a manufacturer-prepared, commercial-scale aseptic filling process for premixed drugs in flexible IV bags.

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B. Braun Melsungen AG

Company description

B. Braun supplies healthcare markets worldwide and is employing approx. 50,000 individuals in more than 60 countries. Based on this expertise the B. Braun OEM Division serves the pharmaceutical and medical devices industry with standard and customized products (contract manufacturing, product development, private labelling, product combination).

Markets served

B. Braun supplies healthcare markets worldwide. Based on this expertise the B. Braun OEM Division serves the pharmaceutical and medical devices industry.

Major products/services

B. Braun OEM offers standard products or customized versions. Even the standard range contains hundreds of product versions, with which countless applications can be implemented.

Standard products

- Infusion and injection solutions
- Medical devices for drug admixture
- Automated infusion pumps
- Products for venipuncture and injection
- Products for infection prevention

OEM is specialized in developing customer-specific solutions for you. Most of our products can be individually adapted to your requirements.

Customized products and services

- **Contract manufacturing**
  If you are searching for a reliable partner for contract manufacturing of your drugs, B. Braun OEM is the pick of the bunch. Based on our profound experience, we manufacture and fill pharmaceuticals according to your needs.
- **Product development and private labeling**
  If you cannot find a suitable product in our 120,000 articles range, we are happy to provide you with your individual solutions—from product variation to complete new developments.
- **Product combination**
  You have invested years of development work and all your expertise into your drugs. Therefore, it is all the more important that your drugs are administered exactly as you have intended. To be on the safe side, simply use our medical products to configure an individual application kit that corresponds exactly to your needs. Visit www.kitpacking-bbraun.com and create your individual application set in 4 steps.

Facilities

B. Braun is headquartered in Melsungen, Germany. With 60 locations worldwide, B. Braun OEM has a global network of resources to help you design, manufacture, package, sterilize and private label pharmaceutical products and medical devices. Whether you are looking for infusion solutions, administration sets or disinfectants, we offer a full product line of standard or custom devices.

All our production sites meet international product requirements and feature the latest technology while adhering to international quality standards. Leverage our global network to reach North and South America, Europe and the Asia/Pacific region.

B BRAUN
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Catalent Pharma Solutions

Company description

Catalyst + Talent. Our name combines these ideas. From drug and biologic development services to delivery technologies to supply solutions, we are the catalyst for your success. With more than 80 years of experience across Rx and consumer markets, we have the deepest expertise, the broadest offerings, and the most innovative technologies to help you get more molecules to market faster, enhance product performance and provide superior, reliable manufacturing and packaging results.

Catalent develops. With our broad range of expert services, we drive faster, more efficient development timelines to help you take more molecules to market and create more effective products.

Catalent delivers. As the world leader in drug delivery innovations, we have a proven record of enhancing bioavailability, solubility and permeability, improving ease and route of administration, and increasing patient compliance for better treatments.

Catalent supplies. Globally positioned to serve all your manufacturing and commercial packaging needs, we provide integrated solutions to take your product from design, to clinical trial, to plant, and to pharmacy.

Catalent. More products. Better treatments. Reliably supplied.™

Markets served

- Pharmaceuticals
- Nutraceuticals
- Veterinary Medicines

Major products/services

Biologics including analytical and cell manufacturing services for biosimilar development, and ADC technologies for advanced drug therapies.

Oral Technologies Catalent offers a broad-range of services to ensure optimal oral delivery, from customised tablets to softgels. Technologies allow bioavailability of molecules to be enhanced, abuse of pharmaceuticals to be restricted and the controlled release of drugs to be tailored specifically.

Inhalation capabilities allow supply in all dosage forms, including pressurised metered-dose inhalers, dry powder inhalers, nasal sprays and nebulisers and liquid inhalers.

Development Solutions including pre-formulation studies, stability testing and solid state screening of crystalline forms.

Sterile Technologies including Blow/Fill/Seal advanced aseptic techniques, and a wide choice of advanced injectable and inhalation options.

Clinical Supply Services Catalent has a robust global network built around the most complete integrated service offerings for pharmaceuticals in clinical trial phases I–IV, including storage and distribution, direct comparator sourcing, manufacturing and packaging for all dosage forms.

Consumer Health Catalent offers oral and topical technologies for consumer-preferred formats, such as RP Scherer softgels to provide unique, tailored solutions for brands.

Facilities

Catalent is headquartered in Somerset, NJ with a global presence of nearly 30 facilities across 5 continents.

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EtQ

Company description

EtQ is the leading FDA Compliance, Quality, EHS and Operational Risk Management software provider for identifying, mitigating and preventing high-risk events through integration, automation and collaboration. EtQ's modules are tightly integrated to deliver a leading FDA Compliance solution.

Markets served

EtQ's FDA Compliance Management Software is an integrated Quality and Compliance Management system that has been pre-configured to specifically address the needs of the Life Science industry. EtQ's unique modular approach provides unparalleled flexibility and automation, delivering a best-in-class solution.

Major products/services

Change Management: EtQ's Change Management module is designed to manage all aspects of the Change Management process. The process begins with the initiation of the Change Management request, which may come from the customer, the supplier, or from an internal member of the company. Using the Change Management module, the user can provide a change summary that describes the change to be implemented, and identifies the affected documents, planned projects, and action plans. The user can then submit the request to the appropriate individuals for approval. If the request is approved, it then allows them to monitor all associated activities such as implementing the planned projects and action plans, and updating the associated documentation.

Risk Assessment: EtQ's unique FDA Compliance Software System is designed to minimize the number of CAPAs using an advanced filtering model; which features:

- Automatic segregation and categorization of events at the source
- Automatic identification and display of related events
- Built-in risk assessment software module
- Initial assessment to allow early closure
- Risk assessment throughout the process to guide decision making
- Full investigation with step-by-step root cause analysis
- Automatic lookup and display of related investigations and CAPAs
- Comprehensive CAPA action and effectiveness check plan with risk mitigation history.

eValidation: EtQ offers an automated validation module that shortens the company's validation time by as much as 400%—a 4 day validation project can be done in less than a day using EtQ's eValidator. Furthermore, the eValidator can be run by a single employee, and can eliminate the extensive resources needed to dedicate to a typical validation project. Finally, eValidator is able to compile a comprehensive report library of all tests and scripts run on the system. When audited by the FDA or other governing body, the validation reports are immediately available for review. Additional key modules include Corrective Action, Audits, Complaint Handling and more.

Facilities

EtQ is headquartered in Farmingdale, NY, with main offices located in the U.S. and Europe.

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www.etq.com

Eurofins BioPharma Product Testing



Company description

Eurofins BioPharma Product Testing is the largest network of harmonized bio/pharmaceutical GMP product testing laboratories worldwide, providing comprehensive laboratory services for the world's largest pharmaceutical, biopharmaceutical and medical device companies.

Our service offerings are fully comprehensive and include testing of drug substances, final products, intermediates, and starting materials for both small and large molecule drug products.

We give our clients the flexibility to choose from four service models to meet specific project needs, including the award-winning Professional Scientific Staffing℠ (PSS) insourcing solution, which places our scientists at the client's facility.

Whether our traditional Fee-for-Service model, or our Managed Hours, Full Time Equivalent or award-winning Professional Scientific Staffing℠ model, our clients can choose the best, most cost-effective service solution to fit their project goals at any of our global facilities.

We provide timely and secure access to comprehensive laboratory information through our innovative, 24-hour online data access tool, LabAccess.com℠. Clients can view extensive, live project information such as submitted samples, analysts' notebooks, chromatograms, approved test results, Certificates of Analysis, raw data packages and invoices for any project within any of our laboratories.

Markets served

Eurofins BioPharma Product Testing provides full CMC testing services to support more than 800 virtual and large bio/pharmaceutical companies and CMOs. We provide a wide range of testing services that support all functional areas of bio/pharmaceutical drug development and manufacturing, including method development, microbiology, process validation and quality control.

Major products/services

Eurofins BioPharma Product Testing provides the most comprehensive range of large and small molecule testing services available, worldwide. Our service offerings include testing of drug substances, final products, intermediates and starting materials for both small and large molecule drug products, including:

- Testing of all starting materials
- Process and product related impurities
- Method development and validation
- Stability and release testing
- Process/facility validation
- Virus clearance and safety
- Testing of packaging components

Scope of Testing Services

- Chemistry/Biochemistry
- Cell Banking Services
- Facility & Process Validation
- Method Development & Validation
- Microbiology
- Molecular & Cell Biology
- Raw Materials Testing
- Release Testing
- Residuals & Impurities Testing
- Stability Testing & Storage
- Viral Clearance & Viral Safety
- Professional Scientific Staffing℠

Facilities

Clients can work with any of our state-of-the-art facilities to receive the highest level of instrument technology and capacity to support projects of any size and scope. We have a global capacity of more than 50,000 square meters among our 14 facilities located in:

- Gent, Belgium
- Copenhagen, Denmark
- Colmar, France
- Lyon, France
- Paris, France
- Munich, Germany
- Hamburg, Germany
- Dungarven, Ireland
- Milan, Italy
- Siena, Italy
- Barcelona, Spain
- Uppsala, Sweden
- Michigan, U.S.
- Pennsylvania, U.S.

In addition to these laboratory locations, we have teams of scientists placed at more than 40 client facilities throughout the U.S. and Europe through our Professional Scientific Staffing℠ insourcing program.

eurofins | BioPharma Product Testing

Contact details

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www.Eurofins.com/Biopharma

FeF Chemicals A/S

FeF Chemicals is a Novo Nordisk company that specialises in the supply of ingredients for the biopharmaceutical and pharmaceutical industries, such as Insulin Human for cell culture media and cGMP manufactured Quaternary Ammonium Compounds (usually referred to as Quats) such as Benzalkonium Chloride, Cetrimide and Cetrimonium Bromide.

For our Insulin Human products we offer:

- Insulin from the largest manufacturer worldwide
- Pure and animal free cGMP product
- Ph.Eur. and USP compliance
- Full traceability
- Several manufacturing sites
- Safety stock at multiple secured locations
- Multi-ton scale production capacity
- Robust risk mitigation strategy to secure supply safety

For our cGMP manufactured Quats we offer:

- Global regulatory compliance
- Manufacture in accordance with the highest GMP standards on the market, the ICH Guide Q7 for Active Pharmaceutical Ingredients
- High purity products
- Analyses according to multicompendial pharmacopoeias BP, Ph.Eur., USP/NF and JP
- Regulatory documentation

As an approved supplier by a large number of global leading pharmaceutical companies, FeF Chemicals can assure full traceability and reliability of the raw materials. We have a well-developed management system, allowing tracing where the raw materials are used. We also have close contact with our suppliers and can meet with customer requested specifications. For us, reliability is not just in the system but also in the mindset of our employees.

The company was first established in 1949. It was acquired by Novo Nordisk, a Danish healthcare company and world leader in diabetes care, in 1986 and has been part of the pharmaceutical group since then. The group's core values are essentially about a patient centred approach. It is also about striving for excellence, being accountable to customers and stakeholders and for being at the forefront of innovation.

FeF Chemicals comprises today 140 employees divided into Research and Development, Quality Assurance, Regulatory Affairs, Production and Environment, and Sales and Customer Service. As a Novo Nordisk company, we believe in respect for all our employees and in creating a healthy working environment. Most important of all, we never compromise on quality and business ethics and this applies to everyone who works for the company.

Novo Nordisk won a Great Workplace Award in 2010 and 2011, and was ranked as the world's most sustainable company by Corporate Knights at the World Economic Forum in Switzerland in January 2012.

a Novo Nordisk company

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fefinfo@fefchemicals.com
www.fefchemicals.com

Hospira One 2 One

Corporate Description

Hospira's One 2 One™ business is a world leader in the custom development and manufacture of parenteral products packaged in vials, prefilled syringes, cartridges, flexible containers, and ampoules. One 2 One™ offers parenteral development and manufacturing services at its four worldwide facilities.

Whether your product is a small molecule or advanced biologic, One 2 One™'s highly qualified personnel in every world-class facility ensure quality, capacity, and security of supply.

Technical Services

One2One™ is able to manufacture injectable products in a broad range of delivery systems including:

- Vials, bottles, and ampoules
- Glass and plastic prefilled syringes
- Cartridges for self-administration devices
- Flexible containers.

One2One™ has the ability to manufacture a variety of injectable products, and has a broad range of capabilities and experience with different types of molecules:

- Biologics
- Small molecules
- Vaccines
- Beta-lactams
- Cytotoxics
- Controlled substances
- Highly potent compounds
- Aseptic Fill/Finish
- CTM/registration batches
- Lyophilization
- Sterile powder filling
- Terminal sterilization
- Disposable technology
- Multilingual packaging and labeling
- Cold chain management.

Facilities

One2One™ primarily works with four parenteral manufacturing facilities in North America, Europe, and the Asia Pacific regions, each registered with multiple regulatory agencies worldwide:

- McPherson, Kansas, USA: A leader in biologics Fill/Finish
- Liscate, Italy: Powder filling and lyophilization
- Zagreb, Croatia: Biologics Fill/Finish
- Mulgrave (Melbourne), Australia: Cytotoxic Fill/Finish

ONE 2 ONE™

Parenteral Contract Manufacturing Service of Hospira

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+44 0 1926 835 554 (Europe)
Fax. 224.212.3212
one2one@hospira.com
www.one2onecmo.com

I Holland Ltd

Company description

More than six decades of research, development and investment has established I Holland as the pre-eminent supplier of punches and dies to producers of tablets across the globe.

Our commitment to the development of innovative materials and products, combined with state of the art Quality Assurance Technology and unmatched customer service, has seen our solutions being successfully adopted by customers in more than 90 countries worldwide.

Users of our punches and dies benefit from enhanced product quality and increased productivity. Our unwavering dedication to quality, innovation and the understanding of Tabletting Science® has established us as a leading manufacturer and supplier of punches and dies of the highest quality.

Markets served

I Holland sells to over 90 countries worldwide through a network of approximately 50 agents and distributors, providing customer service at a local level.

Major products/services

Punches and dies for all types of tablet press including:

- Multi-tip tooling
- Designer Shapes
- Standard round and shaped punches
- IMA Comprima tooling
- Detergent Tooling
- Nutraceutical Tooling
- PharmaGrade®– refined steel for optimised tooling performance
- PharmaCote®– treatments and coatings to solve problems associated with wear, corrosion and sticking.
- Punch & Die Maintenance Products:
  Ultrasonic cleaners
  Punch and Die inspection/ measurement equipment
  Automated Polishing Machines – MF Series
  Punch and Die storage solutions
- Customer Support group – offers round the clock, pre- & post sales technical support on a variety of issues from tablet design to tooling maintenance and tablet production problems.
- Research & Development – working with customers and academic institutions on research projects to enhance tablet production and tooling performance.
- TSAR Predict – A revolutionary new service forecasting the correct anti-stick PharmaCote® coating solution for any sticky formulation.
- Tooling & Tablet Design services
- Training & Seminars – held at customer sites, or I Holland. Topics include:
  Tooling Specification & Procurement
  Tablet Design & Troubleshooting
  Troubleshooting – Tabletting & Tooling problems
  Tooling Materials, Treatments & Coatings
  PharmaCare® 7 Step Process
  Tooling Measurement
- PharmaCare® 7 Step Audit.

Facilities

Headquarters (production and training facility) — Nottingham UK.

I HOLLAND®
TABLETTING SCIENCE

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www.tablettingscience.com

KIMBERLY-CLARK PROFESSIONAL*

Healthier, safer and more productive

KIMBERLY-CLARK PROFESSIONAL* has built a reputation as the world leader in personal and process protection for laboratories and cleanrooms. Our scientific business specialises in partnering with pharmaceutical and research customers to create exceptional workplaces. Visit www.kcprofessional.co.uk/solutions/exceptional-laboratories for further information.

At KIMBERLY-CLARK PROFESSIONAL*, we know that the challenges you face every day affect every aspect of your organisation. The decisions you make have an impact on the working lives of everyone you work with. As your business partner, we are here every step of the way—understanding your customers' needs, backing your choices and providing you with solutions that enable people to be safer, healthier and more productive in the most environmentally sustainable way possible.

Expertise in regulated environments enables KIMBERLY-CLARK PROFESSIONAL* to incorporate quality by design into innovative products and develop highly effective, added-value engagement tools and services. We are changing the conversation with distributors and customers to simplify the buying process and help laboratory teams focus on engaging employees in safety, health and protection programs. We offer a world-class manufacturing and supply chain, assure quality and compliance, and help customers with extensive training while implementing effective solutions.

KIMBERLY-CLARK PROFESSIONAL* global brands include KLEENEX®, SCOTT®, KIMCARE*, WYPALL*, KLEENGUARD* and KIMTECH*.

Sustainability

KIMBERLY-CLARK PROFESSIONAL* is also committed to reducing environmental impact at every stage in a product's life cycle by obtaining a more holistic approach. At every stage throughout the life cycle we identify source reduction opportunities to help us use less of the world's natural resources and waste less. With our RIGHTCYCLE* Program we make it easy to recycle previously hard-to-recycle products like cleanroom garments and gloves. Now the garments and gloves used in your facility can be turned into a variety of useful, eco-friendly products. RIGHTCYCLE* is good for your business and good for the planet.

Kimberly-Clark Corporation

KIMBERLY-CLARK PROFESSIONAL* is one of Kimberly-Clark Corporation's four business segments. Headquartered in Dallas, Texas, with nearly 58,000 employees worldwide and operations in 37 countries, Kimberly-Clark Corporation posted sales of $21.1 billion in 2012. With brands like Kleenex®, Huggies®, Kotex®, Kimberly-Clark holds the nr 1 or nr 2 brand share in more than 80 countries. Our global brands are sold in more than 175 countries.

Every day, nearly a quarter of the world's population trust Kimberly-Clark brands.

Kimberly-Clark PROFESSIONAL* | Exceptional Workplaces®

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kimtech.support@kcc.com
www.kimtech.eu

NNE Pharmaplan

Company description

NNE Pharmaplan is a leading engineering and consulting company within the life science industry. We work with some of the world's most prominent pharma and biotech companies and help them develop, establish and improve their manufacturing and ensure regulatory compliance. NNE Pharmaplan employs around 2,000 people at more than 25 locations around the world.

Markets served

NNE Pharmaplan provides services to life science companies all over the world, with our main markets in Europe, Asia and the Americas.

Major products/services

At NNE Pharmaplan, we focus on the entire manufacturing life cycle and offer a wide range of consulting and engineering services to help pharma and biotech customers develop, establish and improve their manufacturing.

Single-use expertise

One of NNE Pharmaplan's core expertise areas is single-use technology. We've advised numerous customers on why, when and how to implement the new technology to support their strategies and we've supported them in selecting, installing and validating single-use equipment.

Single-use technology introduces new frontend considerations such as process compatibility, leachables/extractables, film selection, back-up suppliers and waste management. And the manufacturer's quality assurance system is extended to cover not only raw materials but also production technology. Accordingly, going strategic with single-use technology requires a structured and in-depth evaluation of technologies and their implications for your production processes and costs.

We will aid you in evaluating your single-use implementation by:

- Assessing the cost advantages that single-use technology can bring you
- Develop trend curves for cost advantages of single-use technology in a typical bioprocess scope
- Forecasting the savings for alternative single-use technology configurations
- Doing a 360° evaluation of single-use technology's impact on your facility area, HVAC, process equipment, utilities and automation costs
- Conducting workshops to take you through and evaluate all the technology/supplier combinations
- Testing in a pilot plant scale.

At NNE Pharmaplan, technology implementation expertise and hands-on experience with process technologies are trademarks of our process group, which has collected information in an evaluation format that rates technologies and companies with respect to technical approach, process experiences and also strategic considerations, such as geographical locations and number of production sites. We can thus help you find the technology and the supplier which best matches your requirements. Subsequently, we will help you audit suppliers and test the technologies to ensure 100% compliance with your production and quality requirements.

Facilities

NNE Pharmaplan has over 25 locations spread across four continent (Europe, North and South America and Asia). Our headquarters are located in Denmark, just north of the capital of Copenhagen. Many of our global offices are located in pharma and biotech hubs so that we can be close to our customers.

nne pharmaplan®
Engineering for a healthier world

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Schubert-Pharma

Company description

Schubert-Pharma was formed in January 2014—as an expert team—with employees from Gerhard Schubert GmbH and IPS International Packaging Systems GmbH now working together under the new banner to meet the requirements of pharmaceutical customers.

Schubert-Pharma brings together Schubert's expertise with the highly flexible TLM packaging machines and long-term business relationships with pharmaceutical companies, with IPS's extensive experience in project management and consulting on complex packaging systems.

Schubert-Pharma has planned, implemented and qualified packaging lines for a wide variety of products. This includes syringes, vials, ampules, cartridges and hospital-care products.

Markets served

Schubert-Pharma serves markets worldwide.

Major products/services

Schubert-Pharma distinguishes itself as a consulting partner with sound knowledge of handling medicinal products in production, and especially of secondary packaging processes. As an engineering service provider, Schubert-Pharma develops and plans new production capacity, designs upgrades for existing lines based on future requirements, optimises existing packaging systems, supports projects with certified project managers, and develops packaging solutions. Upon request, Schubert-Pharma accompanies pharmaceutical manufacturers from strategy to the development of concrete solutions, all the way through to their implementation —whereby the customer clearly benefits from a single point of contact.

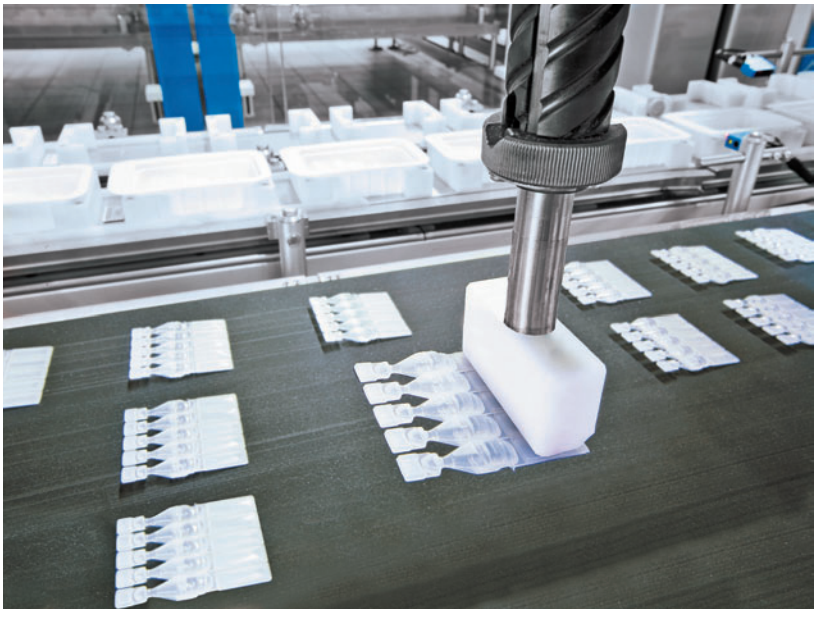
Schubert-Pharma offers Track & Trace solutions that fulfil all current worldwide regulations on pharmaceutical packaging.

While many suppliers in the market can only offer a limited number of the possible services required, Schubert-Pharma is in the position to support you holistically while taking full responsibility, thanks to our comprehensive range of services.

It is especially our focus on robots and highly intelligent software that enables us to create solutions that offer the highest reliability and quality, as well as product traceability.

Facilities

Schubert-Pharma is based in Crailsheim, Germany



SCHUBERT PHARMA

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Shimadzu Europa GmbH

Company description

Shimadzu is one of the worldwide leading manufacturers of analytical instrumentation. The company's equipment and systems are used as essential tools for the quality control (QC) of consumer goods and articles used daily, in healthcare as well as in all areas of environmental and consumer protection. Chromatography, environmental analysis, spectroscopy, balances, biotechnology and material testing make up a homogeneous yet versatile offering.

Markets served

Shimadzu's analysers and equipment are applied in the chemical, petrochemical and pharmaceutical industry, life sciences and biotech, cosmetics, semiconductor and nutrition industry, as well as in the flavours and fragrances business. Research institutes, privately-run laboratories, administrations and universities complete the list of clients. The systems are used in routine and high-end applications, process and quality control, as well as R&D.

Major products/services

i-series

Shimadzu's new *i*-series meet the needs of any analytical environment with high speed, outstanding performance, maintainability and economic efficiency. The *i*-series concept combines innovation, intuition and intelligence for applications in the food, environmental, chemical and pharmaceutical industry. The analyzers fit small labs with limited space, as well as large labs requiring high-throughput operation. Even inexperienced operators easily obtain high quality data and benefit from the improved and automated workflow.

***Nexera-e*, comprehensive 2D-LC system with SPD-M30A photodiode array detector targets complex matrices analysis.**

Nexera-e

The new *Nexera-e* comprehensive LC x LC system combines two orthogonal separation modes to separate even the most complex mixtures, such as structural analogues in food and natural extracts, in just one analysis. The "e" implies exponentially better chromatography due to an exponential increase in peak capacity and resolution, enabling the analysis of multiple compounds and identification of chemical class patterns in a single 2 dimensional contour plot chromatogram. One injection and sample preparation instead of several approaches add to the system's efficiency.

***i*-Series – the new driver of *i*-volution in HPLC analysis**

Facilities

As a global player, Shimadzu operates production facilities and distribution centres in 76 countries. The company's success is based on more than 10,000 employees worldwide. For over 40 years the European headquarters has been located in Germany. In 2013, Shimadzu inaugurated its new training and testing facilities, Laboratory World, for customers from all over Europe. With over 1500 m^2 floor space, Shimadzu's entire product range is available for testing and professional development — from chromatographs, spectrophotometers, TOC analysers, mass spectrometers, and balances to material testing machines. Mass spectrometry, a technology that Shimadzu has shaped significantly in recent years, is highlighted with the LCMS-8050 and GCMS-TQ8040 in its dedicated space. In addition, laboratory areas for customer applications and seminar facilities were being expanded.

In Europe, Shimadzu runs subsidiaries in Austria, Belgium, Bosnia-Herzegowina, Croatia, Czech Republic, France, Germany, Italy, Netherlands, Russia, Slovakia, Switzerland, and the United Kingdom.

SHIMADZU
Excellence in Science

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Valpharma International SpA

Company description

Valpharma Group is a worldwide leading developer and contract manufacturer of modified release solid oral dosage forms (powders, granules, tablets, film coated tablets and pellets to be filled into hard gelatine capsules) and tablets with OROS technology, bulk packed. The pharmaceutical Group has manufacturing authorizations for non-sterile solid oral dosage forms: capsules (soft and hard shells), tablets, hormone tablets and IMPs and is specialized in more than 100 products with own patent formulation (Pharmaceutical Products, Sexual Hormones, Dietetics, Narcotics and Psycotropics, Investigational Medicinal products). Valpharma offers a close collaboration with open and transparent dialogue to pharmaceutical industries all over the world. Among its customers the Group boasts leading pharmaceutical companies, including multinationals. The collaboration is based on signed agreements (actually more than 500), with an actual manufacture of 1,6 billion doses/year and 300 products developed in 36 years of experience. The Pharmaceutical Technologies applied to own formulations in tablets and pellets to fill capsules are:

- Sustained Release
- Delayed Release (enteric coated)
- Pulsatil Release
- Chrono Release
- Targeted Delivery
- Matrix Tablets
- Multilayer Tablets
- MUPS (multi unit pellets system)
- Orally Disintegrating Tablets
- OROS (osmotically controlled drug delivery system)
- Bioavailability Enhancement Co-Precipitation.

Markets served

Australia, Brazil, Japan, Europe, Mena countries, New Zealand, Singapore, South Africa

Major products/services

Major products

- S.R. Diclofenac Sodium tablets/ capsules
- S.R. Diltiazem capsules
- E.C. Duloxetine capsules
- E.C. Esomeprazole MUPS tablets
- S.R. Galantamine capsules
- S.R. Gliclazide tablets
- S.R. Isosorbide-5-Mononitrate tablets
- S.R. Ketoprofen capsules
- S.R. Nifedipine tablets
- S.R. Nitroglycerin tablets
- S.R. Theophylline tablets
- S.R. Tolterodine capsules
- S.R. Venlafaxine capsules

Services

Services provided:

- Pharmaceutical development and industrial manufacture
- Sponsoring of Pharmacokinetics and Bioequivalence Studies
- Documentation for Marketing Authorization Applications (e-CTD management available).

Facilities

Valpharma SpA. Via Ranco 112, 47899 Serravalle - Republic of San Marino; operating since 1987; covered area 6000 sqm

Valpharma International S.p.A. - Via G. Morgagni 2 - 47864 Pennabilli (Rimini) .- Italy; operating since 2002; covered area 34000 sqm

FACTA NON VERBA

VALPHARMA INTERNATIONAL SpA

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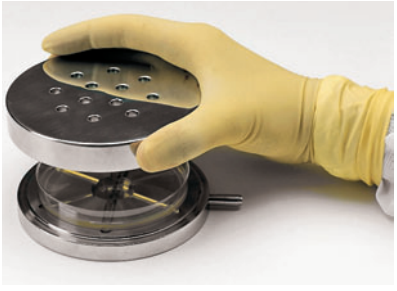
Veltek Associates, Inc.

Since 1981, Veltek Associates, Inc. (VAI) has played an innovative role in the pharmaceutical, biotechnology and medical device industries. This has been accomplished by partnering with clients to develop strategic products and services, therefore, notably improving operations and reducing costs associated with the ingress of contamination.

VAI is an EPA and FDA registered manufacturing facility, located in Malvern, Pennsylvania, USA. VAI houses four main divisions, three of which are the Sterile Chemicals Manufacturing Division (SCMD), the Environmental Control Manufacturing Division (ECMD), and the Disposable Products Manufacturing Division (DPMD). The SCMD features a comprehensive range of sterile pharmaceutical grade disinfectants, sanitizers, sporicides, cleaners, lubricants, and detergents. On the other hand, in the ECMD we manufacture viable monitoring systems, including, our new SMA OneTouch ICS complete with digital control panel monitoring. In addition to these two divisions, we have our DPMD that offers our patented Easy2Gown coveralls, facemasks, sweat-less headbands, bouffant hats, hoods and, just recently launched, our cleanroom paper & supplies.



Furthermore, our fourth and final division is our VAI Laboratory Testing Division. VAI Labs provides microbiological testing services ranging from the identification of microorganisms, to antimicrobial effectiveness studies that prove or deny the effectiveness of disinfectants in your operations. Included in this division is our consulting services. This consulting service called, Aseptic Processing Inc., available worldwide, can work to combine all contamination control aspects within an organization into one overtone system that is compliant and effective. Repeatable success has been and will be assured.

Markets served

- Pharmaceutical
- Laboratory research
- Biotechnology
- Compounding pharmacies

Products and Services

- Disinfectants
- Cleaners
- Cleanroom garments
- Cleaning Systems
- Sporicides
- Viable Environmental Monitoring Equipment
- Laboratory Services
- Cleanroom paper and products

Facilities

Corporate Headquaters:
15 Lee Boulevard, Malvern, PA 19355-1234, USA. Satellite offices located worldwide.

VELTEK ASSOCIATES, INC.

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Fax back on (00)1-218-740-6417 or (00)1-218-740-6437

Answer all questions by filling in the circles ●

1. What is your company's primary business? (Fill in ONE only)
100 ◯ Pharmaceutical Manufacturing
110 ◯ Biopharmaceutical Manufacturing
150 ◯ Ingredients (e.g. Raw Materials, APIs, excipients, chemicals, water)
141 ◯ Contract Services
160 ◯ Drug Delivery/Medical Product and Device Manufacturing (e.g. inhalers)
105 ◯ Engineering/Facilities/Construction
80 ◯ University/Academia/Education
90 ◯ Government (including regulatory agencies and bodies)

2. What is your function? (Fill in ONE only)
10 ◯ Research/Development/Formulation
20 ◯ QA/QC/Validation/Regulatory Affairs
33 ◯ Supply Chain
44 ◯ Manufacturing/Processing
45 ◯ Information Technology
60 ◯ Engineering
80 ◯ Corporate Management
90 ◯ Project/Purchasing/Procurement/Contract Management
95 ◯ Education Professional

3. Would you also be interested in Pharmaceutical Technology Europe's weekly e-newsletter?
(Your Email address is required below.) Y ◯ Yes

4. Do you recommend, specify, or authorise the purchase of services, equipment, and supplies? Y ◯ Yes N ◯ No

5. Do you plan to purchase any of the following in the future?
(Fill in ALL that apply)
A ◯ Raw Materials
B ◯ Processing/Manufacturing Equipment
C ◯ Drug Delivery
D ◯ Packaging
E ◯ Cleanrooms & Contamination Control
F ◯ Laboratory & Analytical Equipment
G ◯ Process Automation & Control
H ◯ Outsourced Services
I ◯ Compliance & Validation/QA/QC

Which version of *Pharmaceutical Technology Europe* would you like to receive?

◯ **Digital** ◯ **Print** ◯ **Both**

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PROMO CODE: PTEAD2

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GDP: Who is Responsible?

Siegfried Schmitt, principal consultant, PAREXEL International, discusses the requirements for good distribution practices.

Q. We are expecting routine inspections of our solid dosage manufacturing plants by the European Union competent authorities. We have a good inspection history and high standards for GMPs. We have been told that the inspectors may want to review GMP and good distribution practices (GDP). As we have outsourced all distribution activities, is it sufficient to have service agreements in place and audit the providers? Or are we missing something?

A. GDP is crucial as an industry standard to ensure quality control and ultimately, improve distribution and clinical-trial management. To determine who is responsible for GDP, the applicable regulations must first be considered. In Europe, GDP regulations were revised following the issuance of the Falsified Medicines Directive (FMD), which came into play in January 2013 to help prevent falsified medicines from entering the legal supply chain. The directive substantially changed the European framework for the supply of medicines and affected businesses that have not traditionally been directly monitored through medicines regulation (e.g., brokers) (1).

The FMD was followed by the release of the Good Distribution Guidelines in March 2013 (revised in November 2013) (2). These guidelines ensure the level of quality determined by GMP is maintained throughout the distribution network, safeguarding the distribution of authorised medicines to retail pharmacists through the eventual end-consumer, without any alteration of their properties (3).

As you are being inspected, I assume you are the marketing authorisation holder (MAH) and, therefore, responsible for the secure, controlled, and compliant pharmaceutical supply chain — from raw material supplies to shipments of products to customers. GDP must be covered by the MAH's quality system.

You mention that you audit your distributors, which is an excellent practice. It is important, however, that your audits cover current regulatory requirements. For example, does your audit programme include all wholesalers, warehouses, freight consolidators/freight forwarders, and brokers within your supply chain? In many companies, some of these third parties are managed through the logistics department and may not be under the same scrutiny of quality control. To fully understand logistics, supply chain, and distribution channels, a comprehensive assessment of each department is crucial. Ideally, these assessments would be part of a greater risk assessment to ensure all regulatory requirements are being met. Further, this approach helps reveal possible GDP gaps in quality and regulatory oversight among third parties.

As with all newly enforced regulations, interpretation of GDP regulations will become clearer over time. For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA) published this information on 18 Aug. 2014 (4):

"The GDP Inspectorate is raising awareness of the impact of the new regulations to those parties that are either directly or indirectly affected and any freight consolidator or freight forwarder either in the air, sea, or road transport sector that is either holding ambient medicinal products on site for more than 36 hours or has cold room facilities will require a Wholesale Distribution Authorisation WDA(H) in order to comply with the Human Medicines Regulations 2012 [SI 2012/1916] (as amended) and with Directive 2011/62/EU." (4)

Considering this example, it is quite possible that goods stored intermittently in warehouses now fall under the above definition. The warehouse management team may not be aware of the changed requirements. Regardless, ultimate responsibility for compliance remains with you, not the third party. Through technical/quality agreements, the contractor and third party can confirm that roles and responsibilities are understood. Any agreement made with the warehouse operators should clarify which licenses will be required for a compliant operation.

A quality and compliant system requires deep understanding of all applicable regulations and how these applications should be applied to any given distribution network. GDP is crucial as an industry standard to ensure quality control and, ultimately, improve distribution and clinical-trial management. GDP should be considered in advance of contracting third-party distributors to ensure best practices in clinical-trial management.

References

1. MHRA, The Falsified Medicines Directive.
2. EMA, *Good Distribution Practice* (March 2013).
3. EC, *Good distribution practice of medicinal products for human use* (5 Nov. 2013).
4. MHRA, MHRA position on freight consolidation depots (freight forwarders), www.mhra.gov.uk/PrintPreview/DefaultSP/CON447997, accessed 11 Nov. 2014. **PTE**

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