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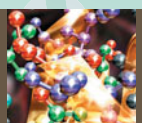

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September 2013

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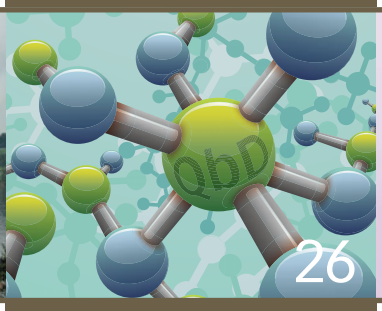

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CPhI Report Highlights Quality Concerns

CPhI Worldwide and CPhI Pharma Evolution recently conducted a survey on the current status of the formulation and ingredients market. The results, which were released in the first of a series of monthly reports, with the headline *"Survey Suggests a Need for Greater Control of Formulation & Ingredient Management,"* revealed overall trends and areas of concern in the pharmaceutical industry.

Tablets and capsules still represent the majority of the market with an increasing focus on extended release and orally disintegrating products. Bioavailability remains the top challenge in formulation, followed by stability, dissolution and release profile. The most difficult unit operation to control in final drug-product manufacturing is particle size reduction as agreed by 60% of survey respondents. Process analytical technology and quality by design are playing greater roles in formulation projects, with nearly 35% of respondents already using both and nearly 36% planning to use them in the future.

For APIs and ingredients, India was the top source as indicated by more than 45% of respondents, while 25% answered China and 19% said Europe. Quality and supply were, however, seen as top issues for the industry. The importance of working with third-party auditors to vet suppliers, as advocated by EMA and FDA, was reflected in the survey results, with more than 55% of respondents describing supplier's certification as "extremely important" and 39% as "somewhat important." Yet, it is surprising to see less than 25% of respondents actually working with third-party auditors to verify supplier compliance with GMP, suggesting that the industry is still avoiding the problem despite the need for greater vigilance.

The safety and quality of APIs have never really been officially addressed in GMP guidelines but regulators in the EU and US are now stepping up efforts to fill this gap through the Falsified Medicines Directive and the FDA Safety and Innovation Act. As API expert, Girish Malhotra, president of Epcot International and CPhI expert industry panel member, pointed out in the survey report, quality must not be taken for granted. Pharmaceutical companies are urged to work with their suppliers and emphasise to them the value of quality. The game has changed, according to Malhotra, and purchasing departments must be made aware of it. Suppliers and buyers must agree on what certifications are required and there are no shortcuts when it comes to ensuring quality.

Adeline Siew, PhD
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Omega Design Corporation offers the LabelSync 450 Vision Module, designed to capture and sync a bottle's unique serialised label with its individual line code. The machine can handle bottles 30–1500 mL in volume at speeds up to 300 per minute. Compatible with a range of serialisation software and vision components, the LabelSync 450 verifies each code's readability, confirms that each bottle belongs on the line, establishes a one-to-one relationship between the two codes and enables high-integrity identification processes downstream. The LabelSync 450's vision system is comprised of four cameras whose combined viewpoints offer 360-degree label inspection as well as a fifth camera to read secondary line code.

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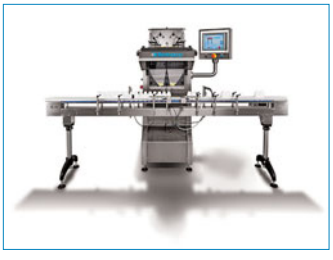

Bosspak VTC 100 Tablet and Capsule Counter

The Bosspak VTC 100 electronic tablet and capsule counter from Romaco's is designed to fill pharmaceutical solids or food supplements into bottles at high speed. The machine works independently of particular formats, allowing the product and packaging to be changed quickly. The tablets, caplets or gelatine capsules are fed to the counting stations by means of vibratory feed trays. The new sensor generation features built-in microprocessors that adjust the count trigger point automatically during production. The Bosspak VTC 100's pre-dosing system can improve both counting accuracy and filling speed. The machine counts a maximum of 100 bottles a minute and can be installed either as a standalone unit or integrated in a line.

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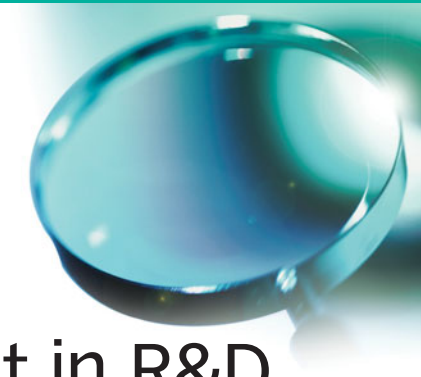

The Importance of Continued Investment in R&D

There has been a notable shift in interest for life-science companies over recent months from institutional investors investing through the public markets, but any plans to release further capital will rely on first-rate R&D.

Mark Howard is a partner at Charles Russell LLP.

Good quality research and development (R&D) is crucial to the long-term success of the pharmaceutical industry and more generally, the wider life-sciences sector, but acquiring adequate funding is often viewed as a challenge, particularly at the feasibility or concept stage of R&D. There are, nonetheless, a number of funding sources available for companies and recent trends on the public markets may mean that an initial public offering (IPO) could be an option over the longer term. Given that traditional providers of debt finance remain cautious in their lending approach to companies conducting early-stage R&D, next generation businesses are finding alternatives in government and national development funds, such as the UK's Biomedical Catalyst programme and the Wales Life Sciences Investment Fund (WLSIF).

Biomedical Catalyst programme

The UK government's Biomedical Catalyst programme, a £180 million translational funding programme operated by the Medical Research Council and the Technology Strategy Board, is actively investing in the life-sciences sector. The aim of the Biomedical Catalyst is to provide funding and support for small and medium-sized enterprises (SMEs), academics and universities in the UK to accelerate R&D in innovative healthcare projects. David Willetts, Minister for Universities and Science, stated that this "investment will help keep us at the very forefront of life sciences by supporting some of our most innovative SMEs and universities. It will help take excellent ideas through to market, driving growth and helping patients benefit from the very latest technologies and treatments" (1).

In November 2012, it was announced that in its last round of funding, Biomedical Catalyst had provided grants totalling £39 million to speed up the development of healthcare technologies, of which £29.6 million went to 22 projects led by SMEs (including Cantab Biopharmaceuticals Ltd, Glide Pharmaceutical Technologies Ltd and Kalvista Pharmaceuticals Ltd) and a further £9.5 million to 10 projects led by academic institutions (including the University of Oxford and University College London). The fourth round of funding was launched on 29 July 2013 and it is expected that a further £30 million will be issued to researchers through the scheme in 2013/14. The Chancellor, George Osbourne, also announced that additional government funds shall be used to top up the programme, demonstrating the government's commitment to ensuring that the UK remains a world leader in science and research (2).

Funding through such development funds not only assists with the funding of R&D, but recognition from these funds and the positive public relations it generates may be a catalyst for additional investment. An example of this benefit can be seen by the recent successful funding round by Glide Pharma, which is a pharmaceutical development and device company focused on needle-free administration of solid dose formulations. Glide Pharma announced on 26 February 2013 that it had completed a £14 million investment round, with funds managed by Invesco Perpetual investing the majority of such funds (3). In relation to the fundraising, Mark Kirby, chairman of Glide Pharma said that "this fundraising follows recognition of Glide's novel technology by the UK government-backed Biomedical Catalyst scheme, which awarded the company £2.3 million funding for the development of a novel formulation of teriparatide (parathyroid hormone) for the treatment of osteoporosis."

Wales Life Sciences Investment Fund

It was announced in May this year that the WLSIF had made its first investment in Simbec Research, a UK-based clinical research organisation providing worldwide services to pharmaceutical and biotechnology companies specialising in early clinical development of new pharmaceuticals. The WLSIF opened in the first quarter of 2013, with the purpose of investing in life sciences and related medical, pharmaceutical and healthcare companies based

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in Wales. It's investment strategy is to focus on a small number of companies and provide them with both financial and business support. The WLSIF will invest in businesses at all stages of growth, including those requiring seed capital funding to fund R&D. Howard Jenkins, CEO of Simbec Research said, "This new partnership with the Wales Life Sciences Fund is a major step towards creating an invigorated and more dynamic company and we look forward to a highly stimulating period of growth for Wales and for all involved" (4).

While the market appears to be strong for the pharmaceutical industry in general, for companies involved in drug discovery, the market remains challenging. However, certain institutional investors are showing interest in this sector as well, and the successful float of Retroscreen Virology demonstrates a willingness to invest in businesses carrying out quality R&D. Such admissions show that companies with a strong pathway to profit are investable from an institutional investor perspective. In particular, investors are looking to invest in companies that

While there are a number of opportunities available to pharmaceutical companies looking for funding in the R&D and commercialisation stage, another option for such companies is to raise funds on public markets.

In addition to investment activity, the WLSIF aims to attract companies, entrepreneurs and corporate venture spin-outs to Wales and encourage its investee companies to form international partnerships. To date, more than 160 businesses have applied to the WLSIF, showing a clear need for such funding and business support.

Listing on the public markets

While there are a number of opportunities available to pharmaceutical companies looking for funding in the R&D and commercialisation stage, another option for such companies is to raise funds on public markets. Although this approach has been a challenge since the 2007/08 financial crisis, particularly for the pharmaceutical sector, there has been a notable shift in recent months, with institutional investors showing renewed interest in investing in life-sciences companies through public markets, both in the UK (e.g., Clinigen Group plc, Retroscreen Virology plc and Venn Life Sciences Holdings plc, all three recently floated on AIM) and elsewhere (e.g., Stemline Therapeutics Inc., recently floated on NASDAQ). In addition to providing access to funding, the public markets offer life-sciences companies a range of benefits, including enhanced status and public profile, the ability to incentivise employees through share-option schemes, a transactional currency in the form of their listed shares and a potentially profitable exit option for investors. For example, on admission, the existing shareholders of Clinigen achieved a significant sell-down with an aggregate consideration in excess of £40 million.

can demonstrate strong underlying fundamentals, a strong management team (preferably with a proven track record of bringing life-sciences companies to market) and established revenue streams or a clear pathway to profit.

As a further boost to companies in the life-sciences sector, on 27 March 2013, the London Stock Exchange launched a new high-growth segment of the main market, which aims to address the needs of fast-growing European technology companies with a view to providing such companies with a transitional route to the UK listing authority official list. Initiatives such as the Biomedical Catalyst are also proving to be crucial resources in assisting companies to fill the R&D funding gap early on in their lifecycle, and with the Office for Life Sciences firmly focussed on promoting UK life-sciences companies, this position looks set to continue.

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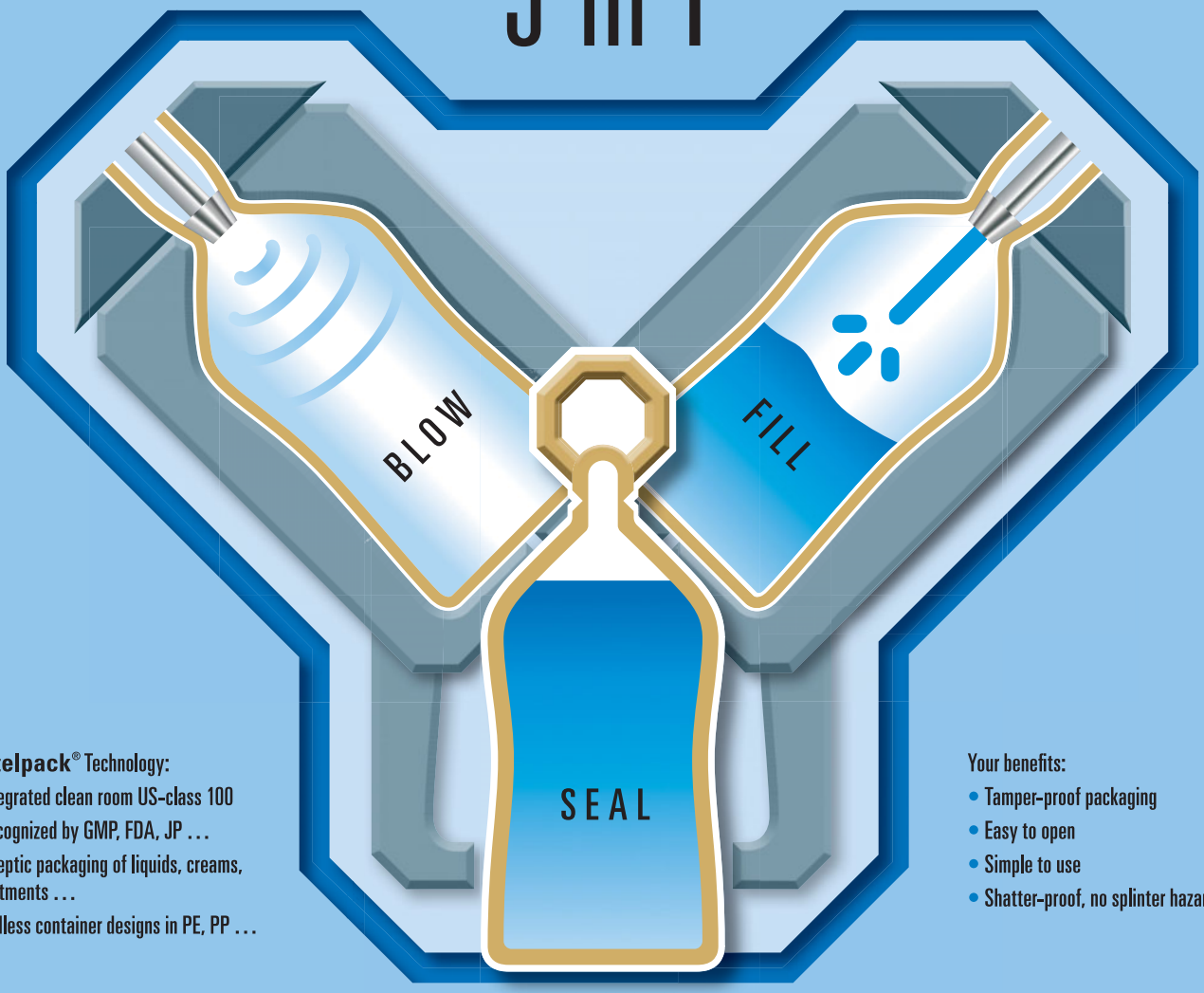

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Outsourcing Partnerships for CMC Development

Are strategic partnerships in clinical research a model for CMC services?

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The first generation of strategic sourcing relationships in clinical research is coming up for renewal, and the CRO industry is watching carefully to see how they renew. Strategic sourcing relationships, which involve global bio/pharmaceutical companies contracting large portions of their clinical research programs to the largest CROs, have transformed the clinical research industry. CROs that have won strategic relationships, including Icon, Parexel, Quintiles and Covance, now control substantial shares of the clinical research market while smaller CROs have been forced to fight over the "leftovers" from mid-size and emerging bio/pharma companies.

All indications are that clients are happy with most aspects of their strategic sourcing relationships. For the most part, these arrangements are delivering on their promise to the global bio/pharmaceutical companies, especially lower costs, better trial execution and reduced staffing. Given their performance and the high costs that would be involved in switching vendors, it is likely that most (probably all) of these deals will renew.

That's good news for the CROs that have been able to secure these strategic relationships. Not only have they received the project volumes negotiated in the original deals, they have received work well beyond the original scope, including projects in adjoining activities that were not part of the initial arrangement. As a result, their revenues have been growing at the annual rate of 15–20%. Profits have not grown as quickly due to the costs of expanding capacity to handle the burgeoning volume, but margins are expected to improve over time.

Suitable for CMC development?

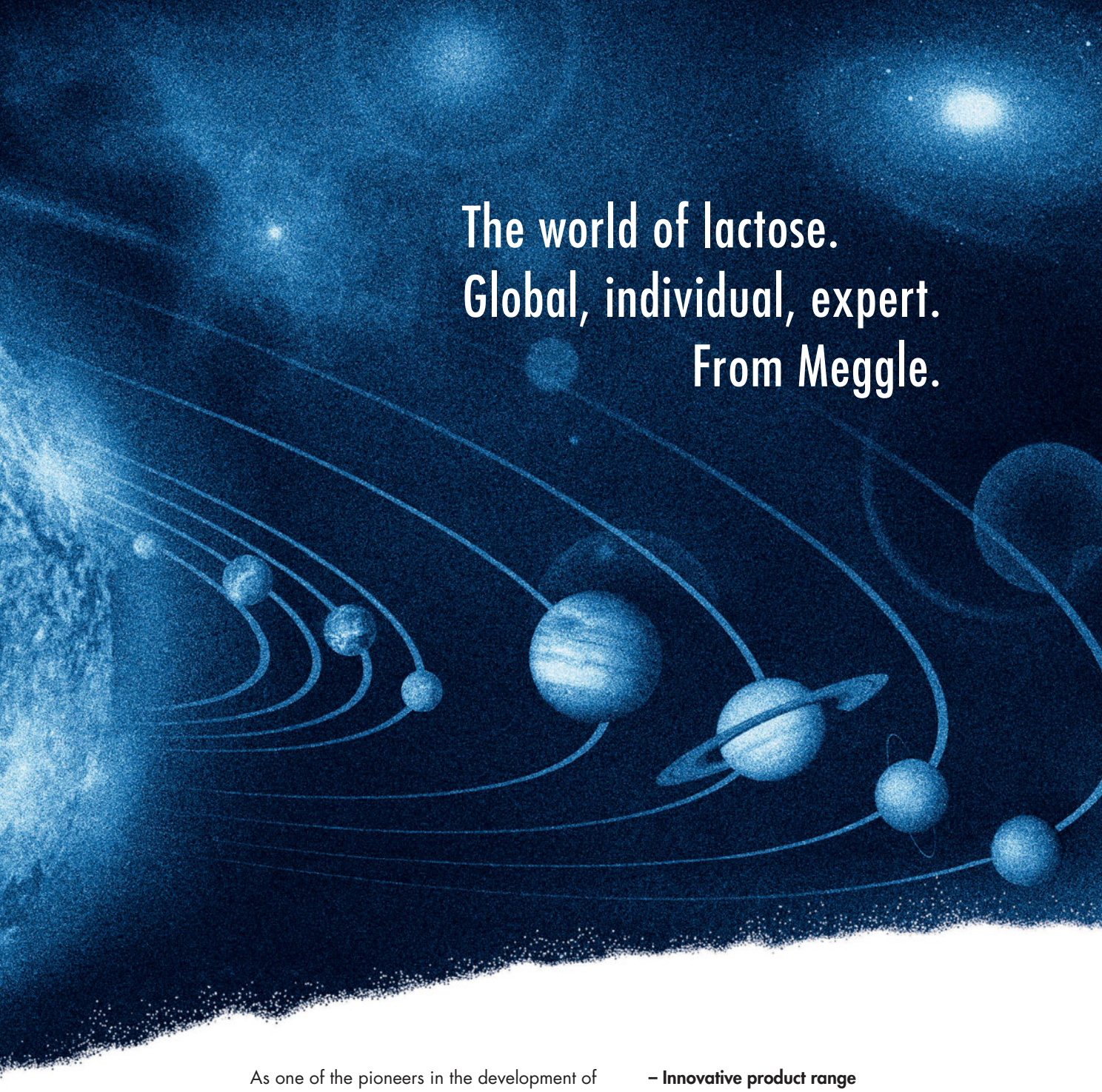
Given the success of the strategic relationships in clinical research, CDMOs should be thinking hard about when and if that model will be adapted to chemistry, manufacturing and control (CMC) services. If it can be ported into the CMC environment, the model could drive a radical restructuring of the industry by creating big opportunities for some CDMOs but also shutting out others, which would result in a flurry of acquisition activity. Whether the model can be fully adapted to the CMC world, however, is open to question.

Perhaps the biggest difference between clinical research and CMC development is that CMC development is all about creating knowledge, innovation and intellectual property that ultimately differentiates a product in the market. CMC creates a lot of knowledge about the molecule, some of which is captured in laboratory data but much of which is generated and understood less formally, just by working on the process or product. Further, CMC development generates innovations such as more efficient processes for manufacturing APIs or improved formulations to aid drug delivery.

Bio/pharmaceutical companies recognise that knowledge and innovation creation is part of CMC development, and companies are understandably reluctant to give it up entirely. They want to retain the knowledge that is generated and want to own or protect the intellectual property (IP) that is created.

By contrast, clinical research is only about collecting and analysing data on the effectiveness and safety of the product in the patient. It seldom leads to product innovation directly (the famous case of Viagra [sildenafil citrate], first discovered as a cardiovascular drug and later developed as a treatment for erectile dsyfuntion, is the rare exception), and the information technologies that clinical research leverages are not core competencies for bio/pharmaceutical companies.

Another major characteristic of CMC development that may mitigate against strategic partnerships is the diversity of technologies and know-how that are used to develop a drug. It would be uneconomical and infeasible for a CMC-services provider to acquire and maintain all of the technologies used to manufacture or deliver a drug. Think of all the possible types of reactions used to synthesise small-molecule compounds and the way certain companies have carved out special niches for themselves for technologies such as high-energy reactions that are only appropriate in particular circumstances. Similarly, expertise and equipment for solubility-enhancing technologies such as spray drying or micronising



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Information technology has made collaboration and knowledge-sharing possible over great distances, so the opportunity to disperse those activities may be increasing.

The diverse range of technologies would seem to guarantee that bio/pharmaceutical companies will always need a wide array of CMC service providers to meet their development requirements.

Strategic models

The nature of CMC development would suggest that it may not be as suited to the strategic partnership model as clinical research. While there are some CMC activities that have gone a long way to adopting that model, namely clinical packaging and analytical testing, those activities have more in common with clinical research. Neither of those activities generates IP and both require more operational expertise than scientific expertise.

As the bio/pharmaceutical industry continues to adapt to a changing market and scientific environment, however, some of the forces that have driven strategic clinical research relationships may come to bear on CMC development as well. Consider global reach. CMC expertise is more widely available, especially for small-molecule API development and for basic formulations. As cost pressure increases, companies seem to be more open to exploring CMC development in lower-cost locations. Further, global bio/pharmaceutical companies recognise the need to develop products specifically for those emerging markets.

At the same time, information technology has made collaboration and knowledge-sharing possible over great distances, so the opportunity to disperse those activities may be increasing. CMC providers with truly global operations that can access and network lower-cost resources in emerging markets might be able to build favourable positions as strategic providers.

The other big opportunity for strategic partnerships may lie in integrated service offerings. Time and cost are of the essence in drug development today, and companies offering a combined service developing an API and drug product may be able to offer significant reductions in both. One-stop offerings have the potential to reduce the leakage of knowledge as projects are handled off from one provider to another, and they can eliminate or reduce the periods of inactivity between development activities. Delivering the promise of one-stop models, however, will require a level of operational excellence that few in the CMC industry have yet been able to achieve. **PTE**

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EU Raises API Standards: A Curse in Disguise?

The aim of the newly enacted European Falsified Medicines Directive is to improve the quality of imported APIs, but does the pain now outweigh the gain?

The number of substandard pharmaceutical ingredients coming into the EU has increased in recent years; however, when the European Commission (EC) first revealed details of the implementation of new EU rules for GMP standards for imported APIs, both the pharmaceutical industry and regulators warned about the potential dangers of these restrictions in causing medicines shortages. The new regulation, part of the EU's Falsified Medicines Directive (FMD), requires that imports of APIs into the EU must be accompanied with written confirmation by a national regulatory authority that the manufacturing plant complies with GMP standards. This requirement has raised concerns that the importation of a large proportion of APIs would be severely hampered as a result. And yet, six weeks after the new rules came into effect on 2 July 2013, there has been no evidence of any major upheaval in the supplies of APIs in the EU—approximately 70% of which are imported, with 60% of these imports coming from India and China.

"Currently, we have not been notified of any critical disruption of API supplies, or manufacture of medicinal products, linked to the enforcement of the new EU rules on the importation of active substances," a spokesperson for the EC told *Pharmaceutical Technology Europe*. The European Federation of Pharmaceutical Industries and Associations (EFPIA), the main trade body for research-based pharmaceutical companies, also confirmed that it had not yet received any reports from its members about any immediate difficulties with imported API supplies after 2 July. An EFPIA official, however, informed *Pharmaceutical Technology Europe* that "it is too early to assess properly the impact of the new system."

Exemption from written confirmation

To date, four countries (i.e., US, Japan, Australia and Switzerland, which is a non-EU country), have been excluded from the requirement for written confirmation on grounds that their regulatory and monitoring standards on GMP are equivalent to those of the EU. Several other countries, including Brazil, Mexico, Singapore and Israel, have applied to be exempted, or to have previous refusals of exemptions reviewed, according to the EC. The regulation also enables the authorities in the EU's 28 member states to apply various waivers when implementing the written confirmation requirement. If, for example, an API plant has already been inspected and given a GMP certification by EU inspectors, written confirmation may be considered to be unnecessary.

Nonetheless, exactly how the new rules are being applied in individual EU countries has been unclear because of delays in including the FMD regulations in national statutes. By early August, eight of the 28 member states were yet to transpose the written confirmation obligation into their laws. In other countries, the implementation date has been held back. For example, in the UK, the requirement was not in full effect until 20 August.

In most countries, the checking of whether an imported API is accompanied by a written confirmation is left to the individual pharmaceutical manufacturers. Without the confirmation, a medicine with the imported API cannot be marketed legally in the EU. "(We) will monitor compliance with the rules in relation to finished-product manufacturers as well as companies importing active substances," explained the Danish Health and Medicines Authority in a statement on the new rules (1). "The Danish customs authorities will not check whether the import rules have been observed." On the other hand, countries, such as Spain, are verifying compliance through import controls at their borders while Germany and the Netherlands are planning to do the same.

Alternative suppliers

Some manufacturers were quick to react to the possibility of new restrictions on imported APIs at the time when the FMD was being debated in the European Parliament and the European Council representing EU governments. They signed deals with alternative API suppliers with GMP certification, particularly those based in the EU. "In a recent survey of our members, we found that many of them had been asked by European pharmaceutical companies to become second-source suppliers of their active substances," said Tony Scott, advisor to the European Fine Chemicals Group (EFCG), representing EU producers of APIs.

National licensing authorities have been working closely with their countries' pharmaceutical manufacturers to pinpoint API sources that may have difficulties complying with the new EU restrictions. Risk assessments of potentially problematic active ingredients have been carried out. These assessments investigate reasons for the absence of written confirmations, levels of existing stocks of the APIs with the medicine manufacturers and the availability of alternative products and treatments. "(We are) aware of 107 risk assessments being carried out by member states although it is highly likely that many more have been done," says an official at the European Medicines Agency (EMA). EMA has been monitoring the implementation of the written confirmation requirement.

On the basis of the results of the risk assessments, national authorities have been helping pharmaceutical companies to take precautionary measures. "Some API sources for UK finished-product manufacturers were (shown to be) potentially at risk," a spokesperson for the UK Medicines and Healthcare Products Regulatory Agency (MHRA) told *Pharmaceutical Technology Europe*. "However, further analysis by the manufacturers showed that such risks could be mitigated, for example, by stocks being held and the use of alternatives from approved API sources. The situation is being kept under review by MHRA at a UK level and by the weekly meetings at an EU level."

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EUROPEAN **REGULATORY** WATCH

Due to concerns about possible medicines shortages in the short to medium term, EU regulators have been prioritising inspections of some non-approved plants outside Europe by EU GMP inspectors. "(We know) of 12 future planned inspections of sites for which no written confirmation is available although some of these inspections may ultimately not be necessary as more non-EU authorities start issuing written confirmations," the EMA official told *Pharmaceutical Technology Europe*. "In addition, EMA is aware of three EU inspections that have been carried out although it is highly likely that there have been more."

India and China step up GMP standards

In the longer term, EU regulators are hoping that India and China, which between them have more than 900 sites exporting APIs to Europe, will establish comprehensive and reliable GMP inspection systems that will eliminate the problem of certification of exported active substances. In India, the Central Drugs Standard Control Organisation (CDSCO), part of the country's Ministry of Health and Family Welfare, has been issuing written confirmations. Details of the confirmation with names of the APIs are available on the CDSCO website.

China only began issuing written confirmations this spring through the Chinese Food and Drug Administration (CFDA), which supervises GMP inspections but only in pharmaceutical plants. It has no responsibility for GMP standards in chemical plants making and exporting APIs. "China is a very big country so there are difficulties with quality standards in APIs production while there is also a need for harmonisation of GMP inspections," commented Stefan Kettelhold, lead auditor at Germany's blue inspection body GmbH, which does a lot of auditing work in China. "The Chinese government used to concentrate on raising production standards of companies supplying the domestic market. With the new legislation, it is also focusing on GMP of API suppliers for the international market. The Chinese authorities want to see a general upgrading of standards in pharmaceuticals."

One likely result of tougher domestic and international regulations on production standards in India and China will be a consolidation among API manufacturers. There will be fewer of them, but they will be able to ensure that their active substances are of a more consistently acceptable quality than at present.

Reference

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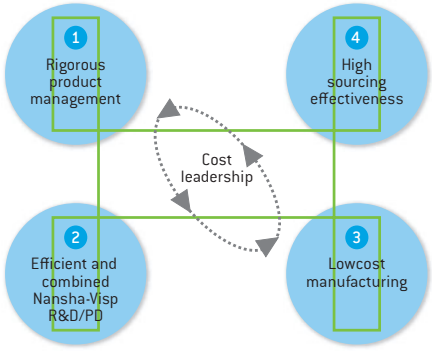

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FDA Works to Secure Drug Supply Chain

New policies aim to strengthen inspection and oversight processes.

Key to implementing the United States FDA Safety and Innovation Act (FDASIA) of 2012 is for the US Food and Drug Administration to issue new regulations and guidance that will help manufacturers understand how the agency aims to strengthen oversight of today's global drug industry. Title VII of FDASIA provides added authority for FDA to inspect drug-production facilities; to block import of adulterated and substandard medical products; to require adherence to manufacturing standards and to crack down on violators.

New provisions under Title VII of FDASIA

Agency leaders marked the first anniversary of FDASIA at a public meeting on 12 July 2013. The meeting updated industry on how the new policies will affect operations and ensure a more level playing field between suppliers and manufacturers at home and abroad. It also gave all parties an opportunity to comment on agency proposals for strengthening FDA authority over drug imports. FDA commissioner Margaret Hamburg opened the meeting by noting the importance of collaborative efforts with other regulators, with the industry and with crucial stakeholders in better securing a "more complex and more global supply chain." Most notable was her announcement of a new proposed rule and a draft guidance document, the first of several such documents required to flesh out the FDASIA policies.

John Taylor, counselor to the commissioner and now acting deputy commissioner for global regulatory operations and policy, similarly noted the vast increase in countries, importers and foreign facilities that produce FDA-regulated therapies. Title VII provides FDA with stronger tools to use against firms that refuse inspections or seek to import noncompliant products. And stiffer penalties for drug counterfeiting have been authorised by the US Sentencing Commission to go into effect in November 2013.

Additional data and information on facilities and operations will support a more effective system for targeting inspections and oversight of imports. These data are important for implementing Title VII's various programs and requirements, explained Susan de Mars, senior advisor to the Office of Global Regulatory Operations & Policy. All manufacturing establishments now have to register with FDA and provide unique facility identifiers (UFIs) that will populate an electronic database able to track manufacturer operations, identify importer compliance and generate information related to lost, stolen or counterfeit products.

FDASIA's provisions enhance partnerships and collaboration with foreign regulators, making it easier for FDA to exchange confidential information with peer regulators. The agency gains flexibility to recognise or rely on inspections of other regulators, which can help extend FDA's limited resources, de Mars noted. FDA has been engaged in several inspection collaborations, and the legislation should lead to more formal recognition and mutual reliance on foreign government inspection findings.

Inspections intensified

A key FDASIA goal is to strengthen FDA's authority to inspect manufacturing facilities in the US and abroad. By eliminating the traditional requirement that FDA inspect domestic drug facilities every two years, the legislation supports a shift to a risk-based inspection system that targets high-risk firms. FDASIA also authorises FDA to examine facility records electronically and in advance of a site visit, which can help the agency determine whether or not to actually conduct the inspection at that time.

If FDA determines during an inspection that certain drugs may be adulterated or misbranded, it now can detain those products, instead of waiting for a court order to do so, which can give unscrupulous operators a chance to distribute the violative products. FDA describes how it will implement this new policy in a proposed regulation, which is similar to the policy already in force for medical devices and food (1).

New draft guidance further clarifies how FDA plans to conduct full and complete inspections of factories, warehouses and other facilities involved in drug production (2). The guidance spells out how firms that delay, deny access or limit inspections may have their products deemed misbranded and adulterated and not fit for sale in the US. The document lists prohibited behaviours that could delay the scheduling of inspections or an inspection in process, such as failure to produce requested records in a timely manner. And it spells out how manufacturers can run into trouble by preventing an inspector from beginning or completing a site visit. FDA specifies that its agents have the right to access and copy records and to collect product samples as needed, including samples of finished products, raw materials, in-process materials, reserve samples and environmental samples.

One notable paragraph states that FDA inspectors have authority to photograph facility conditions, an issue that has been the subject of heated legal debate for years. Lawyers already are questioning whether FDASIA actually does permit agency officials to use cameras during an inspection, and Doug Farquhar of Hyman, Phelps & McNamara speculates in the *FDA Law Blog* whether a company that refuses to permit photography will end up as a test case in court (3). FDA would like to receive comments on the guidance by 13 Sept., 2013.

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Overseeing imports

A main purpose of the July public meeting was to provide manufacturers and other stakeholders with an opportunity to comment on FDA proposals for setting standards for imports, for registering commercial importers and for devising good importer practices (GIPs). FDA expects GIPs to address registration requirements for commercial importers, exemptions (possibly for research products) to importer regulation and the importance of importers meeting broader compliance standards, such as GMPs or demonstrating a satisfactory inspection history. One issue, noted FDA senior policy advisor Brian Pendleton, is whether importers should be required to establish drug-safety management programs as part of GIPs.

There was discussion about how useful a certificate of analysis is in documenting product authenticity, or if these forms are too easily falsified. The United States Pharmacopeia Convention (USP) proposed that compendia standards serve as a key marker for importer compliance. Excipient producers requested an exemption from import restrictions, noting that foreign producers ship large quantities of excipients to the US for a broad range of uses, making it impossible to segregate out those products specific to pharmaceutical production.

Another important topic is whether to permit compliant importers to qualify for expedited clearance procedures. US manufacturers would like to see risk-based standards for those importers that meet high standards, noted Sarah Spurgeon, assistant general counsel at the Pharmaceutical Research and Manufacturers of America (PhRMA). Industry representatives also proposed that GIP requirements might differ based on the type of drug imported, company inspection history and evidence of supply-chain controls.

The globalisation of drug production is a positive development, in that manufacturers can make products anywhere and market them worldwide via the Internet, noted John Taylor. But FDA "can't just do more inspections and more examinations of imports," he said. Instead, the agency needs to engage in inter-agency activities within the US and collaborate more with international regulatory and health organisations. FDA will be issuing a number of regulations and guidance documents to implement its new programs and is looking for manufacturers to help weigh all the options.

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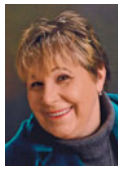

Susan J. Schniepp
is vice-president of quality and regulatory affairs at Allergy Laboratories and is a member of the *PharmTech* Editorial Advisory Board.

The Elements of Training

Establishing a well-defined training programme that ensures employees have the appropriate combination of knowledge, skills and experience to perform their job functions is a crucial activity for any organisation.

Training represents one of the key elements that management can use to assure a consistent, high quality, product. Codifying the elements of the training programme will help a company maintain compliance to the regulations and address regulatory concerns about employee qualifications that might arise during inspections. Some companies are fortunate to have either a training department or a training coordinator to define and administer the programme. Companies that do not have either should establish a training team with representatives from the quality assurance, quality control and operations departments at a minimum. There should be approximately four parts to any training program: the introductory training requirements for new employees, the annual training requirements for all employees regardless of function, the continuing education training expectations, and special training requirements that may be required for continuous quality and process improvements. The first three may be tracked with a training matrix.

Introductory training requirements

New employees should be initially trained on applicable GMPs, good documentation practices (GDPs), and any additional global requirements impacting their jobs. It is prudent for a company to develop a quiz or test to demonstrate the new employee's comprehension of these basic requirements with an established minimum passing percentage. The minimum percentage must be achieved before the employee is considered to have the basic knowledge needed to work in the company. Incorrect answers should be discussed as part of the process. If the required minimum is not achieved, the prospective employee should be provided additional instruction on the material and a different test should be employed to measure comprehension. If the minimum required comprehension level is still not achieved, the quality assurance department should inform the hiring manager and indicate the new employee is not suitable for employment. Once new employees have passed the minimum understanding requirements on the quizzes, they should then be trained on company policies and specific job-related standard operating procedures (SOPs).

Annual training requirements

Companies should perform annual refresher training on a variety of topics. At a minimum, it is recommended that employees be retrained annually on cGMPs and cGDPs. Additional yearly training topics could be tailored to the type of operations being conducted at the facility. If the company is manufacturing parenteral products, the annual training programme might include modules on microbiological control in aseptic manufacturing and conducting investigations/root cause analysis. This yearly training should also measure employee comprehension of the material. This comprehension might be measured in a variety of ways including but not limited to written quizzes, oral quizzes and hands-on demonstration. Whichever way is chosen to assess the employee's comprehension of the material, it should be noted on individual training records.

Continuing education training requirements

Employees should be encouraged to enhance their job-specific knowledge and skills by attending external training conferences, seminars and activities. The training team should be responsible for reviewing literature and recommending which employees should attend specific courses to enhance their skills and knowledge. The benefits of the external training should be discussed with senior management. There are several organizations that provide seminars, training classes and symposia including the American Society for Quality, the Parenteral Drug Association, the American Chemical Society, and for-profit organisations.

Special training

Companies need to recognise there may be occasions when special training is required for employees. The responsibility for determining the need for special training will reside with the training team but should be performed using qualified trainers with recognised expertise in the specific discipline being addressed. Using qualified trainers in this situation assures the attendees will be trained by experts that will understand questions that may arise during training. As with all training, a record of the training should be put into the employee's personnel folder.

When a company invests in the future of its employees by establishing a comprehensive training programme, they need evidence that the monies were well spent. To assure continued funding for training, management should establish metrics to monitor performance as a practical measure of the ongoing effectiveness of training activities. By continuing to invest in training, companies invest in their employee's futures and develop a knowledgeable, skilled and experienced workplace as well as a culture supporting continual improvement and growth. **PTE**

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EMERGING MARKET REPORT

Report from: Brazil

Hellen Berger

Pharma eyes biologics production in Brazil as the government begins to recognise the potential of these drugs.

In Brazil, there are indications that the pharmaceutical industry has been living relatively comfortably despite global difficulties. Due to improved wages and jobs created over the past few years, thousands of Brazilians who never had access to drugs have been investing in healthcare and purchasing medicines, not only to treat illnesses but also as a means of prevention.

According to the Brazilian Association of National Laboratories Distributors (Abradilan), figures from IMS Health show that sales of pharmaceutical drugs in Brazil are expected to rise 15–20% this year compared to (Brazilian Real) R$49.6 billion (approximately US$21.6 billion) in 2012. The Gross National Product (GNP) for 2013 is expected to be 2.28% higher this year, according to Brazil's Central Bank.

In 2011, the so-called "C class," which represents 53% of the 200-million population in Brazil, contributed to 42% of the domestic sales of pharmaceutical drugs in 2011, while the wealthy "A and B classes" were responsible for 48% of total sales, according to IMS Health. Companies operating in Brazil are beginning to understand that it is important to target the middle class as they outnumber the wealthier classes and are willing to pay for all types of goods, including pharmaceuticals. As a result, production of pharmaceutical drugs is on the rise despite the high costs and taxes in Brazil. Investment plans, however, are ongoing with opportunities seen ahead, especially for biological drugs.

Government plans include local production

Biological drugs are cellular- or tissue-based medical products. They include, among others, vaccines, blood components and living cells used to treat various diseases. The production is mainly though gene-modification processes, rather than synthetic. Producers have reported that biological drugs have greater accuracy to treat illnesses according to the Industry Syndicate of Pharmaceutical Products in the State of São Paulo (Sindusfarma).

The government is willing to pay as much as 25% more for locally produced biological drugs compared to what it pays for imported products.

In an interview with *Pharmaceutical Technology Europe*, Nelson Mussolini, executive president for Sindusfarma, said that "there is no doubt that biological drugs have great potential in Brazil. They will add to other drugs offered by the country's public health system to treat illnesses such as rheumatoid arthritis, asthma and various types of cancer. This fact can be proven by the actions developed by the Brazilian government to implement local production of biological drugs, through its Health Ministry and the Bank of Economic and Social Development (BNDES)."

According to Mussolini, Sindusfarma associates correspond to more than 90% of Brazil's pharmaceutical market share, hosting companies that promote both national and international research as well as commercialise biologics and biosimilar products. "The health ministry would guarantee purchasing these drugs under the public health system and

JEREMY WOODHOUSE/GETTY IMAGES

the BNDES would guarantee funding and financing for research and production of biological products," added Mussolini.

The topic of biologics production has definitely caught the interest of policy makers, and the pharmaceutical industry sees it as an opportunity given that the government in Brazil is developing the biologics market. The Brazilian government strongly supports research partnerships in this field and is encouraging local production of biological drugs. According to Sindusfarma, the government is willing to pay as much as 25% more for locally produced biological drugs compared to what it pays for imported products.

Mussolini noted that while Argentina is also taking steps to localise production of biologics, Brazil will likely be the main player in Latin America for these products because of its growing pharmaceutical market. Although the biologics market is in its infancy and, therefore, specific figures are difficult to obtain, investments in this area have already been officially confirmed.

New production facility confirmed

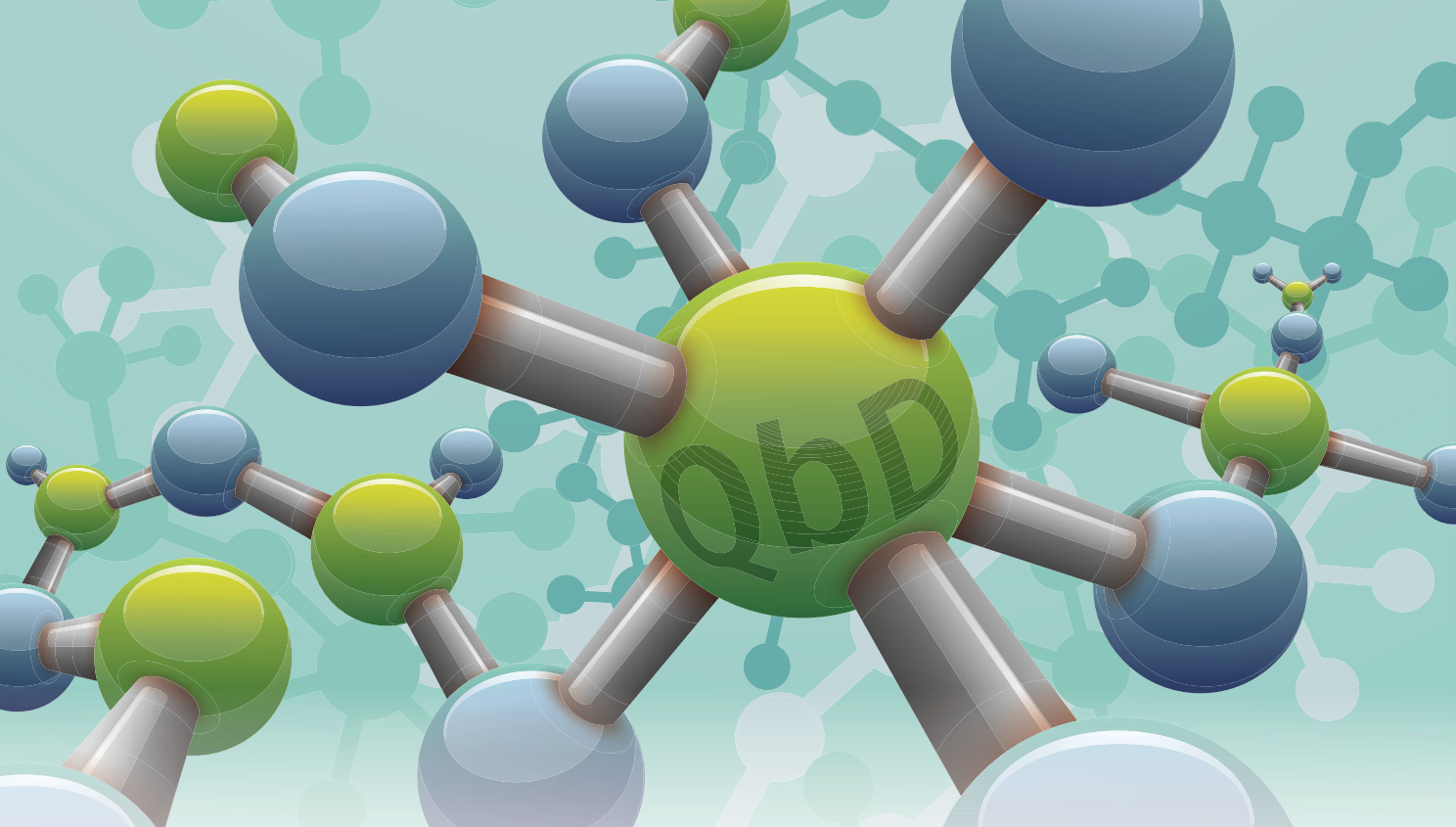
Novartis told *Pharmaceutical Technology Europe* that the company will be building a new facility to produce biological drugs in Brazil. The Swiss pharmaceutical company will invest R$1 billion (approximately US$ 435 million) in a unit located in Jaboatão dos Guararapes, in the Northeastern state of Pernambuco, to produce vaccines against Hepatitis B.

Novartis Brazil said this plant will be the company's first vaccine production site in Latin America. Construction is expected to be completed by June 2014, while production has been scheduled to start in 2016 according to the company.

According to Novartis, the company plans to export part of its vaccines output from the new plant and gradually transform the unit into a full-scale biologics producer. Novartis and Brazil's federal government have signed transfer-of-technology (TOT) deals to produce drugs in government-owned facilities, hence, making the country less dependent on imported products and technologies.

Novartis is not the only company to sign TOT deals with the federal government. The country's health ministry stated that it is negotiating approximately 27 deals with public and private laboratories to produce as many as 14 biological drugs nationally. The ministry's objective is to increase the number of locally produced biological drugs for the treatment of breast cancer, leukemia, rheumatoid arthritis and diabetes among others. According to government figures, the country would save around R$225 million (approximately US$ 97.8 million) a year with local production, using transferred state-of-the-art technology. With so many incentives, perhaps many other eyes will soon turn to the biological products market in Brazil. **PTE**

*— **Hellen Berger** is a business news correspondent based in São Paulo, Brazil.*



Quality by Design for APIs

The adoption of quality by design in small-molecule drug development and manufacturing continues to evolve as the industry seeks ways to augment process understanding for APIs.

Patricia Van Arnum
is Executive Editor of *Pharmaceutical Technology Europe.*

The science- and risk-based approach in quality by design (QbD) entails greater product and process understanding as a means to ensure product quality. These concepts are embodied in ICH guidelines Q8 (R2) *Pharmaceutical Development*, Q9 *Quality Risk Management*, Q10 *Pharmaceutical Quality System*, and most recently, Q11 *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* (1–4), which offer a lifecycle approach to continual improvement to drug manufacturing.

Traditional versus enhanced approaches

ICH Q11 focuses specifically on the development and manufacture of drug substances. It specifies that a company can follow "traditional" or "enhanced" approaches or a combination of both in developing a drug substance (4). In the traditional approach, set points and operating ranges for process parameters are defined, and the drug-substance control strategy is typically based on process reproducibility and testing to meet established acceptance criteria (4). In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that affect critical quality attributes (CQAs) (4). The enhanced approach further includes the development of appropriate control strategies applicable over the lifecycle of the drug substance that may include the establishment of design space(s) (4).

Manufacturing process development should include, at a minimum, according to ICH Q11:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug-product quality can be studied and controlled
- Defining an appropriate manufacturing process
- Defining a control strategy to ensure process performance and drug-substance quality (4).

An enhanced approach to manufacturing process development would additionally include:

- A systematic approach to evaluating, understanding and refining the manufacturing process, including identifying—through prior knowledge, experimentation and risk assessment—the material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters that can have an effect on drug substance CQAs
- Determining the functional relationships that link material attributes and process parameters to drug substance CQAs (4).

The enhanced approach, in combination with quality risk management, is used to establish an appropriate control strategy. Those material attributes and process parameters important to drug-substance quality should be addressed by the control strategy. The risk assessment can include an assessment of manufacturing process capability, attribute detectability and severity of impact as they relate to drug-substance

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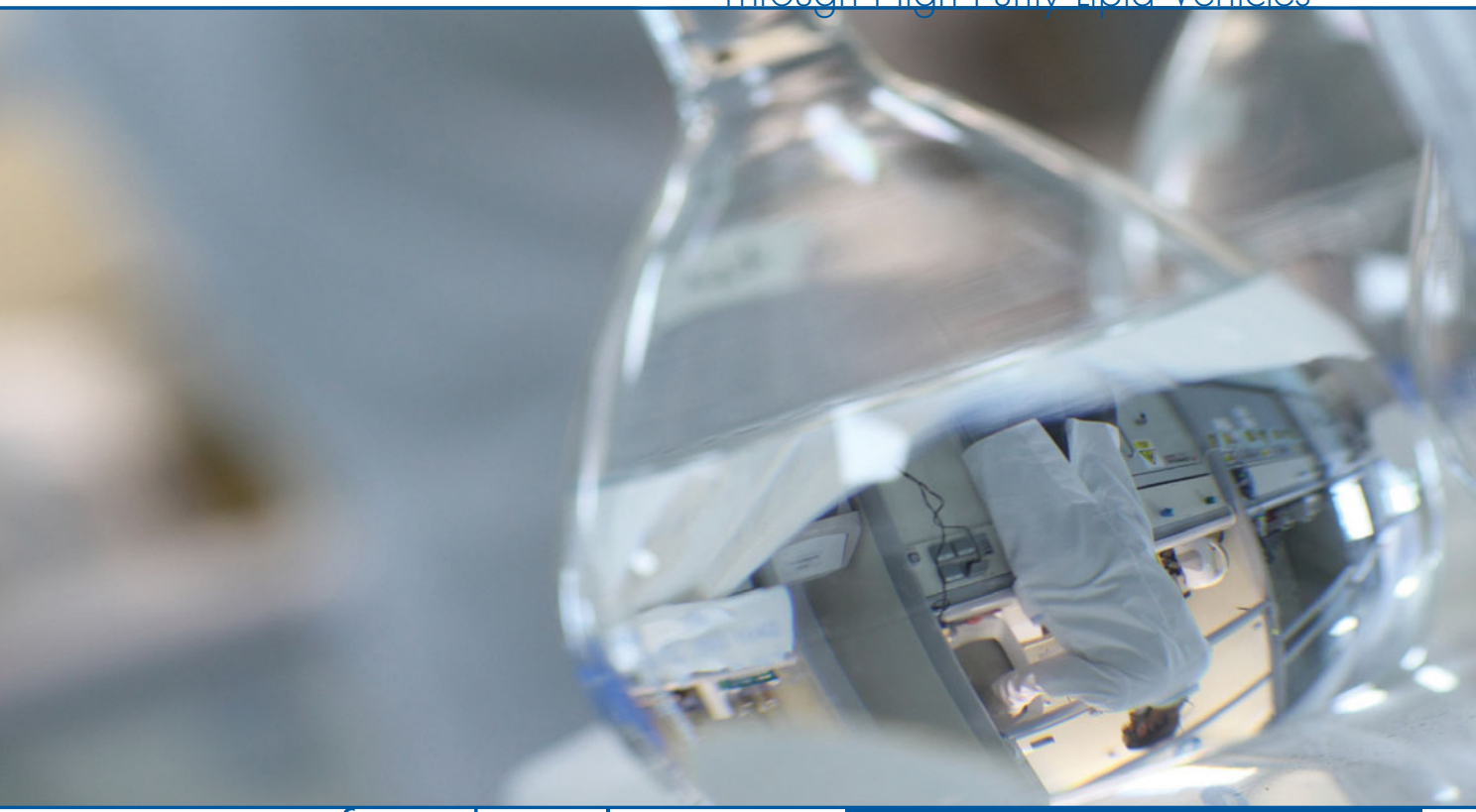

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quality (4). For example, when assessing the link between an impurity in a raw material or intermediate and drug-substance CQAs, the ability of the drug-substance manufacturing process to remove that impurity or its derivatives should be considered in the assessment (4). The risk related to impurities can usually be controlled by specifications for raw material/intermediates and/or robust purification capability in downstream steps. It is important to understand the formation, fate (whether the impurity reacts and changes its chemical structure), and purge (whether the impurity is removed via crystallisation, extraction, etc.) as well as their relationship to the resulting impurities that end up in the drug substance as CQAs (4). The process should be evaluated to establish appropriate controls for impurities as they progress through multiple process operations (4).

Those material attributes and process parameters that are found to be important to drug-substance quality should be addressed by the control strategy.

Understanding regulatory expectations

In March 2011, the European Medicines Agency and US Food and Drug Administration launched a three-year pilot program for a parallel assessment by both agencies of certain quality and chemistry, manufacturing and control (CMC) sections of new drug applications submitted to FDA and marketing authorisation applications (MAAs) submitted to EMA that are relevant to QbD, such as development, design space and real-time release testing. The objective of the pilot, which is scheduled to end 31 Mar. 2014, is to ensure consistent implementation between the European Union and the United States of ICH guidelines Q8, Q9, Q10 and Q 11 and to facilitate sharing of regulatory decisions (5–7).

In August 2013, the agencies reported that the first EMA–FDA parallel assessment of QbD elements of an initial MAA was successfully finalised as well as some consultative advice procedures. In a question-and-answer format, the EMA and FDA reported on their expectations as they relate to quality target product profiles (QTPPs), CQAs, classification of criticality and application of QbD in analytical method development (7).

With respect to the QTPP, the agencies specified that they expect applicants to provide the QTPP, which describes prospectively the quality characteristics of a drug product that should be achieved to ensure the desired quality, safety and efficacy of the drug product. With respect to CQAs, the agencies expect applicants to provide a list of CQAs for the drug substance, finished product and excipients when relevant. This list should also include the acceptance limits for each CQA and a rationale for designating these properties as a CQA. Furthermore, there should be a discussion of how the drug substance and excipient CQAs relate to the finished product CQAs based on prior knowledge, risk assessment or experimental data. The basis of the control strategy is to ensure that the drug substance and finished product CQAs are consistently within the specified limits (7).

Another issue was whether the agencies would accept a three-tier classification of criticality for process parameters. The agencies responded that ICH Q8 (R2) specifies that a critical process parameter is one whose variability has an impact on a CQA and needs to be monitored or controlled to ensure the process produces the desired quality. EMA and FDA cited a regulatory submission in which the applicant proposed an approach to risk assessment and determination of criticality that included a three-tier classification ("critical," "key," and "noncritical") for quality attributes and process parameters. Using this classification, a "critical" factor was defined as a factor that led to failure during experimentation. A factor that had not led to failure within the range studied, but still may have an impact on product quality, was considered as a "key" factor. The agencies said that they do not support the use of the term "key process parameters (KPP)" because it is not ICH terminology and there is differing use of the term "key" among applicants. Although FDA and EMA said they are amenable to this terminology in the pharmaceutical development section to communicate development findings, they are not in describing the manufacturing process, process control and control of critical steps and intermediates, where the description of all parameters that have an impact on a CQA should be classified as critical (7).

The agencies further specified that process manufacturing descriptions be comprehensive and describe process steps in a sequential manner, including batch size(s) and equipment type. The critical steps and points at which process controls, intermediate tests or final product controls are conducted

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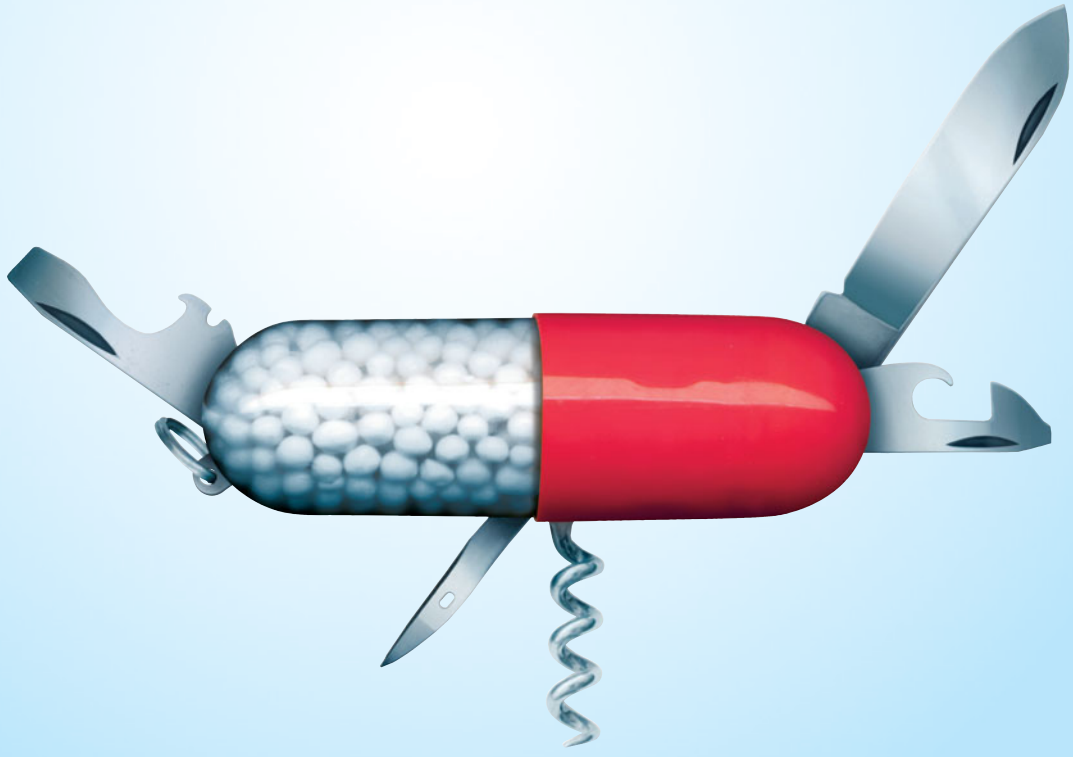

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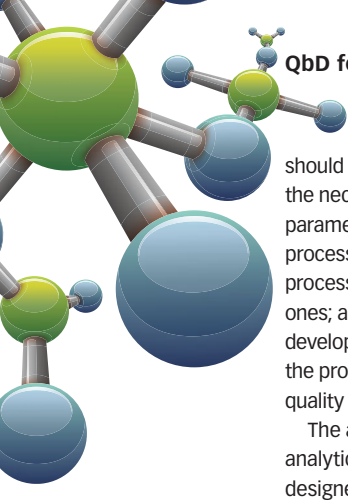

should be identified (7). Steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges. The process parameters that are included in the manufacturing process description should not be restricted to the critical ones; all parameters that have been demonstrated during development as needing to be controlled or monitored during the process to ensure that the product is of the intended quality need to be described (7).

The agencies also commented on QbD as it relates to analytical methods using risk assessments and statistically designed experiments to define analytical target profiles (ATP) and method operational design ranges (MODR) for analytical methods (7). "There is currently no international consensus on the definition of ATP and MODR," noted the agencies. "Until this is achieved, any application that includes such proposals will be evaluated on a case-by-case basis" (7). The agencies noted, however, that an ATP can be acceptable as a qualifier of the expected method performance by analogy to the QTPP as defined in ICH Q8 (R2), but the agencies would not consider analytical methods that have different principles (e.g., high-performance liquid chromatography and near-infrared [NIR] spectroscopy) equivalent solely on the basis of conformance with the ATP. "An applicant should not switch between these two types of methods without appropriate regulatory submission and approval," they said. The agencies also noted that similar principles and data requirements could apply for MODRs. For example, data to support an MODR could include: appropriately chosen experimental protocols to support the proposed operating ranges/conditions and demonstration of statistical confidence throughout the MODR. Issues for further reflection include the assessment of validation requirements as identified in ICH Q2 (R1) throughout the MODR and confirmation of system suitability across all areas of the MODR (7). The agencies further indicated that future assessment of the pilot program will include other lessons learned in areas such as design-space verification, the level of detail in submissions for design space and risk assessment, continuous process verification and continuous manufacturing.

QbD at work

A review of recent literature reveals some interesting applications of QbD in drug-substance development and manufacturing. For example, scientists at Bristol-Myers Squibb reported on a process-modeling method using a QbD approach in the development of the API ibipinabant, a cannabinoid receptor 1 antagonist being developed to treat obesity (8). In its development, the molecule had volume requirements of 6 kg for toxicology studies and formulation development, which later increased to 175 kg for late-stage clinical trials. The researchers used mechanistic kinetic modeling to understand and control undesired degradation of enantiomeric purity during API crystallisation. They implemented a work flow, along with kinetic and thermodynamic process models, to support the underlying QbD approach and reported on the use of risk assessment, target quality specifications, operating conditions for scale-up and plant control capabilities to develop a process design space. Subsequent analysis of process throughput and yield defined the target operating conditions and normal operating ranges for a specific pilot-plant implementation. Model predictions were verified from results obtained in the laboratory and at the pilot-plant scale (8). Future efforts were focused on increasing fundamental process knowledge, improving model confidence and using a risk-based approach to re-evaluate the design space and select operating conditions for the future scale-up (8).

Scientists at Merck & Co. reported on their work in applying QbD to set up an improved control strategy for the final five steps in the production route of a legacy steroidal contraceptive, which has been produced for more than 20 years within its facilities (9). A generic ultra-high-performance liquid chromatography method was developed according to QbD principles to create a range of proven acceptance criteria for the assay and side-product determination for the final five steps in the production route of the API (9).

Scientists at Eli Lilly reported on a systematic approach consisting of a combination of first-principles modeling and experimentation for the scale-up from bench to pilot-plant scale to estimate the process performance at different scales and study the sensitivity of a process to operational parameters, such as heat-transfer driving force, solvent recycle and removed fraction of volatiles (10). This approach was used to predict process outcomes at the laboratory and pilot-plant scale and to gain a better understanding of the process. The model was also used further to map the design space (10).

contin. on page 70

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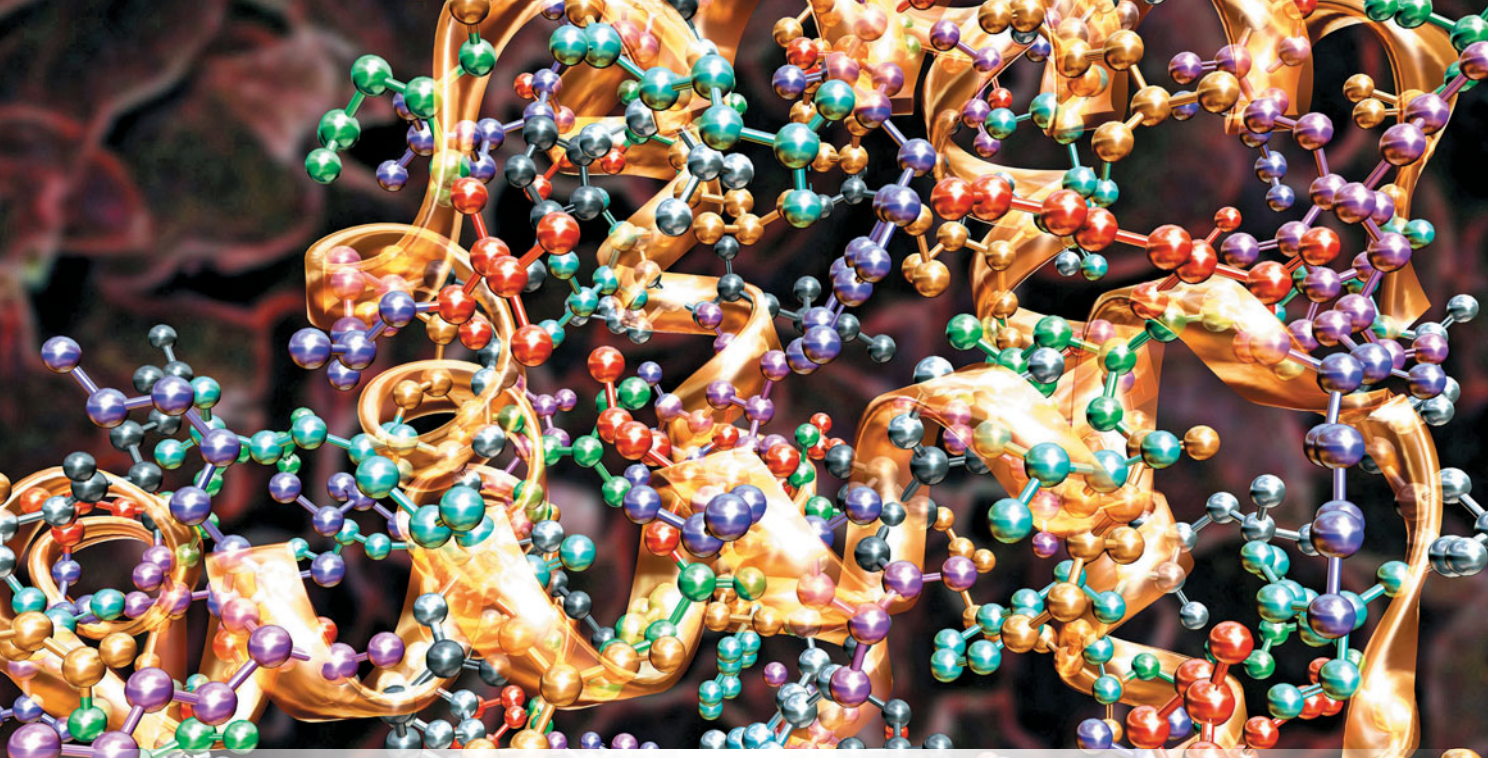

The Importance of Characterisation in Biosimilars Development

Industry experts discuss the requirements and challenges involved in getting a biosimilar product from bench to launch.

Adeline Siew, PhD

The global market for biosimilar drugs has been forecasted to be worth $2.445 billion in 2013 (1). The growth corresponds to a 20% increase from last year's figures and accounts for approximately 2% of the overall biologics market (1). Although narrowly focused on only a few therapy areas at present, the biosimilars market is set to expand over the next decade and beyond as a result of two major factors: the impending patent expiries on blockbuster biologics and the financial crisis that is driving payers to push for wider adoption of biosimilars to manage the escalating costs of healthcare.

Many companies are keen on getting a share in the biosimilars market given its promising outlook; however, bringing these complex molecules from bench to launch can be a challenge, not just during the development stage but also in terms of the manufacturing process involved. *Pharmaceutical Technology Europe* conducted a roundtable to gain further insight on this topic. Participants included: Sheen-Chung Chow, PhD, professor, Department of Biostatistics and Bioinformatics at Duke University School of Medicine; Christina Satterwhite, PhD, director of laboratory sciences, Charles River Laboratories; Fiona Greer, PhD, global director, biopharma services development, Bruno Speder, team leader of clinical trial regulatory affairs, Clinical Research, and Rabia Hidi, PhD, director of biomarkers & biopharmaceutical testing, Laboratory Services, all three at Life Sciences Services at SGS.

The complex nature of biosimilars

PTE: Why are biosimilars not approved in the same way as generics?

Sheen-Chung Chow, PhD, professor, Department of Biostatistics and Bioinformatics, Duke University School of Medicine

Chow (Duke University): The regulatory approval pathway is well established for generic drugs; however, it cannot be applied to biosimilars due to fundamental differences between generic drugs and biosimilars. For example, generic drugs are small-molecule drug products that contain 'identical' active ingredient(s) as the branded drug. Biosimilars, on the other hand, are made of living cells or living organisms that are sensitive to environmental factors such as light and temperature during the manufacturing process. Biosimilars usually have mixed and complicated structures that are difficult, if not impossible, to characterise. As a result, biosimilars are not generic drugs.

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Fiona Greer, PhD, global director, biopharma services development, SGS

Greer (SGS): Biosimilar drugs cannot be regarded in the same way as generics. The exact structure of small-molecule synthetic drugs and their impurities can be well defined chemically, which enables generic manufacturers to avoid full, costly clinical studies if they are able to establish that their product is 'bioequivalent' in pharmacokinetic studies to the branded or listed drug. However, unlike small-molecule drugs, biologically derived products are large, complex protein molecules, usually comprising of a mixture of closely related species that undergo post-translational modifications, which influence the anticipated protein structure. When produced in mammalian expression systems, these proteins can also be glycosylated (i.e., the carbohydrate is attached to the protein backbone), thereby, further increasing the amount of heterogeneity in the glycoforms produced.

In addition, the complexities of cellular expression and biomanufacturing make exact replication of the originator's molecule nearly impossible; the process will certainly be different. Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants, or post-translational modifications (e.g., the glycosylation profile) can be significantly altered by changes, which may initially be considered to be 'minor' in the manufacturing process, but can greatly affect the safety and efficacy profiles of these products. Biosimilars are, therefore, not simple generics. The fundamental difference with complex protein molecules is that they cannot be absolutely identical to the original. Instead, companies developing these 'copies' must demonstrate that they are similar by performing a side-by-side comparison with reference samples of the originator.

Christina Satterwhite, PhD, director of laboratory sciences, Charles River

Satterwhite (Charles River): Biosimilars are not approved in the same way as generics because they are similar but not identical to the original biological products due to the manufacturing processes used to generate these types of molecules. A biosimilar is a biologically derived product that can have subtle structural differences with each manufacturing process, which may result in different properties.

Biosimilars are made of living cells or living organisms that are sensitive to environmental factors such as light and temperature during the manufacturing process.—*Chow*

The road to approval

PTE: Could you briefly describe the legal and regulatory approval pathways for biosimilars in Europe and the United States?

Bruno Speder, team leader of clinical trial regulatory affairs, Clinical Research, SGS

Speder (SGS): Both the European and US regulatory pathways depend on being able to demonstrate 'biosimilarity' involving rigorous comparison against batches of originator product, initially at the physicochemical level, then in a step-wise manner in safety, potency and clinical studies. Only an originator product that was licensed on the basis of a full registration dossier can serve as a reference product (i.e., centralised procedure in Europe and new drug application in the US). Both in Europe and the US, extensive consultation with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), respectively, is required.

Greer (SGS): The European Union established the first legal regulatory guidelines for 'similar biological medicinal products' (i.e., biosimilars) (2–4). Subsequently, specific product annexes were published (5). Several of the original guidelines have been, or are in the process of being, revised. The first biosimilar molecule approved in Europe in April 2006 was Omnitrope, a version of somatropin. All guidelines, plus current revision concept papers and drafts, are available on the EMA website (5).

Meanwhile, in the US, the Biologics Price Competition and Innovation Act (BPCIA) provides a new pathway for biosimilars—the 351(k) route of the Public Health Service (PHS) Act. This pathway also requires comparison of a biosimilar molecule to a single reference product that has been approved under the normal 351(a) route with reference to prior findings on safety, purity and potency. In contrast, one aspect of the legislation unique to the US is the provision for two levels of product—'biosimilar' and 'interchangeable biosimilar.' An interchangeable biological product is one that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. Therefore, more data are required for a product to be labeled as interchangeable rather than biosimilar.

In February 2012, FDA published three draft guidance documents to assist biosimilar developers: *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (6), *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (7) and *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (8). Earlier this year, a fourth guidance, dealing with scientific meetings, was issued (9).

Satterwhite (Charles River): The EU has developed a science-based regulatory guidance framework from 2005 to the present to ensure high-quality biosimilar drugs. The biosimilars pathway in the US was created under the Patient Protection and Affordable Care Act in 2010; however, US regulations are still

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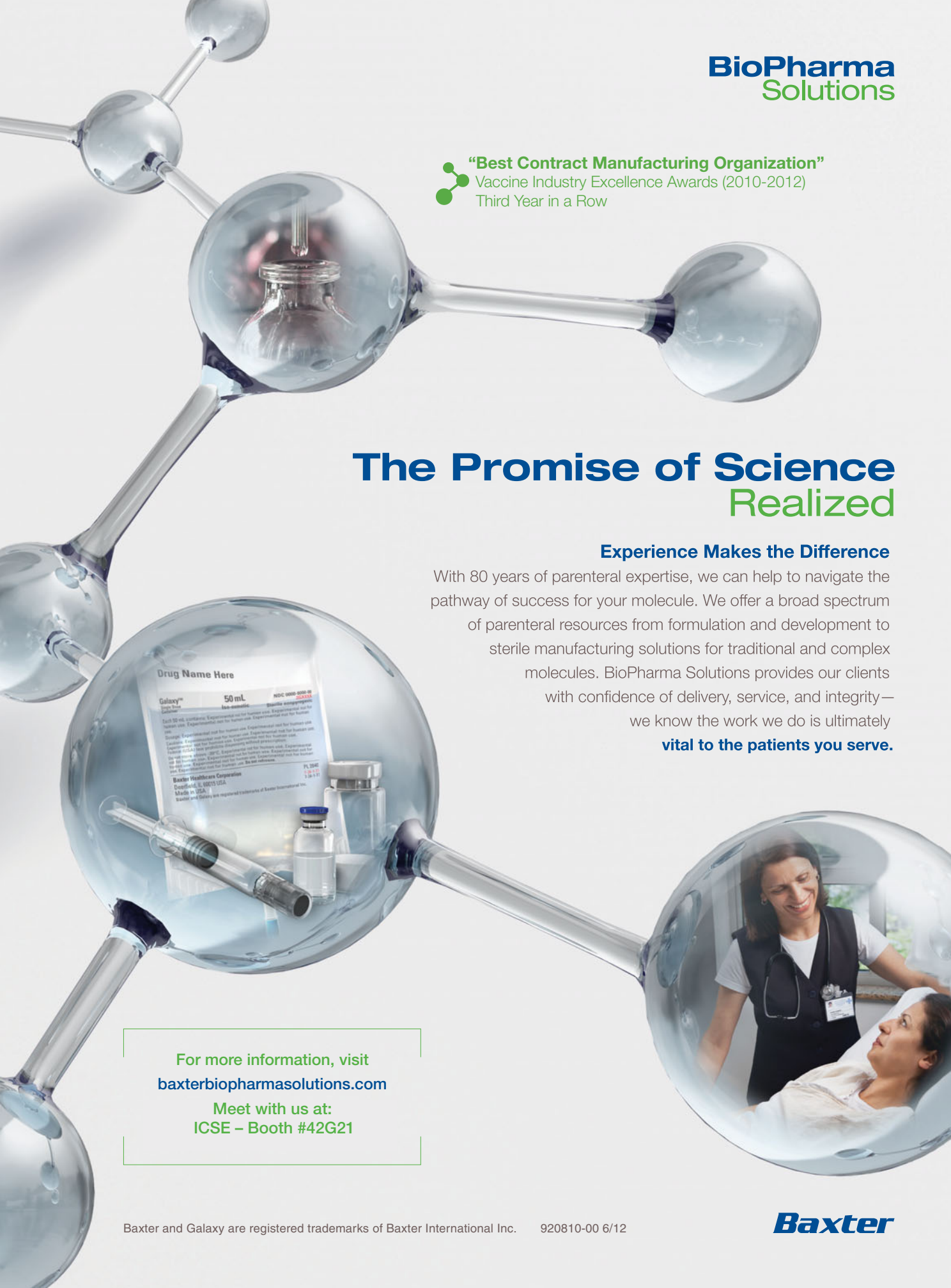

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pending. Three draft guidances were released in February 2012 with a focus on the analytical characterisation and totality of evidence approach to the program. A fourth draft guidance was released in 2013 that emphasised formal meetings between the sponsor and regulators. Many pharmaceutical and biotechnology companies are moving forward using the International Conference on Harmonisation (ICH) and FDA regulatory guidances currently governing biologic submissions and strategies that incorporate the EU biosimilar regulatory guidance. Although the draft guidance is available, there remains some confusion within the industry.

One of the major differences in the testing of biosimilars as opposed to generics is that the drug-development package must not only test structure but also function.—*Satterwhite*

Bioequivalence testing

PTE: Can you explain the procedures for testing the bioequivalence of biosimilars and how it differs from bioequivalence testing for generic drugs?

Chow (Duke University): The current regulation for approval of generic-drug products is based on testing for average bioequivalence. For assessment of biosimilars, it is suggested that testing for biosimilarity should focus on variability rather than average bioavailability alone. Besides, it has been criticised that the one-size-fits-all criterion is not appropriate for assessment of biosimilars.

Satterwhite (Charles River): One of the major differences in the testing of biosimilars as opposed to generics is that the drug-development package must not only test structure but also function. A biosimilar program should commence with a strong analytical package that typically incorporates the testing of protein quantity and purity, amino-acid sequence, glycosylation, physicochemical properties and aggregation analysis. Lot release and stability testing should also be incorporated. In addition, these properties need to be known for the originator drug and multiple lots of the originator drug should, therefore, be evaluated. The type of functional tests evaluated should be based on the mechanism of action of the drug. For example, an anti-CD20 monoclonal antibody may include the following assessments: antibody-dependent cell-mediated cytotoxicity (ADCC) assay, complement dependent cytotoxicity (CDC) assay, flow-cytometry apoptosis assay, flow-cytometry binding assay and Fc receptor assays.

Speder (SGS): Testing the bioequivalence of biosimilars differs from that of standard generics, both in the nonclinical testing as well as in the design of the clinical studies. The bioequivalence of generics is compared in a randomised, two-period, two-sequence, single-dose, crossover-design study. The treatment periods should be separated by a wash-out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally, at least five elimination half-lives are necessary to achieve this. In most cases, no nonclinical studies need to be conducted on the generic product.

For biosimilars, most of which have long half-lives, a crossover study would be ineffective and unethical due to the fact that the wash-out period would be quite long. The patient is not allowed to take the drug during this wash-out period, and hence, will have no treatment for his/her condition. Therefore, parallel-group studies are required, but these studies do not provide an estimate of within-subject variation. For biosimilars, extensive head-to-head nonclinical testing with the originator product is required.

Characterisation studies

PTE: Why is structural and functional characterisation especially important for biosimilars?

Satterwhite (Charles River): The analytical packages that are required for a robust program should be conducted prior to any *in-vivo* testing. The structural *in-vitro* tests, along with the functional *in-vitro* tests, provide necessary information to assess the biosimilarity of the molecules. Similarity is difficult to establish as different manufacturing processes can result in differences in glycosylation sites as well as aggregates. It is important that

Biosimilars development and supply: how complex can the process be?

Martin Van Trieste, senior vice-president of quality at Amgen

The increasing demand for good-quality healthcare comes with the challenge of controlling healthcare expenditure. Biosimilars offer the potential of increasing access to much-needed biologic medicines for patients at a reduced cost, but as this new class of therapeutics is introduced into healthcare systems worldwide, there must be an uncompromising commitment to patient safety, which starts with high regulatory approval standards and ongoing manufacturer accountability. In this article, Martin Van Trieste, senior vice-president of quality at Amgen, explains how the development and supply of these complex molecules is not only scientifically challenging but also capital intensive. Developing a high-quality biologic medicine that is safe and effective requires a commitment to manufacturing excellence and innovator companies often need to invest up billions to bring a biologic product to market.

The full article is available at:
PharmTech.com/biosimilars_MartinVanTrieste

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analytical tests including structural and functional characterisation provide data in which subtle differences are revealed and risk assessment is conducted prior to continuing to the next step in the development program.

Glycosylation is arguably the most important of the numerous post-translational modifications, but what is undeniable is that it presents a unique challenge for analytical methods.—*Greer*

Greer (SGS): The development pathway for a biosimilar is unlike that of a novel biotherapeutic. Undoubtedly, there is an increased requirement for analytics. This enhanced analytical effort, which may be rewarded in the reduced requirement for clinical trials, entails initial physical, chemical and biological characterisation of the biosimilar in comparison to the originator reference product. If found to be 'similar' during this extensive characterisation, subsequent nonclinical and clinical data are then required to demonstrate the same safety and efficacy profiles as the originator compound. However, the premise is that the amount of nonclinical and clinical data required will be much less than for a novel stand-alone application, and generally, a Phase II trial is not necessary. Extensive studies should, therefore, be conducted to provide comparative data for the biosimilar side-by-side with the originator.

Strategies at this stage must include assessment of primary and higher-order structure as well as batch-to-batch variation for the biosimilar and the reference product. In practice, analytical characterisation will follow the requirements of the ICH guideline Q6B (10), including determination of amino-acid sequence, post-translational modifications, including disulfide bridges and glycosylation, and spectroscopic profiles.

One of the most important analytical techniques for biomolecule structural characterisation is mass spectrometry (MS). Usually several different types of instruments are used in the detailed study of a glycoprotein so that the overall structure can be elucidated, including electrospray–mass spectrometry (ES–MS), online ES–MS where the MS is coupled to a high-performance liquid chromatrography (HPLC), matrix-assisted laser-desorption ionisation–mass spectrometry (MALDI–MS), and for derivatised carbohydrates, gas chromatography–mass spectrometry (GC–MS). Apart from the ability to study nonprotein modifications such as sulfation and phosphorylation, the other major strength of an MS approach is in the analysis of mixtures, which has obvious applications in the analysis of heterogeneous glycoforms.

The objective of the comparative study is to establish whether the biosimilar has the same primary protein sequence of amino acids as the reference product. This can be done by using classical protein sequencing (automated Edman degradation), peptide MS-mapping, MS/MS sequencing and amino-acid analysis.

For products that are glycosylated, characterisation of the carbohydrate structure is essential too. Glycosylation is arguably the most important of the numerous post-translational modifications, but what is undeniable is that it presents a unique challenge for analytical methods. The population of sugar units attached to individual glycosylation sites on any protein will depend on the host cell type used, but it will be a mixture of different glycoforms, on the same polypeptide. Powerful MS-based strategies can be used to analyse both free (i.e., underivatised) and derivatised samples to determine sites of glycosylation of both N- and O-linked structures, the identity of terminal nonreducing ends (potentially the most antigenic structures) and the types of oligosaccharide present. Chromatographic anion-exchange methods can also be used for glycan profiling (i.e., the relative distribution of carbohydrate structures).

In addition to MS, a host of other analytical techniques should be used to compare the structure of both the biosimilar and originator at primary and higher-order levels. Various chromatographic, spectroscopic and electrophoretic methods can be used to interrogate and compare on the basis of size, charge and shape. Co- and post-translational modifications, fragmentation, aggregation, deamidation and oxidation should all be studied and compared. Techniques such as near and far UV circular dichroism provide information on the folding and secondary and tertiary structure of the protein and can be used in

Gauging the outlook of the biologics market

Mike Jenkins, general manager of Catalent Biologics development and manufacturing facility in Madison, WI

Biologics are among the most expensive pharmacotherapies as noted by IMS Health, and yet, there is a growing demand for these specialty drugs as they continue to outperform in the global market, delivering novel treatment alternatives for a variety of diseases. The biologics market is fuelled by launches of recombinant insulins, human growth hormones, erythropoietins, granulocyte colony stimulating factors, and the monoclonal antibodies, which are reported to have the strongest R&D pipeline. *Pharmaceutical Technology Europe* spoke to Mike Jenkins, general manager of Catalent Biologics development and manufacturing facility in Madison, WI, about the evolving landscape of the biologics market and the development and manufacture of these innovative products.

The full interview is available at:
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a comparative sense. Depending on the molecule, nonroutine techniques such as protein nuclear magnetic resonance (NMR) and x-ray crystallography may also be used. In fact, a whole panel of methods should be employed, including orthogonal techniques to analyse particular quality attributes. The concept of 'fingerprinting' the molecule has been raised in the FDA guidelines.

It is clear from the new EU guidelines that the primary protein structure (i.e., the amino-acid sequence) must be the same. The guidelines, however, anticipate that minor differences in post-translational forms or product-related impurities may exist and that these products should be investigated with regard to their potential impact on safety and efficacy so that it is the total package of data that will be taken into account on a case-by-case basis. FDA has adopted a similar approach, in that the analytical characterisation should show that it is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components.'

Rabia Hidi, PhD, director of biomarkers & biopharmaceutical testing, Laboratory Services, SGS

Hidi (SGS): An initial step of the comparability exercise is the analysis of the primary structure of the molecule. Change in the primary structure of a biotherapeutic compound could affect the down-stream higher-order composition, which could have impacts on the clinical activity. Essentially the tridimensional structures (tertiary or quaternary) are very important as they could greatly impact the biological function. Finally, post-transcriptional modifications (e.g., phosphorylation, glycosylation, lipid attachment and/or intentional modifications, such as PEGylation), should be thoroughly characterised as these can affect all forms of higher-order structure and can impact efficacy as well as immunogenicity in the clinic.

Bioassays should be developed for high precision and sensitivity to detect *in-vitro* functional differences between the biosimilar and the reference compound.—*Hidi*

Functional assays for testing biological activity can play an important role in filling the gaps in data from higher-order structural qualities. Bioassays should be developed for high precision and sensitivity to detect *in-vitro* functional differences between the biosimilar and the reference compound. These assays should express the relative potency in which the activity of the biosimilar is determined by comparison to the reference compound according to *European Pharmacopoeia* and *US Pharmacopeia* recommendations.

Ideally, bioassays should allow an assessment of all functional domains of a biosimilar candidate during comparison to the originator.—*Hidi*

Ideally, bioassays should allow an assessment of all functional domains of a biosimilar candidate during comparison to the originator. An example of multifunctionality is the therapeutic monoclonal antibodies. Conventional assays for testing the functions of Fab and Fc domains of therapeutic antibodies are widely available. These include *in-vitro* target binding (either on intact cells or using soluble target), ADCC, CDC, programmed cell death (PCD) and surface plasmon resonance (SPR) Fc receptor binding assays.

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The extended version of this article, which includes a discussion on the safety issues that must be considered when developing a biosimilar product, is available at PharmTech.com/biosimilars_characterisation.

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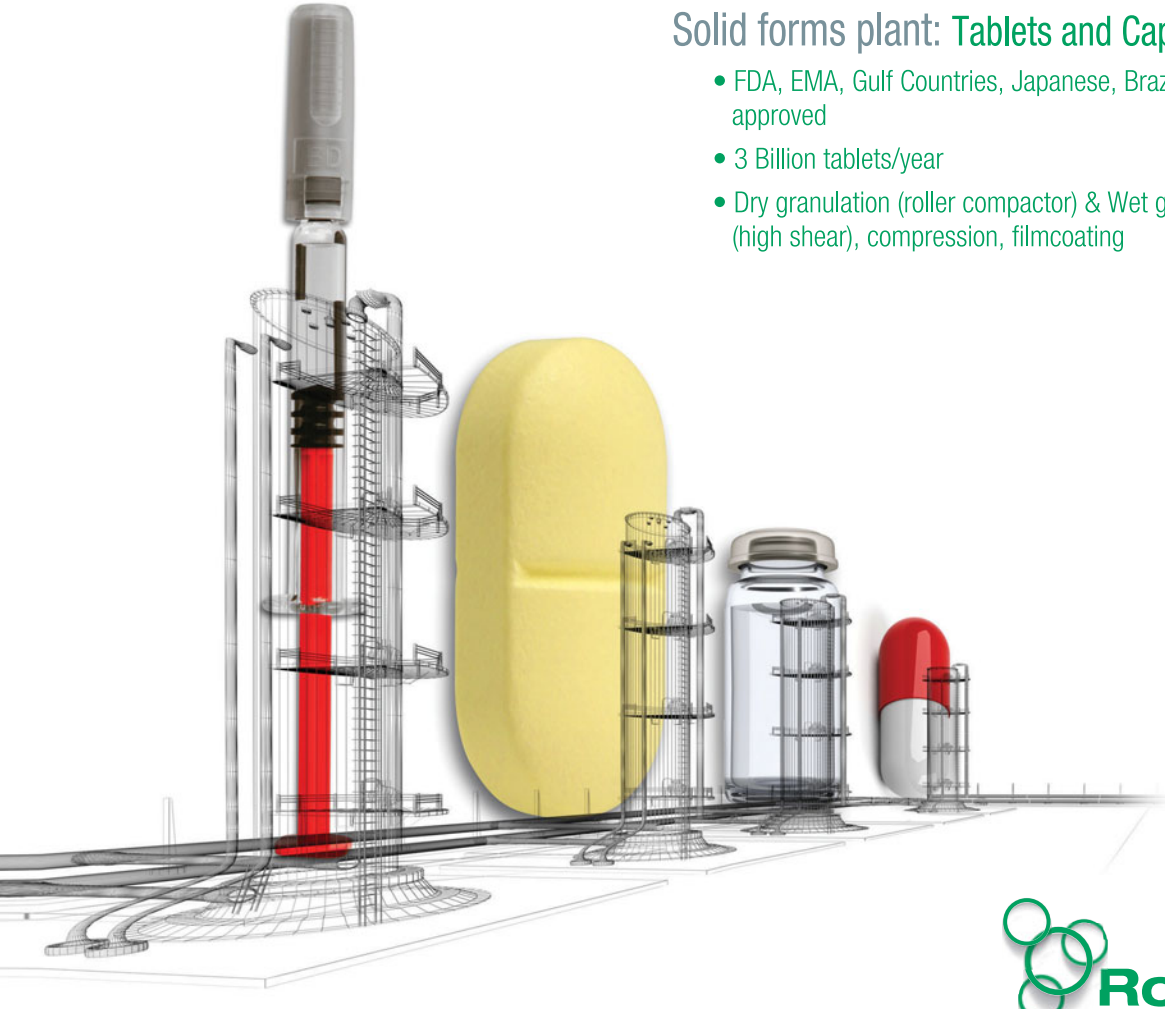

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Best Practices for Restricted Access Barrier Systems

RABS maximise product control but minimise operator interaction.

Joerg Zimmermann
is director of process development and implementation at Vetter, www.vetter-pharma.com.

It seems intuitive that the manufacture of pharmaceutical products must be free of all contamination risk. After all, patients must rely on the safety of the final product. Looking back, as early as 1822, a French pharmacist demonstrated that physicians could use solutions that contained chlorides of lime or soda as disinfectants. He concluded independently that the hands of health personnel spread puerperal fever and that sterilisation measures could be taken to prevent transmission of pathogens.

Today, almost 200 years later and with approximately 2200 commercial production lines in conventional cleanrooms in operation worldwide (1), we still deal with the introduction of the human element as we seek the highest possible level of sterility and the prevention of cross contamination in aseptic manufacturing. In the highly competitive and global world of parenteral manufacturing, along with ever-growing costs and increasingly stricter regulatory demands, optimised processes to reduce contamination sources are essential.

Since the early 1990s, two systems emerged that have helped the manufacturer assure a higher level of contamination-free product—the isolator and the restricted access barrier system, commonly referred to as RABS. The isolator was the first system developed to help enable a high level of sterility. By definition, the isolator allowed for full isolation of the machinery from the environment. Such units help keep the processing of the product separate from human intervention.

In the earlier phase of its development, technical issues and discussions around validation of sterilisation or decontamination of the isolator were a problem. These issues have since been overcome and vast improvements have helped make the isolator a safe and proven process that is used in over 430 commercial lines (1). However, the limitation of the isolator continues to be lengthy changeover time. Thus, isolators are most effective in mono-lines that run the same product continuously, especially products requiring containment such as potent/cytotoxic drugs.

The second manufacturing system developed in the mid-90s was the RABS (see **Figure 1**). Recently, the demand for RABS lines has become more prominent. A primary reason for this development is the enhanced flexibility RABS offers beyond the isolator. RABS can allow for faster start-up time, ease of changeover, and reduced capital costs, particularly with retrofits and renovations. As a result, today there are approximately 250 RABS units in operation worldwide.

What is a RABS?

With the emergence of RABS among contract development and manufacturing organisations, agencies involved in overseeing those manufacturers, such as FDA, demanded that a more precise definition of RABS be put into place to ensure consistency among its users. They believed that simply installing restricted access barrier hardware in the manufacturing facility does not create a RABS. In 2005, FDA commissioned a study group to develop a definition and determine what elements need to be included to ensure that a RABS system is truly in place before a manufacturer can make such a claim. The International Society for Pharmaceutical Engineering (ISPE) study group consisted of experts from major manufacturers including Bosch Packaging Technologies, Pfizer, Merck, GSK and Vetter, along with members of the US Food and Drug Administration (FDA).

By the definition developed by this group (2), any system claiming to be a RABS must include quality-designed equipment, and operators must receive comprehensive training in key practices such as proper gowning practice. All RABS must include the following:

- A barrier to prevent human intervention directly into the critical zone
- Airflow for an ISO 5, at least in the critical zone
- Glove ports and transfer ports used for interventions (see **Figure 2**)
- High-level disinfection
- Highly automated processes and well-defined procedures for rare open-door interventions.

The system goes beyond encasing the production lines from the environment only. RABS combines the high aseptic safety of an isolator with the flexibility of a conventional cleanroom. The inclusion of rare open-door interventions in the definition often leads to criticism. These interventions, however, are not considered a best practice.

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Best practices for RABS

RABS provides a level of separation between the operator and product that affords product protection superior to traditional systems. However, to operate a RABS cleanroom successfully, several best practices must be followed.

No open-door intervention allowed. During operation, the barriers may not be compromised; lifting the separation can lead to contamination and increased risk to the product. Therefore, when aseptic operations are carried out in a RABS, it is the intent to fully eliminate the need to open RABS doors. If the filling is interrupted with an open-door intervention, a complete cleaning and line clearance must be carried out, and the batch is eliminated.

During the line set-up stage, all machine parts and formats must be installed with the barrier closed by using a special glove-portal system. Thorough mock-up studies when designing a machine are essential. Such studies allow a well thought-through configuration of the machine and the barrier around it that allows the operator to reach all areas within the machine using the gloves. The mock-up studies simulate all routine operations and potential interventions on the machine. Operators of different departments (e.g., engineering and quality assurance) join forces to ensure the mock-up studies are as effective as possible.

High-level disinfection. Disinfection after each production batch must be completed. Once the filling process and the monitoring of the microbiological environment have been completed, the barriers are opened for cleaning. This is followed by a high-level disinfection with a sporicidal agent (e.g., peroxide suspension), which generates oxygen radicals to avoid build-up of resistance.

Figure 1: A commercial restricted barrier access system (RABS).

Figure 2: Glove ports are used for a filling operation.

Integrity of gloves. Following production, all gloves must be tested for integrity and sterilised. Using a pressure-decay test, the gloves are removed and tested for even the smallest damage that could compromise the system. If the gloves are found to be airtight, they can be cleaned, steam-sterilised and remounted back into the glove ports for use in the next production batch.

Aseptic transfer systems for zone transition. Materials and formats are only carried into the ISO 5 area using aseptic transfer systems. Any parts used in the production, including any raw materials such as syringes and stoppers, are sterilised in steam or dry heat and double packed. The outer packaging is sprayed with a sterilising agent containing alcohol before being transferred to the ISO 5 area through a lock, and the outer packaging is removed. All steps are performed using the glove portal system. Packaging materials are also put into sterilised bags and placed in special containers. The containers are sprayed down prior to introduction so when they are opened inside the barrier, the content is exposed to ISO 5 conditions only.

Conclusion

A RABS process is secure, with both a cleanroom design and aseptic safety comparable to an isolator, but with a higher degree of flexibility. Automation of the system reduces variability due to operators and makes the entire process reproducible. At Vetter's Ravensburg South production facility, for example, approximately 4,000,000 media-fill units were filled over seven years in three different cleanrooms with RABS units with no resulting contaminated units.

The RABS system is a proven and effective approach to favorably impact cleanliness in the finished product. RABS is also one of the most effective and efficient responses to current and future challenges in the manufacturing of aseptic products.

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All figures are courtesy of the author.

Advancing Chiral Chemistry in Pharmaceutical Synthesis

Developments involve stereoretentive cross-coupling, enantioselective alcohol silylation, strategies for amplifying signals in circular dichroism spectroscopy and a synthetic route to the natural product ingenol.

Chiral chemistry plays an important role in pharmaceutical development and manufacturing. Strategies in asymmetric synthesis to produce single enantiomers as well as methods for detecting and quantifying chirality are important tools for pharmaceutical chemists. Some recent developments involve stereoretentive cross-coupling for producing libraries of single enantiomers, an approach in enantioselective alcohol silylation, strategies for amplifying signals in circular dichroism spectroscopy and a synthetic route to the natural product ingenol.

Stereoretentive cross-coupling

Mark R. Biscoe, assistant professor of chemistry at the City College of New York (CCNY), and his team recently reported on a new method for preparing libraries of single-enantiomer molecules for therapeutic and toxicity studies that is faster and potentially less costly than methods now used in the pharmaceutical industry, according to a 15 Aug. 2013 CCNY press release. Specifically, the researchers developed a general palladium-catalysed process for the stereoretentive cross-coupling of secondary alkyl azastannatrane nucleophiles with aryl chlorides, bromides, iodides and triflates (1). The researchers reported that coupling partners with a wide range of electronic characteristics were well tolerated and that the reaction occurred with minimal isomerisation of the secondary alkyltin nucleophile (1). The researchers assert that the process constituted the first general method to use secondary alkyltin reagents in cross-coupling reactions (1).

Enantioselective alcohol silylation

Researchers at Boston College (BC) reported on a new computational approach for enantioselective alcohol silylation (2) that reduced the reaction time to less than one hour, down from a period of two to five days, reduced catalyst loading and produced an overall more efficient reaction, according to a July 2013 BC press release. Based on a computational projection, the researchers used cocatalysts to achieve the reaction improvements in enantioselective silyl protection of alcohols promoted by a combination of chiral and achiral Lewis basic catalysts (2). The researchers used a cocatalyst model involving two Lewis base molecules adding the achiral molecule to an already present chiral molecule. These cocatalysts operated in concert, with the chiral molecule activating an alcohol, and the additional achiral molecule, from commercially available 5-ethylthiotetrazole, activating silicon, according to the BC release. Identifying the influence of ethylthiotetrazole was a key component and provided the researchers the ability to effectively control the interplay between the cocatalysts. Together, the Lewis bases served as a closely related Brønsted base to allow the catalyst to work faster while retaining high enantioselectivity.

"The bottom line is the reaction goes a lot faster," said Marc Snapper, professor of chemistry at BC, in the BC release. "The practical advance is adding the tetrazole, which greatly accelerated the pace of the reaction by doing a much better job activating the silicon reaction partner." The BC researchers suggest that the new conceptualisation of the catalyst could lead to the development of new processes that require separate and independently operational Lewis basic cocatalysts, which can overcome the overlapping functions of cocatalysts and eliminate detrimental effects on the production of new molecules with high enantioselectivity (2).

Nanotechnology in discerning chirality

Researchers at the US Department of Energy's Brookhaven National Laboratory (BNL) and Ohio University have developed a simpler way to discern chirality by using gold and silver cubic nanoparticles to amplify the difference in the enantiomers to circularly polarised light, according to a 26 June 2013 BNL press release. The researchers showed that nonchiral nanoparticles, specifically gold/silver core/shell nanocubes, can act as plasmonic reporters of chirality for attached molecules by providing two orders of magnitude circular dichroism enhancement in a near-visible region (3).

"Our discovery and methods based on this research could be extremely useful for the characterisation of biomolecular interactions with drugs, probing protein folding and in other applications where stereometric properties are important," said Oleg Gang, a

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is Executive Editor of *Pharmaceutical Technology Europe.*

Michael Banks/GettyImages

researcher at Brookhaven's Centre for Functional Nanomaterials in the BNL release. "We could use this same approach to monitor conformational changes in biomolecules under varying environmental conditions, such as temperature—and also to fabricate nano-objects that exhibit a chiral response to light, which could then be used as new kinds of nanoscale sensors."

The use of nanoparticles to amplify the signal was done to overcome the weak signal when applying circular dichroism spectroscopy in the ultraviolet range for chiral molecules. The researchers were guided by experimental work that showed that coupling certain molecules with metallic nanoparticles would increase their response to light (4) as well as theoretical work that suggested that the plasmonic particles, which induce a collective oscillation of the material's conductive electrons to create stronger absorption of a particular wavelength, could move the signal into the visible spectrum, where it would be easier to measure, according to the BNL release.

The researchers experimented with different shapes and compositions of nanoparticles and found that cubes with a gold centre surrounded by a silver shell are not only able to show a chiral optical signal in the near-visible range, but also were effective signal amplifiers. For their test biomolecule, they used synthetic strands of DNA. When DNA was attached to the silver-coated nanocubes, the signal was approximately 100 times stronger than it was for free DNA in the solution, according to the BNL release. The observed amplification of the circular dichroism signal is a consequence of the interaction between the plasmonic particles and the energy absorbing-electrons within the DNA-nanocube complex, according to the BNL release. The researchers note that the work can serve as a platform for ultrasensitive sensing of chiral molecules and their transformations in synthetic, biomedical and pharmaceutical applications.

In another development, researchers at Harvard University, the Centre for Free-Electron Laser Science (CFEL) and the Max Planck Institute in Germany reported on enantiomer-specific detection of chiral molecules by microwave spectroscopy (5, 6). The approach sought to overcome limitations in circular dichroism and vibrational circular dichroism, which are commonly used in analysing chiral molecules, but which produce weak signals and require high sample densities (5, 6). The researchers carried out nonlinear resonant phase-sensitive microwave spectroscopy of gas-phase samples in the presence of an adiabatically switched nonresonant orthogonal electric field. They used this technique to map the enantiomer-dependent sign of an electric dipole Rabi frequency onto the phase of emitted microwave radiation (5, 6) and described how this approach can be used for determining the chirality of cold gas-phase molecules. They implemented the approach experimentally to distinguish between the *S* and *R* enantiomers of 1,2-propanediol and their racemic mixture. "We can soon measure mixtures of different compounds and determine the enantiomer ratios of each," said Melanie Schnell, co-author of the study in a CFEL release. The researchers plan to apply the technique in a broadband spectrometer at CFEL that could measure the enantiomer ratios in mixtures of substances, and longer term, the method opens a way for separating enantiomers (6).

Researchers have developed a way to discern chirality by using gold and silver cubic nanoparticles to amplify the difference in enantiomers to circularly polarised light.

Synthesis of natural products

Natural products are well-established sources for drug candidates but developing synthetic routes to natural products can often pose a problem. Scientists at The Scripps Research Institute (TSRI) recently reported on their work in developing what they characterise as the first efficient chemical synthesis of ingenol, a plant-derived compound with anticancer potential, according to an 1 Aug. 2013 TSRI press release. The work enables the synthesis of various ingenol derivatives and also sets the stage for the commercial production of ingenol mebutate, the API in Picato, a drug to treat actinic keratosis, a common precursor to nonmelanoma skin cancer. Picato was approved by the US Food and Drug Administration and the European Medicines Agency in 2012.

Ingenol mebutate, a macrocyclic diterpene ester, is a purified ingenol angelate extracted from the aerial parts of *Euphorbia peplus* plant. The molecule has eight chiral centres and one "nonrestricted" double bond, thus, there is a theoretical possibility of up to 512 stereoisomers (7). The ingenol mebutate is obtained from the dried, milled aerial parts of the plant by extraction followed by a series of purification steps. The final step of the process involves crystallisation (7). In late 2011, the drug's manufacturer, the Danish pharmaceutical company LEO Pharma, collaborated with TSRI to develop an efficient way to synthesise ingenol mebutate and ingenol derivatives. The scientists developed a stereocontrolled synthesis of (+)-ingenol in 14 steps from inexpensive (+)-3-carene and used a two-phase design (8). The researchers assert the results validate that two-phase terpene total synthesis is an alternative to isolation or bioengineering for preparing polyoxygenated terpenoids (8).

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Effective and Efficient Weighing of Potent Compounds

George Hartford, Patty Cheung, Karen Whitaker, Roy Helmy and Joanne Ratcliff

Working safely with potent compounds presents challenges for the pharmaceutical industry because exposure to minute quantities could potentially cause health effects. Typically, an isolator would be the preferred containment technology for working with the most potent (occupational exposure band five [OEB 5]) compounds but it has drawbacks in terms of cost, space, efficiency and ergonomics. The authors describe the advantages of using an automated powder dispensing system in a ventilated balance enclosure (VBE) for efficient handling and effective containment of potent compounds. A review of the data proves that air and surface contamination is well within the acceptable limits, demonstrating the applicability of the automated powder dispensing unit in a VBE for weighing potent compounds in the pharmaceutical industry.

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In recent years, pharmaceutical companies have increasingly begun to work with potent compounds (i.e., compounds that are very active pharmacologically, with efficacy at sub-milligram doses). These compounds allow patients to take smaller doses and potentially experience fewer side effects. While this property is advantageous for the patient, it presents a greater risk to the health of analytical chemists working with these compounds because exposure to very small quantities has the potential to cause health effects. In some cases, the quantity of potent compound that can lead to health effects can be extremely small, being practically invisible in air or on work surfaces, which makes containment of these compounds in the workplace especially challenging.

The list of potent compounds of interest to the pharmaceutical industry includes hormones, steroids and many oncology drugs. These compounds have airborne occupational exposure limits (OEL) ≤ 10 µg/m^3 as an eight-hour time-weighted average (1). For handling these compounds in the laboratory, a classification system is used to assign materials into a series of health hazard categories, or occupational exposure bands (OEB), of increasing severity based upon their inherent pharmacological and toxicological properties. This classification system helps companies identify risks associated with handling the compounds and provides guidance on how to manage them (2). While no official industry standard exists around the banding of compounds, companies typically utilise OEB systems with four to six categories (1). Each health hazard category corresponds to a predefined strategy known to provide the necessary degree of exposure control to protect employees and the environment.

To support research and development as well as manufacturing of potent compounds, several contract manufacturers have made significant investments to build facilities to control exposure to potent compounds (3). Merck & Co., like other companies, has been developing potent compounds. Merck's most potent compounds, known as OEB 5 compounds, typically require an isolator for dispensing milligram to gram quantities to maintain airborne levels below 1 µg/m^3 and surface contamination below 10 µg/100 cm^2 (see **Table I**).

User safety at the forefront

Working safely with these potent compounds presents challenges. Employers are required to minimise the exposure risk by following the "hierarchy of controls." Since substitution is not an option when developing or manufacturing

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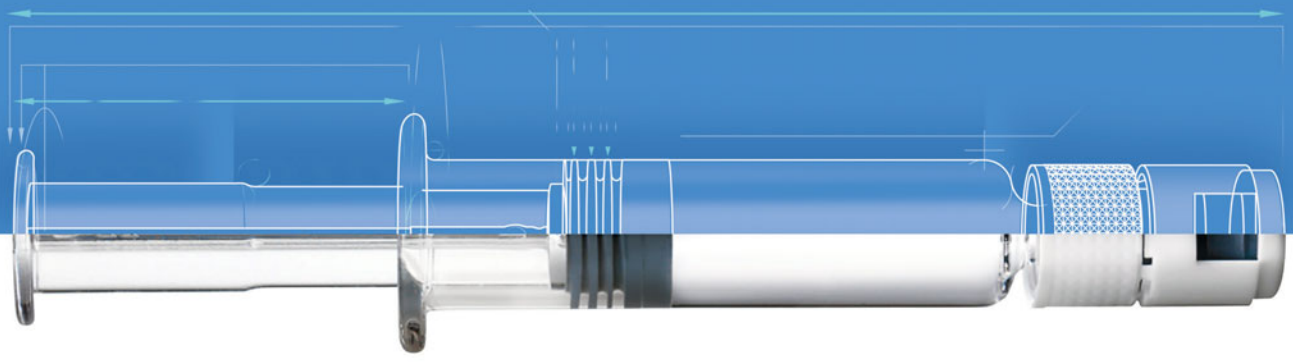

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Table I: Merck & Co.'s occupational exposure bands. HEPA is high-efficiency particulate air, LEV is local exhaust ventilation.

Occupational exposure bands (OEB)	OEB 1	OEB 2	OEB 3	OEB 4	OEB 5
Potency/toxicity	Slightly toxic	Moderately toxic	Toxic	Potent, toxic, potentially genotoxic	Highly potent, highly toxic
Occupational exposure limits (OEL) (μg/m^3)	≥ 1000	≥ 100 < 1000	≥ 10 < 100	≥ 1 < 10	< 1
Handling requirements	Good laboratory/ manufacturing practices (GLP/GMP). LEV may be needed. No special containment.	GLP/GMP. LEV may be needed. No special containment.	Virtually no open handling. Closed systems and/or controlled by LEV, hoods or HEPA-filtered ventilated enclosures designed for personnel protection.	No open handling. Closed systems and/ or controlled by LEV, hoods or HEPA filtered ventilated enclosures designed for personnel protection.	No open handling. High containment required.

potent drugs, engineering controls are required to be used as the primary control. The preferred containment technology is often an isolator that maintains exposures below applicable limits. Using an isolator for dispensing and weighing small quantities of these compounds, however, presents space, ergonomic, efficiency and cost challenges for an analytical laboratory. Merck needed a simple solution to allow analytical chemistry researchers to work in a laboratory environment with OEB 5 compounds. The workflow needed to be safe, simple, efficient and accurate enough to allow precision weighing while maintaining cGMP compliance.

Automated powder weighing

Merck's analytical laboratory originally invested in a semi-automated powder dispensing unit (Mettler Toledo) to address an increasing demand for routine weighing of non-potent compounds. The system, however, subsequently proved to be an effective solution for handling potent compounds as well (see **Figure 1**).

It consisted of an enclosed semiautomated dispensing unit attached to a regular analytical balance. The compound is sealed in a vial with a dosing head attached to the top of the container. The dosing head is inserted into the unit, and the balance doors are closed before dispensing takes place. Dispensing the compound from a sealed container reduces the risk of airborne contamination. Each dosing head contains a radio-frequency-identification (RFID) chip to enable identification and tracking of the compound, providing process security by eliminating the possibility of selecting or dispensing the wrong substance. The dispensing system is able to accurately weigh compounds from 1 mg to 5 g with a 2% variance and dispenses the required amount of material into a container that is securely located on the balance. Once the desired weight has been dispensed, the researcher can remove the container and place another one on the balance for the next weighing step. Alternatively, a 30-position autosampler can be added to automate the change of target container, which enables up to 30 weighing operations to take place without any user intervention. It is also possible to link a solvent dispensing module, which accurately adds the desired weight of solvent into the target container based on the actual amount of solid dispensed to achieve a desired concentration. This method is an even more precise way to prepare analytical solutions. Compared to conventional manual dispensing, the automated process can be as much as 20 times faster.

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Table II: Containment verification data: Air sampling results. VBE is ventilated balance enclosure, < is less than the laboratory limit of detection.

Iteration 1–6 sample numbers	Sample location	Results in micrograms per cubic meter of air (µg/m³)
02S, 07S, 12S, 17S, 22S, 27S	Personal breathing zone samples	< 0.0025 – < 0.0030
03S, 08S, 13S, 18S, 23S, 28S	Left side of VBE face 200 mm from opening	< 0.0025 – < 0.0030
04S, 09S, 14S, 19S, 24S, 29S	Right side of VBE face 200 mm from opening	< 0.0025 – < 0.0030
05S, 10S, 15S, 20S, 25S, 30S	1.8 m from VBE face at height 1.5 m	< 0.0025 – < 0.0030
06S, 11S, 16S, 20S, 26S, 31S	VBE exhaust 200 mm from outlet	< 0.0025 – < 0.0031

Table III: Containment verification data: Surface sampling results. VBE is ventilated balance enclosure.

Iteration 1–6 sample numbers	Sample location	Results in micrograms per 100 centimeters square on the surface (µg/100 cm²)
05S, 09S, 13S, 17S, 21S, 25S	Floor below VBE face opening (right)	< 0.01
06S, 10S, 14S, 18S, 22S, 25S	Floor below VBE face opening (left)	< 0.01
07S, 11S, 15S, 19S, 23S	Horizontal airfoil (left)	< 0.01
26S		0.028
I08S, 12S, 16S, 20S, 24S, 27S	Horizontal airfoil (right)	< 0.01

Figure 1: Example of an automated powder dispensing unit.

A key benefit of automated dispensing is that it reduces user exposure by eliminating the handling of the substance with a spatula and minimising the risk of spillage. It also reduces the manual actions required by the user, by eliminating the need for repeated opening of the balance door and transferring the compound from the main container to the secondary container to achieve the desired weight.

The automated dispensing system was situated within a high-efficiency particulate air (HEPA)-filtered ventilated balance enclosure (VBE) (Pharmaceutical Containment Technologies [PCT]). The VBE has features key to effective containment such as rounded airfoils around the entire face, a waste chute to minimise researcher movement in and out of the face, safe-change HEPA filtration and a flow alarm to ensure the face velocity does not drop below 60 fpm (0.3 m/s). The laboratory initially used this equipment to weigh less potent, OEB 3 and OEB 4 compounds, a task that the device performed remarkably well. A question was raised as to whether the capability of the unit could be expanded to handle the safe and efficient dispensing of OEB 5 compounds. After several discussions between Merck Global Safety and the Environment and Mettler Toledo, an experimental evaluation plan was created to assess the ability of the system to reduce airborne and particulate surface contamination during weighing of OEB 5 compounds. As part of the evaluation, OEB 5 materials were provided to the analytical laboratory in containers compatible with the dosing heads as historical air and surface contamination data indicated manual subdivision by analytical chemists in a VBE would not maintain airborne and surface contamination levels below applicable limits for some OEB 5 compounds.

Surrogate control performance evaluation

Verification sampling was performed to validate the equipment containment. Personal protective equipment (PPE) worn during the sampling included safety glasses, a disposable laboratory coat, disposable sleeves and double nitrile

gloves. Air and surface samples were collected during the dispensing of 2 g of naproxen sodium and subsequent cleaning and PPE removal. Naproxen sodium, a nonsteroidal anti-inflammatory drug, was used because it is recognised by the International Society of Pharmaceutical Engineers (ISPE) as a rigorous challenge agent and a suitable surrogate for assessing containment of potent compounds (4). The sampling protocol included cleaning of the VBE, containers, balance and the removal of outer gloves and sleeves within the VBE given that proper technique during these activities is crucial to containment and the prevention of surface contamination. Six iterations of the dispensing task were performed, and air and surface samples were collected during each iteration to demonstrate that the controls and the procedures used by the researchers did, in fact, protect them.

In total, six personal air samples and 24 area air samples were collected. All samples collected were below the laboratory limit of detection and well below OELs for the OEB 5 compounds currently being handled in the laboratory (see **Table II**). Additionally, all wipe samples were below the surface contamination limits (see **Table III**).

Conclusion

A review of the air and surface contamination data showed that exposures are low, generally nondetectable. It was concluded that researchers can safely utilise the automated dispensing system to dispense up to 2 g of OEB 5 compounds with OELs > 3 ng/m^3, provided that the VBE is properly sited in the laboratory and use of the system is coupled with appropriate personal protective equipment, a written procedure, hands-on training on proper handling of potent compounds in a VBE, good handling practices and an annual preventative maintenance program for both the dispensing system and the VBE.

Automated powder dispensing offers an efficient combination of both strategies of containment and improved sample handling techniques. Combining the dosing head, a HEPA-filtered VBE and good potent compound handling techniques can eliminate the need to use an isolator to precisely weigh OEB 5 compounds for analytical testing. An added benefit is that any researcher can undergo simple training and be qualified to operate the automated system, which also removes user variability from the process. Overall, the use of the automated dispensing system in a VBE affords accurate and reproducible weighing of potent compound while keeping researchers safe and protecting the laboratory environment from contamination.

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Webcast: Safe automated weighing of potent compounds in the pharmaceutical industry

Roy Helmy, PhD, director of analytical chemistry at Merck Research Laboratories, and **Joanne Ratcliff, PhD,** communication project manager at Mettler Toledo AG, explain how the use of automated dosing, a high-efficiency particulate air (HEPA)-filtered ventilated balance enclosure (VBE), and good potent-compound handling techniques have eliminated the need to utilise an isolator to precisely weigh small quantities of occupational exposure band five (OEB 5) compounds for analytical testing. The webcast will provide insight on:

- How researchers can work in a laboratory environment with OEB 5 compounds without the need for an isolator
- How automated weighing of potent compounds can increase the safety of researchers while delivering accurate and reproducible weighing
- How automated weighing of potent compounds can be 20 times faster than the manual equivalent.

The webcast will be broadcast 17 Sept. at 11:00 am EST and available for on-demand viewing thereafter. For additional information, go to www.pharmtech.com/potent.

Overcoming Limitations of Vapourised Hydrogen Peroxide

Hydrogen peroxide is highly potent and highly problematic.

James P. Agalloco and James E. Akers

The use of hydrogen peroxide (H_2O_2) in the global healthcare industry and other industries that require high levels of contamination control has grown steadily. This growth is attributable to the chemical's ability to kill spores and sterilise materials, which has been demonstrated in a variety of practical applications. Properly used, H_2O_2 is an effective sterilant capable of efficient and rapid elimination of contaminating microbes. Some difficulties have been associated with the implementation of H_2O_2 processes in the healthcare field although these issues appear to have been avoided in commercially sterile food and beverage manufacture. Specifically, persistent problems regarding the development of H_2O_2 processes and their subsequent validation have been reported. The author discusses the technical issues associated with achieving lethal concentrations of H_2O_2 delivered in vapourous form on decontamination targets, explores the core scientific principles behind H_2O_2's use in decontamination and sterilisation, and provides experience-based solutions to frequently encountered operational issues.

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Hydrogen peroxide (H_2O_2) is an extremely powerful oxidant that is capable of effectively killing resistant spore-forming bacteria over a wide range of concentrations. At concentrations of 3% or less, it is suitable for use as a topical antiseptic (1). H_2O_2 has been accepted by both the US Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) as a sterilising agent for many years (2, 3). In the food industry, H_2O_2 is widely used to sterilise containers, closures and aseptic chambers (i.e., isolators) used for manufacturing low-acid and dairy-based beverages as well as other applications (4).

The potency of H_2O_2 as a sterilant and its usefulness in a broad range of antimicrobial applications are beyond dispute. The problems associated with vapourised H_2O_2 processes in the healthcare industry lie in fundamental misunderstandings concerning physicochemical characteristics of H_2O_2 sterilisation. These errors profoundly influence real-world H_2O_2 applications.

Understanding vapours

To fully understand the physical factors that affect the distribution of H_2O_2 in the vapour phase, one must consider the factors that affect vapours in general and the factors that allow them to exist in air, which is the medium in which H_2O_2 in the vapour phase is distributed within a decontamination target. Air contains varying but small amounts of water in the vapour phase, which is described using the term relative humidity (RH). An important factor in the distribution of a chemical is the dew point. The dew point is, in simplest terms, a function of both concentration and temperature. When the concentration of water exceeds the saturation point at a particular temperature, condensation occurs. The gaseous water converts to the liquid phase, and droplets of liquid water may appear. On the other hand, if the water concentration is below the saturation point, it will remain in the gas phase. When the temperature of the air is actively lowered (or simply drops as a function of thermodynamics) below the dew point, some portion of the water (H_2O) present as a gas mixed with air condenses and forms liquid droplets. We observe this as clouds, dew, fog or frost.

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The typical H_2O_2 process

The process that most H_2O_2 generator and isolator manufacturers use for H_2O_2 introduction is one in which a hot air stream is used to introduce a heated H_2O_2/H_2O gas into the target environment, which may be an aseptic chamber or isolator. Within the generator, the temperature of the air/H_2O_2/H_2O mixture is sufficiently high that all three materials are in a gaseous state. The hot air is conventionally at temperatures in excess of 100 °C, which takes advantage of the respective boiling points of the pure components (i.e., H_2O = 100 °C, H_2O_2 = 150.2 °C, and a 30–35% aqueous solution of H_2O_2 = approximately 108 °C). At these temperatures, both H_2O_2 and H_2O are present as gases and are carried into the target vessel with the hot air. The H_2O_2/H_2O is supplied as an aqueous solution of H_2O_2 in varying percentages typically ranging from 31% to 50% H_2O_2. At typical room temperatures, each of these solutions is predominantly liquid, and the headspace air within the closed containers has a small amount of gas phase H_2O_2/H_2O that is in equilibrium with the liquid.

If the concentration remains below the saturation point upon introduction into the target environment, then both the H_2O_2 and H_2O will remain in the gas phase. When the hot and relatively humid gas mixture from a H_2O_2 generator is introduced to the target chamber, it will encounter colder air as well as ambient temperature surfaces of the chamber and materials inside it. As the hot gas mixture cools to the temperature of the chamber, it will fall below the dew-point temperature of both H_2O_2/H_2O, and some portion of these materials will condense on the surfaces as liquids. In effect, the H_2O_2/H_2O are returning to their initial equilibrium state of liquids in equilibrium with the adjacent gas, which they possessed before being converted to a gas in the generator.

Condensation that forms on the surfaces will tend to be nonuniform in concentration across the chamber for several reasons:

- The H_2O_2 will condense first due to its lower equilibrium vapour pressure (i.e., lower dew point) relative to H_2O.
- The temperature in the system may be non-uniform across the chamber and is generally hottest near the inlet where the hot gas mixture is introduced; for the purposes of vapour-phase hydrogen peroxide (VPHP) technology, ± 2.5 °C can be considered effectively uniform.
- The continued introduction of the hot gas mixture into the chamber, in which VPHP generators rely on continuous replenishment of mixture vapour, results in a slow increase in temperature within the chamber. This effect is more pronounced in smaller enclosures and those with relatively low mass.
- In larger enclosures, the amount of heat added by the hot air stream laden with H_2O_2/H_2O will have little impact on temperatures remote from the injection port.
- Where the localised temperature within the enclosure is low enough and concentrations of H_2O_2 and H_2O are high enough, they will condense. Many present-day H_2O_2 generator systems are designed such that the process relies on the presence of condensation. In these cases, one should recognise that the heated gas or vapour is used only as a convenient delivery system for the H_2O_2/H_2O to the target environment. The sterilisation or decontamination is accomplished by H_2O_2 in the form of liquid condensate on surfaces.
- Depending upon the decontamination approach used, H_2O_2/H_2O introduction during the process dwell period can be continuous, intermittent or absent entirely. In cases where the hot air/vapour stream is present only during a comparatively short initial introduction period, the effects of the hot air stream on target chamber temperatures will be less profound.
- Chambers with a large number of objects to be decontaminated have added surfaces upon which condensate may accumulate. As the load size increases, the amount of H_2O_2 added and/or the process dwell period may need to be increased to ensure condensation on all target surfaces.

The extent of condensation that occurs depends upon the temperature (i.e., colder locations will have more condensation), the concentration or amount of H_2O_2/H_2O introduced (and removed if a circulating process is used), the size of the enclosure (i.e., affects the surface/volume ratio) and the

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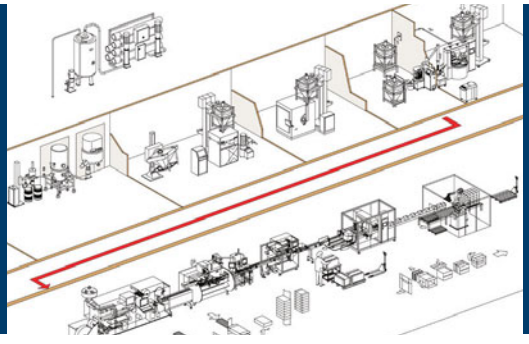

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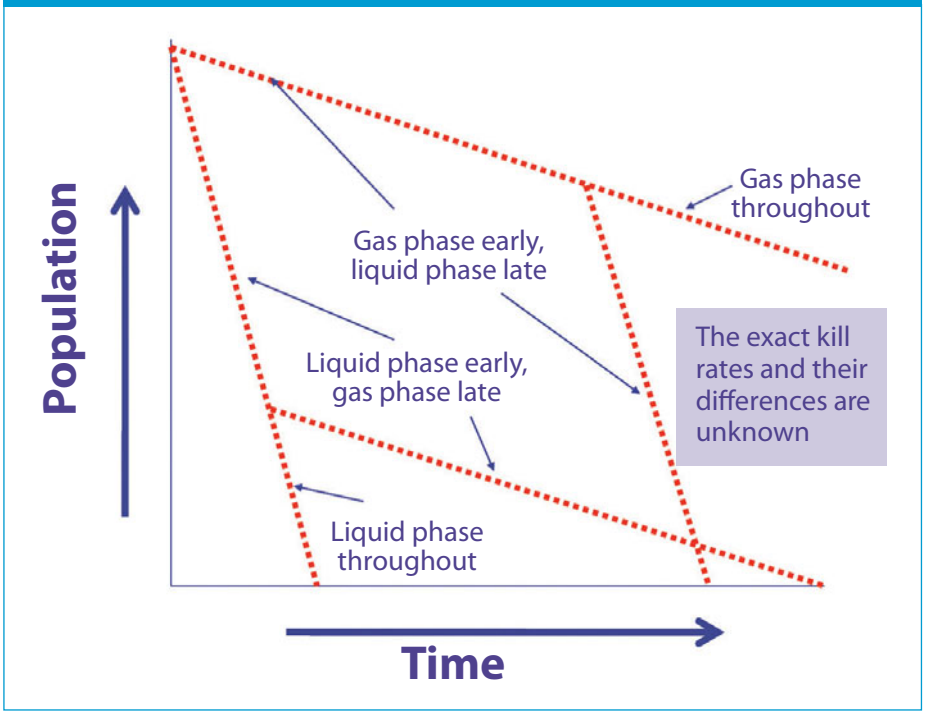
Figure 1: Estimated relative kill rates in liquid and gas phases; the exact kill rates and their differences are unknown.



quantity of material within the chamber (i.e., adds to the surface area).

Phase states in the enclosure

It must be understood that the enclosure will contain a mixture of air/H_2O_2/H_2O internally, with some of the H_2O_2/H_2O in a liquid state on surfaces and the remainder in the gas phase. There is no simple means to establish how much H_2O_2/H_2O is in each phase or where in the chamber a particular phase is present. Additionally one cannot know the percentage of H_2O_2 or H_2O at any single location, and certainly not at every location within the enclosure. The Gibbs Phase rule makes it clear that conditions can vary across the system (see **Equation 1**).

$$F = C - P + 2 = 3 - 2 + 2 = 3 \quad \text{(Eq. 1)}$$

where F = number of degrees of freedom (i.e., concentration, temperature, pressure), C = number of components in the system and P = number of phases in the system.

Almost nothing is known with certainty with respect to concentration and location. There is, however, one constant in the process: H_2O_2 is lethal to microorganisms in both the gas and liquid phases. It is reasonable to assume that liquid-phase kill will be somewhat faster than the gas-phase kill for two important reasons as further outlined:

- The concentration of H_2O_2 in the liquid phase will always be higher. A 35% H_2O_2 mixture will have equilibrium concentrations of H_2O_2 of ~2% in the gas phase and ~79% in the liquid phase (5).
- The presence of adequate moisture at the point of sterilisation is certain in liquids, as H_2O is the other component of the liquid phase.

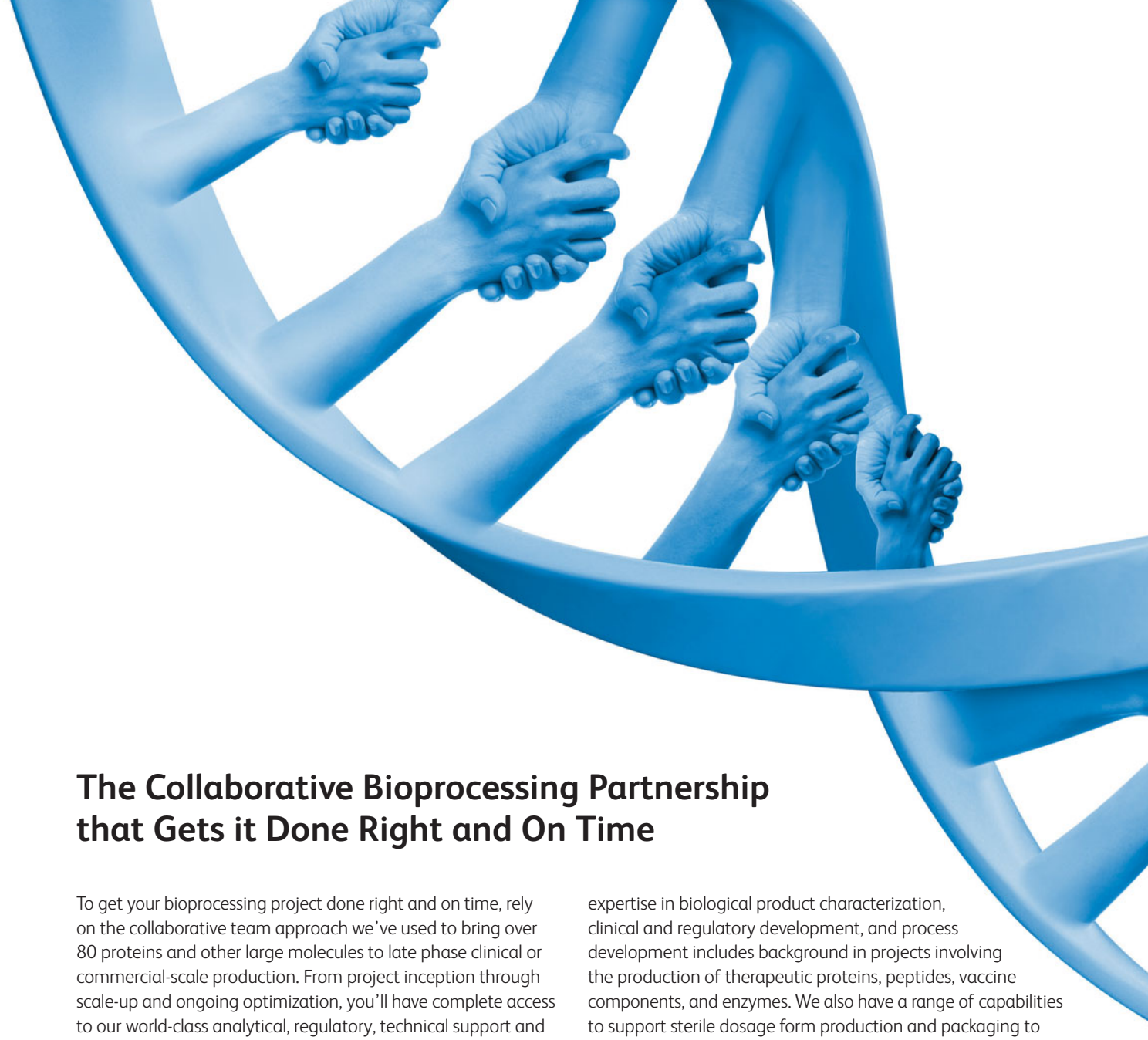
An older reference describes more rapid kill occurring with H_2O_2 in a gas-phase process compared to a liquid-phase process (6). This reference identifies a gas-phase process at 25 °C, with no mention of any liquid H_2O_2 present. At that temperature, however, H_2O_2 is a liquid, so there must be some liquid H_2O_2 in equilibrium with the gas. There is no means to establish that the kill in this "gas" process was actually accomplished in that phase. It is more likely that the cited kill was accomplished in the liquid phase. Misinterpreting what is actually "vapour" as a "gas" has led to the erroneous belief that gaseous-phase kill is more rapid than liquid-phase kill.

The expected microbial kill rates in the system might appear as shown in **Figure 1**, which visualises H_2O_2 sterilisation as a process that occurs within a band, bounded by the extremes of liquid and gas-phase kill. **Figure 1** represents what is believed to occur and does not reflect any specific H_2O_2 process. The absolute slopes of the death curves are unknown. Given that the localised concentrations in both phases are variable due to temperature differences and proximity to the inlet with its heated air supply, it must be recognised that there will be different kill rates in different locations in both the liquid and gas phases. **Figure 1** represents what might occur at a single point within the chamber; similar appearing death curves with differing slopes can be considered for other locations where the local conditions are different. These variations are the underlying cause of the variable performance experienced when using vapour-phase H_2O_2 as a lethal process.

D-values for H_2O_2 decontamination

The death curves in **Figure 1** seem to show that a D-value (or an approximation of one) could be established against a challenge microorganism for the combined processes. That assumption is faulty because there is no way of establishing what conditions (e.g., phase, concentration or humidity) are present in the system at the point where the microorganism is killed. D-value determination requires knowledge of the specific lethal conditions to which a microorganism is exposed. In a single-phase sterilisation process, gas or liquid, information on concentration of the agent, humidity (assumed at 100% for liquid processes),

FIGURE 1 IS COURTESY OF THE AUTHORS.



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and temperature is readily determined. In the context of H_2O_2, this is easiest for liquids, and published D-values for *Geobacillus stearothermophilus* in various H_2O_2/H_2O liquid solutions are available (1). These liquid phase D-values demonstrate extremely rapid kill (in seconds) at even modest H_2O_2 concentrations (7). At the estimated concentrations where condensation first occurs in vapour H_2O_2 processes, the D-values should be lower as the concentration will be substantially higher than that published in the literature. Unfortunately, no comparable data are available on H_2O_2, where a strictly gas-phase process is present. Thus, any labelled "D-values" for vapour H_2O_2 biological indicators must be considered nothing more than an approximation as the killing conditions are unknown. The conditions of kill may be consistent enough that they could be replicated in an independent study in the same test system. What cannot be established from these labelled "D-values" is how that same biological indicator will respond in a different environment where the conditions are also unknown and most likely substantially different.

In the 20-plus years that this industry has been using H_2O_2 decontamination, a BIER (biological indicator evaluation resistometer) vessel for H_2O_2 has not been developed as a standard for compendial or routine use. The same conundrum faced with respect to variable and unknown biphasic conditions in a larger system has prevented the development of a H_2O_2 BIER. The absence of a BIER vessel and, thus, a fully useable "D-value" for H_2O_2 biological indicators has caused some difficulties. What can be established from the vendor "D-value" is the relative resistance of one lot to another from the same vendor. How any individual lot will perform under different conditions is something the user must determine for each application.

One suggested approach to get beyond this lack of a definitive D-value for a biological indicator is to establish a process or system "D-value" for a biological indicator within a large enclosure and rely upon that as the basis for destruction in the system rather than the vendor's reported value. This approach presumes that the conditions used to establish the process/system "D-value" are representative of the entire system. That assumption is decidedly not the case, nor is it known whether the location(s) chosen for the process "D-value" determination are best case or worst case with respect to kill across the chamber. A number, which is not a D-value in the strict sense, can be calculated, but the utility of that number in any estimation kill rate across the chamber is essentially nil.

Reports of vapour-phase "D-value" variations as a consequence of different substrates must also be recognised as uncertain (8, 9). Because there is no objective biological indicator evaluation method available, published "D-values" are not standardised and thus of very limited use. Unless the concentration on the individual surfaces tested can be known and demonstrated to be constant, any hint that the substrate variations are meaningful must be viewed with some skepticism. There is also some published evidence that "D-values" may vary with spore concentration applied to the carrier material, which means kill may not be linear with concentration. That represents a serious flaw in the use of any biological indicator.

Is safety a concern with H_2O_2?

Given the rapid kill observed in the H_2O_2 liquid phase, the difficulties in attaining consistent kill with H_2O_2 vapour processes can only be explained by a lack of adequate condensation, for there is little doubt then when condensation does occur, kill will be quite rapid (10). Many of the newer

What is a Vapour?

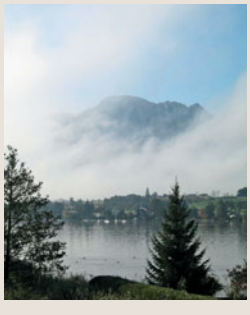

Figure 1. Water phases.

There are three primary states of matter—solid, liquid and gas. The term "vapour" is defined in several ways. Scientifically, a vapour is a gas at a temperature lower than its critical point; a vapour is a gas phase where the same substance can also exist as a liquid. An example is atmospheric water vapour. At temperatures above the dew point, water in the atmosphere is a gas. As the temperature is lowered through the dew point, the gaseous water condenses to form a fog or mist, or it can condense and form liquid water on a cold surface. Another definition of vapour is visible moisture in the air, as in fog or steam—a system in which a liquid is suspended in a gas.

Figure 1 shows water in various phases: the lake, the dense fog at the foot of the mountain, the wisps of cloud and the blue sky above. The lake is certainly liquid water; the blue sky is just as clearly a gas which contains water in the gaseous state. The fog or cloud in the center is a mixture of a gas phase (comprised of nitrogen, oxygen, water, carbon dioxide and trace amounts of inert gases) and a suspended liquid phase (small droplets of water). The density of the fog or cloud varies with its temperature. It is thickest (i.e., suspending the most liquid) near the base of the mountain where it is coldest. It is clearly less dense, with less suspended water droplets near the top of the image where the temperature is higher.

One of the major difficulties with hydrogen-peroxide (H_2O_2) processes is the use of a vapour for delivery of H_2O_2 and water (H_2O) to the target chamber. It must be understood that a vapour is a mixture of air and liquid that is present within the chamber. In decontamination or sterilisation using H_2O_2, the liquid phase is comprised of both H_2O_2 and H_2O, and the concentration of each in the gas and suspended liquid state can vary across the system.

James P. Agalloco and James E. Akers

FIGURE IS COURTESY OF THE AUTHORS.

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generator designs, either freestanding or integrated into enclosures, rely on condensation to decontaminate/sterilise extremely rapidly.

Since the rapid kill provided by liquid H_2O_2 is well documented, why has industry been cautioned to avoid condensation in vapour H_2O_2 processes? The answer lies in the early teachings of AMSCO (now Steris) when the first H_2O_2 generator was introduced in the late 1980s. Caution was routinely raised regarding the potential hazards of high concentrations of liquid H_2O_2. (The H_2O_2 concentration in the gas phase at ambient temperature will always be substantially lower than its equilibrium concentration in the liquid phase.) The relevant safety issues with the use of H_2O_2 vapours are:

- *Explosive vapours.* The caution here relates to concentrations of > 70% H_2O_2 giving off explosive vapours at temperatures greater than 70 °C (11). If this situation were to occur anywhere in vapour processes, the generators themselves would represent the greatest risk. Temperatures inside enclosures rarely exceed 30 °C, and thus the likelihood of this presenting a real-world problem during a sterilisation process is unlikely.
- *Hazardous reactions.* There are reports of H_2O_2 reacting with greases, alcohols, ketones, carboxylic acids (particularly acetic acid), amines and phosphorus. Small amounts of other materials that contain catalysts (e.g., silver, lead, copper, chromium, mercury and iron oxide rust) can cause rapid decomposition and an explosive pressure rupture of the containing vessel if it is not properly vented (12). None of these compounds and materials is typically present in pharmaceutical enclosures.
- *Corrosivity.* This is possible with some materials, but the typical stainless steel, glass and other materials exposed to H_2O_2 are known to be compatible and are chosen explicitly for that purpose. The chemical compatibility of H_2O_2/H_2O solutions is well documented.
- *Worker safety.* The US Occupational Safety and Health Administration has established an 8-hour, time-weighted average for exposure to H_2O_2 of 1 ppm, with an immediate hazard in the presence of concentrations greater than 75 ppm (13, 14). This limit is managed in pharmaceutical facilities through external alarms in the surrounding areas and requirements for aeration before personnel or material exposure.

While there is a need for caution with respect to the use of vapour phase H_2O_2, undue concern is unwarranted. In more than 20 years of use in the global industry, there have been no reported incidents of personal injury or equipment damage associated with this process.

Claims that vapour-phase H_2O_2 processes do not result in condensation are speculative. The laws of physics and temperature within enclosures are such that some measure of condensation will always occur, and in many recent equipment and process designs the creation of condensation is intentional. Thus, within the context of real-world experience, the safety issues associated with vapour H_2O_2 systems where condensation is present appear to be adequately managed, assuming appropriate worker-safety precautions are maintained.

Limitations of multipoint process-control measurements

FDA's *Guideline on Sterile Drug Products Produced by Aseptic Processing* recommends: "The uniform distribution of a defined concentration of decontaminating agent should also be evaluated as part of these studies" (15). This suggestion is made without reference to a specific methodology that could be employed. There is no technology that could address this expectation throughout a two-phase environment. Nor would the resulting data on concentration in the gas phase be useful in correlating to microbial kill on surfaces. When appropriate amounts of H_2O_2 are used for decontamination or sterilisation, some of the available instruments, such as those that rely on near-infrared transmission, are unusable due to condensation on the lenses. Because accurate measurement is not possible, chemical indicators provide the only widely available means to confirm that H_2O_2 is, or was, present at a specific location.

Problems in an unsteady-state process

The introduction of H_2O_2 into a room-temperature enclosure uses vapour-process heating to convert the liquid solution into a gas for mixing and distribution in hot air. The temperatures in vapourisers are in the range of 105–150 °C. This high temperature results in some localised heating of the enclosure, primarily in locations close to the entry point of the heated materials. The effects of this heat input are multiple:

- Temperatures during the process will change over its duration with the greatest impact found in locations nearest the infeed locations. This heating is more pronounced in smaller, flexible-wall and lightly loaded enclosures where there is less overall mass.
- The resulting changes in temperature will result in varying amounts of condensation (and thus kill) across the enclosure (and also varying over the duration of the process dwell period at a single location).
- The conditions close to the infeed are more likely to remain in the gas phase throughout the process, which can result in less condensation (if any) and potentially slower kill rates in those locales. In one project, the authors observed that a biological indicator location directly beneath the supply port was repeatedly found to be the only location where the biological indicator could not be killed.

These phenomena are more problematic in those generators where H_2O_2 is fed and removed throughout the process. Systems that operate in a fill-and-soak mode may attain equilibrium conditions within the targeted volume.

The negative consequences of the unsteady-state nature of vapour-phase H_2O_2 processes are unavoidable in recirculating systems. The only means to establish a consistent process is to use enough H_2O_2 that even the warmest locations attain some measure of condensation. This solution is more easily accomplished in the non-circulating systems.

Penetration and adsorption by H_2O_2

Years of experience with vapour-phase H_2O_2 processes have shown how best to address the adverse impact of its adsorption as further explained:

- H_2O_2 can penetrate high-density polyethylene fiber materials (Tyvek, Dupont), which are primary packaging for many presterilised items. Tyvek-wrapped materials of larger dimension may prove difficult to aerate because there is no internal turbulence to aid in aeration.
- Some polymeric materials will adsorb H_2O_2 readily and desorb it very slowly. A small (1 ft^3), empty isolator manufactured from polycarbonate (Lexan, SABIC Innovative Plastics) was found to require more than 24 h of aeration (16). Careful attention to materials of construction is important to reduce any unintended adsorption.
- Typical sterile-product container materials (e.g., glass vial, elastomeric closure, aluminum crimp) and many polymeric materials are largely impervious to H_2O_2.
- Shorter cycle dwell times allowing less overall time for adsorption are generally preferable.
- Aeration periods can ordinarily be improved by additional air changes.
- Liquid H_2O_2 penetration through Tyvek has not been documented.
- Some biological materials have demonstrated extreme sensitivity to H_2O_2 requiring aeration to levels in the parts-per-billion range (17).

The adverse consequences of decontamination and sterilisation processes should be considered in the development and control of every process. Vapour-phase H_2O_2 processes, because of their dual-phase nature, present new challenges. Were other gases to be used, similar, but different, concerns would present themselves and appropriate solutions would be identified. A more penetrating agent would only increase the penetration/aeration difficulties encountered, so while H_2O_2 penetration/absorption/desorption is a problem, the situation might be worse with alternative materials.

Biological indicator issues

Difficulties encountered in the destruction of biological indicators have been commonly reported and are so well known that there are some who doubt the efficacy of H_2O_2 as a sterilant. These problems are multifaceted but resolvable when the sterilisation process is properly established.

First, H_2O_2 decontamination and sterilisation must be understood as a two-phase system. Considering it as a single, gas-phase process has caused more difficulties than anything else. The variability demonstrated in lethality is the direct result of applying process constraints that are suitable for a gas process but inadequate for two-phase H_2O_2 processes. Adapting process models and approaches from the most common gas sterilant, ethylene oxide (EO), to a vapour process created much of the problem. The largest flaw in this thinking is the deliberate avoidance of condensation in endeavoring to make what must be a two-phase vapour process into one that operates in a single phase. Some wrong assumptions are:

- Process conditions (e.g., temperature, relative humidity and H_2O_2 concentration) throughout the enclosure can be made uniform.
- Condensation is to be avoided at all times.
- Comparatively gentle mixing of the enclosure is adequate.
- D-values for challenge microorganisms can be established.

In the actual two-phase H_2O_2 process, none of these assumptions is correct or attainable at the present time. These assumptions led to the establishment of vapour processes that are inadequate for their intended purpose. They do not adequately induce condensation or use sufficient mixing and thus fail to deliver reasonably consistent conditions throughout the enclosure. The experienced difficulties are a consequence of poor cycle design and not problems with the lethality of H_2O_2.

Second, biological indicators must be specifically designed for the intended process. While there have been attempts at this design, what has been accomplished is largely empirical. The methods used for manufacturing H_2O_2 biological indicators may be identical to those used for other sterilisation processes, but because correlation to actual process resistance is lacking, the process suggestions inferred from labelled resistance values are essentially unusable. In the absence of a BIER (and thus truly reproducible biological indicator resistance), the typical biological indicator process response can not be expected for vapour-phase H_2O_2 processes.

The most important attribute of any biological indicator is its reproducible resistance to the intended process. There is no established D-value method, which severely limits the certainty of process understanding and biological-indicator design and selection. Variable results with biological indicators could be attributable to either variations in the biological-indicator resistance or variation in the conditions resulting from poorly conceived controls for a complex process. Lacking a biological indicator whose response to the process is precise, vapour-phase decontamination and sterilisation becomes a more challenging process to control.

Third, there is a demonstrated biological indicator concentration effect associated with the H_2O_2 processes unlike that seen in other sterilisation processes. Biological indicators with a higher initial population have proven more difficult to kill with H_2O_2 than would be expected based upon the results of the same lot at a lower concentration (18). This phenomenon contradicts the core principle in all sterilisation processes that microorganisms die at a constant logarithmic rate regardless of population. Occurrence of this phenomenon in H_2O_2 processes can be attributed to several possible causes:

- Excess cellular debris and perhaps both organic and inorganic salts provide a protective layer of spores. This problem is somewhat exacerbated by the use of stainless-steel coupons that allow these materials to remain on the surface adjacent to the spores.
- The use of biological-indicator populations above what is necessary for process certainty creates potential for clumping of spores through which H_2O_2 penetration may not readily occur. FDA, US Pharmacopeia EMA, and the Parenteral Drug Association all accept biological indicator log reductions of 4–6 logs, where surface sterilisation is not the objective (15, 19-21).
- Some users adhere to an incorrect belief that a 10^6 spore population of the resistant biological indicator must be used to demonstrate a probability of nonsterile unit (PNSU) of $1x10^{-6}$.
- Inadequate processes that rely more on gas-phase kill than the substantially more lethal liquid-phase kill only serve to exacerbate all of the above problems.

All of these are correctable. Using a lower population biological indicator eliminates the first two of these difficulties. A hundred-fold reduction in spore population reduces the amount of debris present at the edge of the biological indicator drop and eliminates spore clumping significantly. This single change would result in more linear death curves than what has been evidenced. The third difficulty is a common mistake that is all too prevalent in the healthcare industry and has no basis in fact (22). The food industry has used H_2O_2 successfully for sterilisation for many years and operates without this artificial and erroneous expectation. The last issue is an artifact of the limited process understanding still prevalent on many existing H_2O_2 processes. In cases for which condensation is actively promoted in the process, fewer problems with sterilisation are encountered.

Much has been made recently of so-called "rogue" biological indicators. These rogues (i.e., outliers) are presumably biological indicators that failed to conform to the user's expectations of their demise. There is little doubt that the production of spore crops, substrate selection and the manufacture of biological indicators could result in clumping and encapsulation in contaminants that could result in a lack of uniform performance (23). Properly manufactured biological indicators should be largely free of outliers. Greater frequency of outliers detected in vapour H_2O_2 processes seems to be the result of poor understanding of vapour-phase H_2O_2 that results in marginally lethal processes and the creation of biofilms and clumps of spores on stainless steel at 10^6 concentrations, which result in what are effectively false-positive biological indicators that do not represent the elimination of normal flora at more diffuse concentrations.

Summary and recommendations

The successful use of any decontamination or sterilisation process requires a thorough understanding of the underlying principles of the process with particular attention to those aspects that differentiate it from other methods because these represent potential new learning. The two-phase nature of the vapour-phase H_2O_2 process introduces complexities that, if not well understood, can prevent successful use. The healthcare industry has experienced considerable difficulty in the implementation of this process.

The greatest improvements in operating these processes can be obtained through the use of conditions that force some measure of condensation and by recognition that the desired log reduction of these processes need not be excessive given the end use of the enclosure. Only product contact parts must be sterilised, and shifting attention to those locales within the enclosure alone would result in substantial improvements in process outcomes.

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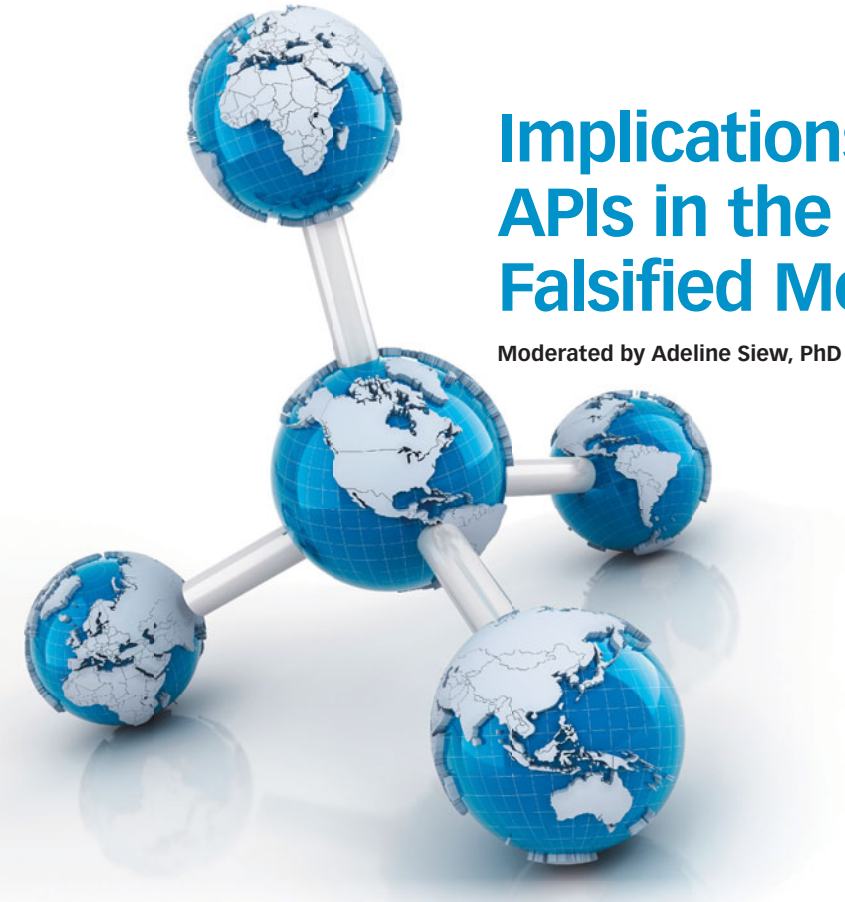

Implications for APIs in the European Falsified Medicines Directive

Moderated by Adeline Siew, PhD

Ensuring the quality of the pharmaceutical supply chain is of utmost importance to the pharmaceutical industry. The European Falsified Medicines Directive (FMD), which became effective in July 2013, requires that all active substances manufactured outside the European Union (EU) be accompanied by a written confirmation from the regulatory authority of the exporting country. These statements are to be issued per manufacturing site and per active substance to ensure that standards of good manufacturing practice (GMP), equivalent to those in force in the EU, are upheld. To gain insight on these provisions, two key industry groups, the Active Pharmaceuticals Ingredient Committee (APIC) and the European Fine Chemicals Group (EFCG), both sector groups of the European Chemical Industry Council (CEFIC), offered their perspectives on the strengths and weaknesses of the FMD.

The European Falsified Medicines Directive (FMD) seeks to prevent falsified medicines entering the legal supply chain in the European Union (EU). The directive was adopted in July 2011, and EU member states began applying provisions in January 2013. The purpose of the directive is to harmonise and strengthen safety and control measures across Europe in four main areas: safety features of medicines, the supply chain and good distribution practices (GDPs), active substances and excipients, and Internet sales (1–3).

From 2 July 2013, all active substances manufactured outside of the EU and imported into the EU must be accompanied by a written confirmation from the competent authority of the exporting country that confirms that the standards of good manufacturing practice (GMP) and control of the manufacturing plant are equivalent to those in the EU (4). These requirements constitute one of the main areas of change of the new FMD to provide a clear legal basis for the concept of international cooperation on active substances, which is based on sharing responsibilities with local regulators (4). The written confirmation is required per manufacturing site and per active substance and should provide the following assurances:

- Standards of GMP applicable at the plant are at least equivalent to those in force in the EU.
- The plant is subject to regular and strict controls and effective enforcement of GMP, including inspections.
- Information on findings relating to noncompliance is supplied by the exporting third country without delay to the authorities in the importing country in the EU.

The duration of validity of the written confirmation is established by the exporting non-EU country (4). As noted by the European Medicines Agency (EMA), these new requirements reinforce the need for pharmaceutical companies to ensure that the active substance manufacturers they are working with are registered with their respective local authorities and subject to adequate regulatory oversight (4).

Additionally, the directive specifies that exporting countries with a regulatory framework equivalent to that of the EU will not need to issue written confirmations subject to approval. Following a request from a non-EU country, the European Commission (EC), together with GMP experts from member states and with the support of the EMA, will assess the regulatory framework of the requesters, and if the assessment is positive, the county will be listed as an "equivalent country" (4). As of 2 July 2013, four countries have been listed by the EC: Australia, Japan, Switzerland and the United States. An equivalence assessment is ongoing for Brazil. Israel and Singapore have requested to be listed as an "equivalent country" (4).

To avoid the risk of shortages of medicines if the required written confirmation cannot be obtained, the FMD provides for a waiver from the written confirmation in exceptional circumstances. The waiver can be used where an inspection by an authority of the European Economic Area has been carried out with a positive outcome and the issue of a GMP certificate (4).

The FMD also puts into place measures on the distribution side of the pharmaceutical supply chain. It includes new responsibilities for wholesalers and a definition of brokering activities as well as new responsibilities for brokers. The EMA's revised guideline on GDP, which was published in February 2013, includes specific provisions for brokering activities (1–3, 5). Reflecting the inclusion of GDP into European provisions, the EudraGMDP database also now includes information on GDP. EudraGMDP is a modification of the EudraGMP database, which was launched in April 2007 to facilitate the exchange of information on compliance and noncompliance with GMP among the regulatory authorities within the European

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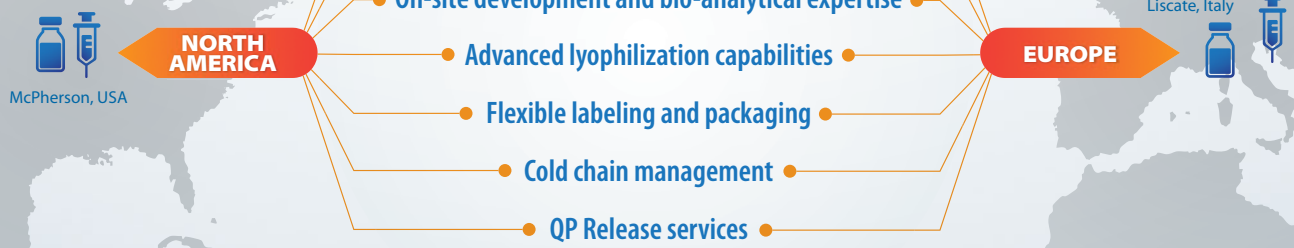

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medicines network. The new database, now called EudraGMDP, was a deliverable of the FMD. It is gradually being updated by medicines regulatory authorities in EU member states with distribution-related information and will be maintained on an ongoing basis (1, 5). The additional information will include: wholesale distribution authorisations; GDP certificates; statements of noncompliance with GDP; and registrations of manufacturers, importers (including information on their suppliers) and distributors of active substances (1, 5).

Although the FMD took steps to fortify the supply chain as it relates to APIs coming into the EU, there is concern that the FMD falls short in adequately strengthening the inspection process for APIs imported in the EU. To gain a perspective on these issues, *Pharmaceutical Technology Europe* discussed the FMD as it relates to API supply with representatives from the Active Pharmaceutical Ingredient Committee (APIC) and the European Fine Chemicals Group (EFCG), both sector groups of the European Chemical Industry Council (CEFIC), the trade association representing 29,000 large, medium and small chemical companies in Europe. APIC represents approximately 65 fine chemical companies, contract manufacturers and pharmaceutical companies. EFCG represents approximately 40 small, medium and large fine-chemical companies including four national and European industry associations: APIC; ASCHIMFARMA—the Italian Association of Manufacturers of Active Ingredients and Intermediates; CPA—Italy's Chemical Pharmaceutical Generic Association; and SICOS, which represents French fine and biochemical producers (6–8).

FMD sparks concerns

PTE: Do you think the measures contained in the FMD are sufficient to ensure the quality of pharmaceutical ingredients coming into the EU or are there other measures that need to be taken?

APIC and EFCG: No, the FMD does not sufficiently ensure the quality of APIs entering the EU. We have been very close to this topic since the FMD

Rx-360 advances supply-chain security

Rx-360, a pharmaceutical industry supply-chain consortium, is advancing approaches between pharmaceutical companies, suppliers and contract manufacturers as a means to better secure the pharmaceutical supply chain. *Pharmaceutical Technology Europe* discussed the group's recent activities and upcoming goals with Brian Johnson, chair of Rx-360 and senior director of supply-chain security at Pfizer.

PTE: Can you outline the key accomplishments of Rx-360 during the past year and what is planned in the near term?

Johnson: We continue to see headlines around the world where criminals are putting patient safety at risk to make money through counterfeiting, product diversion, theft and intentional adulteration. Substandard drugs with little or no active ingredient are being found at very high levels in the legitimate supply chains of many poor countries. Most experts and published data show that the problem is getting worse, not better. Globalisation and increasing supply-chain complexity are contributing to the problem. It is time to take action and Rx-360 is leading the way. Rx-360 is a global nonprofit consortium of more than 80 companies and organisations with a mission to protect patient safety by sharing information and developing processes related to the integrity of the healthcare supply chain and the quality of materials within the supply chain. Rx-360 accomplishes its mission through education, sharing information, promoting best practices and sharing audits. A few highlights from the past year demonstrate our commitment to action.

Education. Rx-360 believes that educating stakeholders on supply chain risks and, more importantly, solutions is key for the industry to be successful. A great example is Rx-360's recent "Protect Your Patients—Know Your Suppliers" campaign targeted at educating healthcare practitioners on the risks of product diversion. Rx-360 also conducted six free educational webinars for the industry this past year providing solutions and best practices for other supply-chain threats.

Sharing information. Supply-chain security is not a competitive advantage. Rx-360 believes that freely sharing information, such as alerts on potential supply-chain threats, is vital to the industry's success. Over the past year, Rx-360 issued 14 alerts, including a potential heparin shortage, use of 'gutter oil' in China, toxins in glycerin, reports on Hurricane Sandy and Avastin (bevacizumab). [Gutter oil is a term used in China to describe illicit cooking oil, which has been recycled from waste oil collected from various sources, such as restaurant fryers, drains, grease traps and slaughterhouse waste; improper use of gutter oil involves its use in excipient manufacture.] Rx-360 also published 80 summaries of new guidances, legislation and regulations.

Promoting best practices. It is not enough to talk about the risks; the industry needs to develop and share best practices. Over the past 18 months, Rx-360 developed and published seven white papers that contain the industries best thinking on various supply-chain security topics such as: preventing cargo theft; risks of drug shortages; tools for product diversion; auditing logistics service providers (LSPs); comprehensive supply-chain security programs; incident management processes; and monitoring the marketplace for threats—these examples are real solutions to real problems.

Sharing audits. Industry collaboration on sharing audit information and jointly conducting audits is crucial to improving the transparency of our increasingly complex and global supply chains. Rx-360 has completed and published almost 100 audits to date, and in 2013, we are on pace to double the number of audits completed in 2012, so we are quickly gaining momentum. Helping drive this initiative was the recent completion of a lean six sigma analysis of our audit programs and making modifications in the process to make it easier, quicker and more cost effective for companies to use. Our new database is also coming online, which takes a manual process and automates it, leading again to a simpler, more efficient process for all involved. We are also launching a pilot to conduct good distribution practice (GDP) audits, which we believe will help Rx-360 meet an important industry need. Finally, over the past year, we have been promoting the licensing of Rx360 audits by making it easy to purchase an audit already conducted by Rx-360 and helping to defer costs that sponsors of the original audit incurred. This approach allows companies sponsoring an audit to put proceeds towards future audits, thereby, increasing capacity and lowering costs.

For more information on Rx-360, including free tools and resources, see www.rx-360.org.

concept was born and we remain concerned that, despite its objectives, it fails to fully meet the needs of EU patients with respect to product quality. Its effectiveness is still too dependent on industry's supply chain self-evaluation and open to corrupt practices. Other measures that are needed include:

- Stricter enforcement of existing laws by all member state regulatory authorities, plus tough sanctions to punish the violators
- A consistent approach of member states when transposing the FMD into national law throughout the EU
- A change in the existing laws to include mandatory inspections by competent authorities of all API manufacturers with the industry paying for extra regulatory resources if needed similar to the Generic Drug User Fee Act (GDUFA) in the United States
- APIs contained in imported finished and semifinished drug products, mixtures of API with excipient(s) and semifinished (crude, moist) APIs should be included in the scope of the FMD.

The EC should have rigorously tested its assumption that there are 15,000–20,000 API manufacturers selling APIs into Europe before they decided not to propose the mandatory inspection of all API producers. In fact, the Heads of Medicines Agencies survey of medicine manufacturers in Europe, published on 27 Mar. 2013, showed that the top 18 third-country manufacturers/exporters of APIs to Europe had only 1479 manufacturing sites (9). It is, however, never too late for the EC to re-consider mandatory inspections to better protect EU citizens and patients.

Inspection process

PTE: One concern raised by the FMD is the adequacy of enforcement measures, particularly the inspection process with the new directive lacking a provision requiring mandatory inspections of API producers in third countries (i.e., countries outside the EU). From an industry perspective, what are the advantages/disadvantages of the current inspection process of API producers in third countries? In what areas can the process be improved and at what level/jurisdiction should it be made?

APIC and EFCG: The advantage of the current inspection process eases the continuity of supply of APIs from third countries for EU patients and, hence, avoids major product shortages. The disadvantage is the continued risk of substandard APIs/products entering the EU due to a lack of adequate enforcement and tough sanctions to punish individuals and companies. We suggest the following process improvements:

- Ideally, change the FMD to provide for mandatory inspections by EU authorities of API producers in third countries with industry helping to pay, or
- Achieve the same end result by providing for mandatory inspections of third-country API producers by European authorities together with other country authorities applying the same EU GMP standards to share the inspection responsibility via mutual recognition agreements (e.g., US, Australia and Japan)
- Inspectors should be trained to detect falsification or fraud, for example, facade constructions, ghost plants and falsified official papers.

GDP guidelines

PTE: Earlier this year, the EU finalised a guideline on GDP for medicinal products in the EU. Although it addresses the distribution of medicinal products from an end-market perspective, the intent of the guideline is to further ensure the quality of medicines coming into the EU. From an industry perspective, what are the implications for suppliers of APIs and other pharmaceutical ingredients?

APIC and EFCG: The industry must ensure transparency of sources and intermediaries (brokers and traders) and a register of evidence of compliance at each step along the entire supply chain from raw-material suppliers to the final medicine. Additionally, the EC published in

Industry perspective: The challenge for regulators

The European Falsified Medicines Directive (FMD) and its implementation continues to engender further insight by industry members. *Pharmaceutical Technology Europe* spoke to Guy Villax, CEO of Hovione, who offered additional perspective on the topic.

PTE: What are your thoughts on the FMD?

Guy Villax: The perspectives offered by the European Fine Chemicals Group (EFCG) and the Active Pharmaceuticals Ingredients Committee (APIC) of the European Chemical Industry Council (CEFIC) represent the view of the vast majority of the European Union's API industry.

In one respect, the European Medicines Agency (EMA) and the European Commission (EC) deserve credit for being innovative and taking a historical step in the defense of the patient. Never before the 'written confirmation' did so many regulators ever truly talk to each other, understanding what systems were truly in place in each country and finding common ground. The written confirmation process is forcing regulators to understand each others' systems and to make use of these systems to protect each others' backs. The collaborative model that the FMD has put forward is the right way to go, and for this, I say congratulations. Yet, the tough job for EMA, the heads of agencies and the EC lies ahead, and their success will be measured on two fronts.

Firstly, European regulators must take an uncompromising stand. Trust and integrity are central for this global process to succeed, and Europe must have the courage to blacklist publicly any country that fails the test and stop goods at the borders. Secondly, will regulators walk the talk? Will regulators truly make the most of the system they have created? For example, will the European Directorate for the Quality of Medicines & Healthcare (EDQM) demand that a current China FDA GMP certificate be included on a mandatory basis before a Certificate of Suitability (CEP) is issued to a China located API producer? And will EDQM suspend all such CEPs if such FDA GMP certificate is not on file by December 2013? And when I say CEPs, I also mean every one of the Chinese drug master files filed in support of marketing authorisations issued by the 28 medicine agencies.

February 2013 a draft guideline on the principles of Good Distribution Practices for Active Substances as part of the implementation of the FMD. Although this guideline only lays down the 'principles' of GDP, it will be a step in the right direction.

Supply-chain security

PTE: From an industry perspective, as regulatory and industry groups seek ways to fortify the pharmaceutical supply chain in an increasingly global environment, what are the implications in the outsourcing relationship, either from the perspective of a sponsor company (i.e., pharmaceutical company) or contract manufacturer/supplier?

APIC and EFCG: The sponsor company needs a contractor that it can trust to meet appropriate GMP standards in terms of product quality, quality culture, regulatory compliance with the laws of the country of product destination and delivery at a price they are prepared to pay. Roles and responsibilities with respect to manufacture and distribution, including sub-contracting or use of third party distributors, should be clearly defined and understood by both parties. The contractor should be aware of the relevant regulations and should be able to comply with them. They must not fail their sponsor by delivering sub-standard products.

Initiatives from APIC and EFCG

PTE: Can you outline key recent activities of APIC and EFCG in 2012 and 2013 in response to the EU FMD implementation and other measures that affect API supply into the EU?

APIC and EFCG: APIC and EFCG have been very active opposite the EC during the implementation of the FMD. We have written letters and made face-to-face representations to the EC's Directorate-General for Health and Consumers (DG SANCO) to point out the continuing risks to EU patients (we are all patients) and to the EU API manufacturing base (our members). The latter suffer unfair competition mainly from Asian API manufacturers, many of whose facilities fall well short of the EU-required GMP standard (ICH Q7) (10). We have challenged the "loopholes" that remain within the FMD, which unless rigorously enforced by the various national regulatory authorities, will not prevent substandard APIs from continuing to enter the EU market, either as bulk API (requiring written confirmations) or through formulated products (where there is no separate check on APIs). We are pleased to note via DG SANCO that the national authorities in China and India have severely limited the number of sites for whom written confirmations are permitted. APIC and EFCG will continue to press for mutual recognition agreements with other countries (e.g., US, Japan and Australia) that operate to the same GMP standards to help level the global playing field.

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Cover Story – *contin. from page 30*

In other work, scientists reported on the application of latent variables-based modeling to a reaction process in a small-molecule synthesis based on continuous-flow hydrogenation (11). In another study, scientists reported on using a QbD approach for designing improved stability studies (12). Also, scientists at UCB and the Institut des Sciences Moléculaires de Marseille in France recently reported on the feasibility of using online NIR spectroscopy as a process analytical technology tool to monitor in real time the API and residual solvent content to control the seeding of an API crystallisation process at industrial scale. A quantitative method was developed at laboratory scale using statistical design of experiments and multivariate data analysis (13).

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Application of Engineering Solutions to Solve Challenges in Pharmaceutical Processing: Case Studies from Development to Production Scale

ON-DEMAND WEBINAR

Register Free at www.pharmtech.com/solutions

EVENT OVERVIEW

Pharmaceutical manufacturing of solid oral dosage forms such as tablets and capsules involves several powder handling steps, including blending, transfer, granulation, fluid bed drying, tablet compression, and encapsulation. The inability to achieve reliable powder flow during these steps can have a significant adverse effect on the manufacturing a product. Production costs can be significantly higher than anticipated due to required intervention on the part of operators, low yield, or unplanned process redesign. Powder characteristics such as particle size distribution, bulk density, cohesiveness, stickiness, and static behavior can have a significant influence on manufacturing processes for small-scale or large commercial-scale operations. Low melting or softening solids can add another handling challenge in dosage form manufacturing, especially in cases where high speed tableting is required for large-scale manufacturing. The experience from multiple projects can help alleviate or solve many of these challenges regardless of the phase of the project.

Key Learning Objectives:

- Techniques to solve and prevent powder handling challenges.
- Innovative solutions to handle low melting, cohesive powders, and granulations in pharmaceutical manufacturing.

During this 60-minute interactive webcast, two industry experts will discuss challenges in powder and product handling such as flowability, stickiness, and the potential to soften or melt during the manufacture of solid dosage forms. They also will discuss the application of engineering solutions to overcome these processing challenges. Case studies will be shared to demonstrate possible solutions.

Anil Kane, Ph.D. Executive Director, Global Formulation Sciences, PDS at Patheon will discuss case studies in application of innovative solutions to solve critical powder handling issues in tableting/encapsulation.

James Prescott, Senior Consultant/Director, Jenike & Johanson, Inc., will discuss the use of bench scale tests to predict powder flow and segregation behaviors at production.

Presented by

Pharmaceutical Technology

Sponsored by

Patheon
Performance the World Over

Who Should Attend:

- Formulation scientists
- Formulation R&D managers, directors, and group leaders
- Process development scientists
- Process development managers, directors, and group leaders
- Section Heads
- Project Managers
- Technical personnel involved in formulation and development
- Scientists, manager, directors, and group leaders involved with formulation
- Manufacturing managers
- Technical personnel involved with QA/QC
- Technical personnel responsible for production scale work
- Process Engineers

Presenters:

Anil Kane, Ph.D.
Executive Director,
Global Formulation Sciences, PDS
Patheon

James K. Prescott
Senior Consultant and Director,
Jenike & Johanson, Inc

Moderator:

Rita Peters
Editorial Director,
Pharmaceutical Technology

For questions, contact Kristen Farrell at kfarrell@advanstar.com

Optimising Quality by Design in Bulk Powders and Solid Dosage

The changing development paradigm resulting from the US Food and Drug Administration's quality-by-design (QbD) initiative and International Conference on Harmonisation (ICH) guidelines requires increased process understanding of the drug substance and drug product throughout development and manufacturing. A lack of information can result in delays in regulatory approval and higher costs. Applying QbD principles leads to greater process understanding, facilitates regulatory approval and streamlines postapproval changes. Case studies on the manufacture of a bulk powder and the development of a tablet show the application of QbD principles, including defining critical quality attributes, implementing risk assessment, optimising process development, developing a design space and performing a criticality analysis.

Conrad Winters*, PhD, is director, Drug Product Development Group, cwinters@hovione.com, and **Filipe Neves, PhD,** is group leader, Drug Product Development Group, both at Hovione FarmaCiencia SA.

*To whom all correspondance should be addressed.

Quality by design (QbD) is often misquoted, misused and misunderstood. Pharmaceutical QbD is a systematic scientific risk-based approach to pharmaceutical development that begins with predefined objectives that address product and process understanding and process control (1). Many articles focus on what is required with respect to product quality, safety and efficacy but successful approaches are not commonly shared. Successful product development relies on consistent application of a proven methodology. The key steps are the same irrespective of the product or formulation being developed. A proven methodology is described in this article, with the framework shown in **Figure 1.** These main steps are further described as outlined below.

Main steps of a QbD process

Critical quality attributes (CQAs). CQAs are defined based on the target drug profile. These are quality characteristics of the drug that must be kept within appropriate limits to ensure the desired product quality (e.g., purity, crystalline form and particle size).

Figure 1: An overview of Hovione's quality-by-design approach. CQA is critical quality attribute, PAT is process analytical technology, NOR is normal operating range, FMEA is failure mode effect analysis.

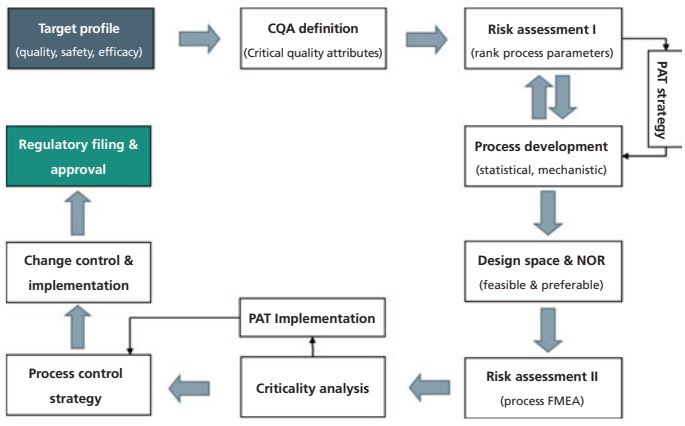
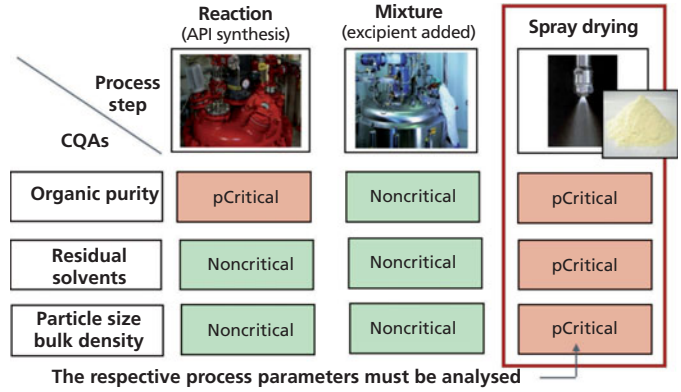


Figure 2: Risk assessment. Decomposing the process in main steps for a more structured criticality assessment (illustrative example for the bulk powder manufacturing process). CQA is critical quality attribute, p is potential.



Risk assessment during the development phase. For each CQA, an analysis of the potential critical process parameters (pCPPs) and potential critical material attributes (pCMAs) is conducted. The aim is to evaluate in each process step, operating parameters or raw materials that have the potential to affect a CQA within the known ranges, and therefore, should be monitored or controlled to ensure the desired quality. Because the number of parameters is usually high, a risk assessment based on prior knowledge of the product or process is used to rank the parameters in terms of perceived criticality. The ultimate goal is to keep the development process as lean as possible by focusing the studies on those parameters with a higher likelihood of having a critical impact.

Process development. The output of the risk assessment is a qualitative match between CQAs and pCPPs/pCMAs. To confirm the dependences and quantify the effects, a process-development stage is conducted. Usually a statistical approach is followed, through a sequence of design of experiments with different objectives—screening, optimisation and robustness studies. This development stage constitutes the core of the QbD methodology since most of the process knowledge is generated during this stage. Although not mandatory, a model, either statistical and/or mechanistic, is a usual outcome of this stage. Process analytical tools can also be considered at this stage based on the need to improve the CQA monitoring as the process is scaled up.

Design space and normal operating ranges (NOR). Once the impacts of the pCPPs/pCMAs are quantified on the CQAs, a feasible operating space can be defined. This space, known as the design space, will consider all the interactions between operating parameters and material attributes and will often be multidimensional. The NOR is established within the design space and can be thought of as the ranges where the process typically operates.

Risk assessment during manufacturing. After defining the design space and NOR, an exhaustive analysis of the process is conducted at the manufacturing scale. In this study, a failure mode effect analysis (FMEA) of all manufacturing aspects are reviewed, challenging the equipment operating ranges and procedures against the process knowledge gathered in the previous steps. The purpose of this study is to understand and quantify the risk of batch or process failure and to define actions to minimise failures.

Criticality analysis. By knowing the feasible operating regions and after evaluating the equipment/procedures at the manufacturing scale and the practical NOR, a final criticality analysis will take place to identify parameters and/or material attributes that will require tight monitoring or control. For example, all parameters for which the corresponding NORs are close to the boundaries of the design space.

Process-control strategy. Once the criticality around a process parameter and/or raw material attribute is confirmed, adequate control strategies will be set in place. The ultimate goal is to assure that the operation is always taking

All figures are courtesy of the authors.

Figure 3: Risk assessment: ranking of potentially critical process parameters per critical quality attribute (CQA) in each process step as the output of a risk-assessment matrix (bulk powder manufacturing process). T_out is drying gas temperature at the outlet of the spray drying chamber (ºC); T_cond is drying gas temperature at the exit of the condenser (ºC); P_feed is atomisation pressure of the feed (pressure nozzle) (bar); D_noz is diameter of the nozzle orifice (mm); T_feed is temperature of the solution fed to the spray drier (ºC), F_feed is flow rate of feed solution (kg/h); and C_feed is concentration of feed solution (% w/w).

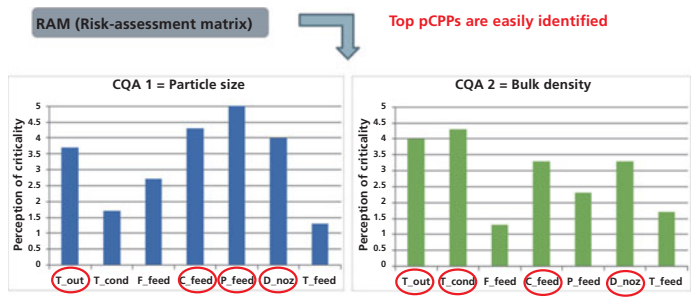
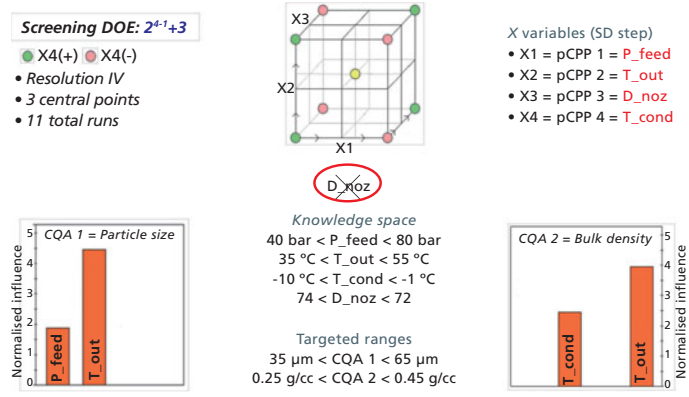


Figure 4: Design of experiments (DOE) (screening phase). Confirming the risk-assessment output by checking statistical significance of the most ranked parameters (bulk powder manufacturing process). CQA is critical quality attribute; SD is spray drying; pCPP is potentially critical process parameter; P_feed is atomisation pressure of the feed (pressure nozzle); T_out is drying gas temperature at the outlet of the spray drying chamber; D_noz is diameter of the nozzle orifice (mm); T_cond is drying gas temperature at the exit of the condenser.



place within the design space, therefore, assuring the quality of the final product. For this purpose and considering the dependence of a control strategy on a given monitoring capability, the final implementation of process analytical technology tools is carried out at this stage. The subsequent steps are mainly focused on the documentation aspects associated with the filing process and will not be addressed in this article.

Bulk powder development case study

CQA definition. This case study examines the preparation of bulk powder that is subsequently formulated as a tablet. The preparation of the powder was broken down into three stages: synthesis, excipient addition and spray drying. The spray-drying stage was identified as being potentially crucial for all CQAs and will be examined in more detail (see **Figure 2**). CQAs for the bulk powder were determined to be purity, residual solvent level, particle size distribution and bulk density among other but will not be addressed in this article.

Risk assessment. A risk assessment was completed to prioritise and reduce the number of parameters to be investigated in the study. This process is subjective and relies on the experience of the team members involved in the assessment. Having four or more inputs will help reduce bias and enable the top pCPPs to become evident in general (see **Figure 3**). It is important to recognise that at this point, all process parameters are only potentially critical; confirmation of criticality is only conducted later in the methodology.

Although identified as being a pCPP, certain parameters may need to be fixed because they impact other aspects of the process such as yield and throughput. In this study, the concentration of the feed solution was fixed and the outlet temperature (T_out), the feed pressure (P_feed) and the spraying nozzle diameter (D_noz) were varied.

A series of experiments were run as a screening study. Using a statistically valid design of experiments (DOE), eleven runs were made. These trials considered a 2^{4-1} half-factorial design with the centre point run in triplicates (see **Figure 4**). Once complete, the ranges of a DOE become the knowledge space for your product. Subsequent studies enlarge the knowledge space.

Data from this study indicated that a large portion of the knowledge space is viable to produce acceptable product. Subsequently, an optimisation DOE was run. Study resolution was enhanced with the addition of a third level at the midpoint. With two center point runs, this second study required 16 runs.

Meeting Regulatory and Technical Requirements for Organic Impurity Analysis

LIVE WEBCAST: US: Tuesday, Sept. 24 at 11:00 am EDT | **EU:** Tuesday, Oct. 1 at 15:00 CET

Register free at www.pharmtech.com/organic

EVENT OVERVIEW:

Organic impurities cover a wide spectrum of compounds that have varying structures, behaviors, and characteristics. Organic impurities can result from manufacturing, storage conditions, or degradation resulting from light, heat, and other external factors. Deciding what technology or analytical methods to use to detect and measure organic impurities is a challenge. This 60-minute webcast will provide insight on regulatory, compendial, and ICH requirements on organic impurity control and analysis. Learn from leading experts on best practices in analytical method development, method selection, and method validation for detecting and quantifying organic impurities in drug substances and drug products.

Key Learning Objectives:

- Learn from experts on the latest regulatory and compendial requirements for organic impurity control and analysis in drug substances and drug products
- Gain insight on selecting the appropriate analytical methods for detection, analysis, and quantification of organic impurities
- Learn from case studies on how best to ensure product quality

Who Should Attend:

- Directors, group leaders, managers, and senior staff of QA/QC
- Directors, group leaders, managers, and senior staff of regulatory affairs
- Analytical chemists
- Formulation scientists
- Process development scientists
- CMC (chemistry, manufacturing and control) managers and directors

Presenters

Tim Watson, PhD
Research Fellow
GCMC Advisory Office
Pfizer

Mark Argentine, PhD
Senior Research Advisor
Analytical Sciences R&D
Eli Lilly

Hildegard Brümmer, PhD
Operational Laboratory Manager
SGS Life Science Services, Berlin

Moderator

Patricia Van Arnum
Executive Editor
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Figure 5: Design of experiments (DOE) (optimisation phase). Increasing the prediction accuracy of screening models (for design space establishment) via refinement of the mathematical relationships (bulk powder manufacturing process). CCD is central composite design; CQA is critical quality attribute; T_out is drying gas temperature at the outlet of the spray drying chamber; P_feed is atomisation pressure of the feed (pressure nozzle).

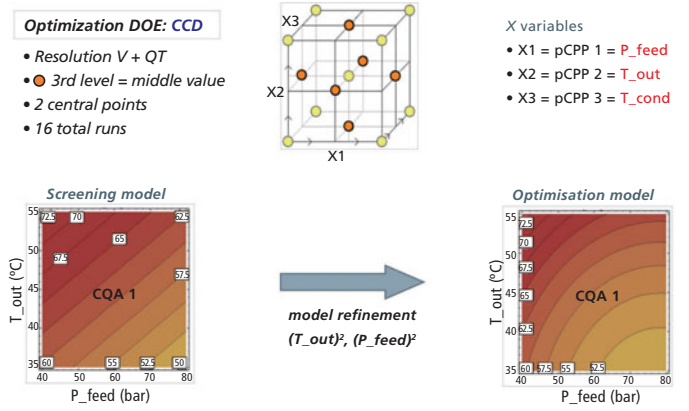
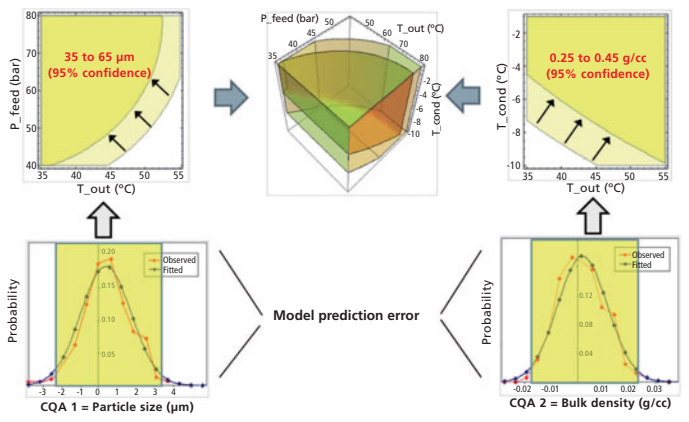


Figure 6: Uncertainty analysis. Considering model prediction errors to regress the boundaries of the design space and, in this way, define confidence levels for the resulting operating spaces. CQA is critical quality attribute; P_feed is atomisation pressure of the feed (pressure nozzle); T_cond is drying gas temperature at the exit of the condenser; T_out is drying gas temperature at the outlet of the spray drying chamber.



Data from this study led to a refinement of the model and the generation of quadratic terms to describe the particle-size relationship (see **Figure 5**).

At this stage, models exist for each CQA. As both CQAs must be met simultaneously, the design space will narrow, adding complexity to the problem. One further level of complexity comes from the uncertainty in the model. Working at the edge of a modeled range brings risk to the process. Working, for example, at the 95% confidence interval of the model reduces the risk of generating material with CQAs outside the specification limits while maintaining a broad operating space (see **Figure 6**).

The NOR is defined as the preferable operating range within the identified design space. Working within this sub-region of the design space, the NOR may have benefits of reduced operating costs and increased productivity or preferential product characteristics. The NOR is dependent on the controllability of the process, which may be equipment or plant dependent. For example, the temperature control of the equipment may be limited to +/- 1.0 °C, thus a NOR tighter than +/- 0.5 °C is not achievable.

A criticality analysis will determine which process parameters need to be most closely monitored. Each process parameter will have a different effect on a CQA. Normalising these impacts will highlight which parameter exerts the greatest influence on a CQA. Larger normalised values imply increased sensitivity and potentially undesirable effects on CQAs. Ideally, the NOR should be away from the edge of the design space and correspondingly, the design space should be away from the edge of failure. Proximity of the design space towards the edge of failure could mean that deviations from the design space result in out-of-specification material. In this specific example, the achievable NOR in equipment "A" was small relative to the design space and control was readily achieved (see **Figure 7**).

Drug product case study

The identical methodology to that used for the bulk powder can be applied to the development of a drug product.

CQA definition. A finished dosage form has a number of CQAs, some under regulatory control and others that are product specific. In this example, a direct compression formulation was considered, where a spray-dried dispersion (SDD) was a significant component of the final formulation. The CQA of tablet hardness will be examined in greater detail.

Risk assessment. The components of the formulation are the SDD, excipients as compression aids, the disintegrant and the lubricant. The level of excipient was fixed to limit the resulting tablet size. The risk assessment for tablet hardness determined that the SDD properties, lubricant level and mixing time, tablet press speed and compression force were pCPPs.

Process development. Figure 8 shows the relationships between particle size (Dv50), bulk density (BD) and moisture content (KF) that were determined from a separate series of DOE studies. Additionally, it also shows the range of material properties that could be prepared. For the compression analysis, materials indicated by the red points were selected to give a broad range of physical properties. Blends were prepared and, after some preliminary ranging studies, were run at two press speeds and two compaction forces.

The resulting correlation with tablet hardness for the process parameters examined show a weak relationship to KF and BD, and more sensitivity to compaction force and press speed despite studying a relatively low range of press speeds (see **Figure 9**). From this study, target hardness specifications were generated and will be re-evaluated as the scale-up work progresses.

Conclusion

In summary, QbD is a synonym for process understanding. The greater the understanding of the process, the less likely the generation of out-of-specification material.
In the development process, a qualitative risk assessment helps contain the development scope and use a manageable number of experiments to define the design space. The use of statistical design approaches is essential to address an appropriate number of parameters and interactions. Once a model is generated, uncertainty analysis should be factored in to the definition of the design space to ensure that the operation is not taking place close to the edge of failure, or when it is, that a proper control strategy is set accordingly.

Reference

1. ICH, Q8 (R2) *Pharmaceutical Development* (2009). **PTE**

Figure 7: Criticality analysis. Proximity of the normal operating range (NOR) towards the boundaries of the linear-design space. Desirable (Equipment A) and undesirable (Equipment B) scenarios (bulk powder manufacturing process). CQA is critical quality attribute; P_feed is atomisation pressure of the feed (pressure nozzle); T_out is drying gas temperature at the outlet of the spray drying chamber.

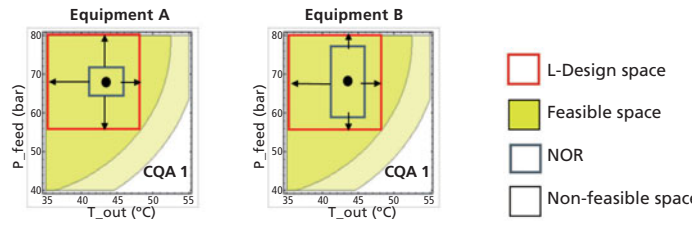


Figure 8: Design of experiments (screening phase). Linking critical quality attributes of the intermediate bulk powder process with potentially critical process parameters of the final dosage form process (tabletting). Dv50 is volumetric mean particle size of the product; KF is the residual moisture of the bulk powder by Karl-Fischer; BD is the bulk density of the product.

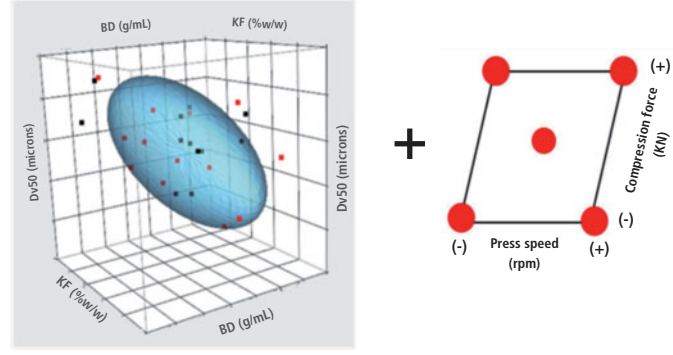
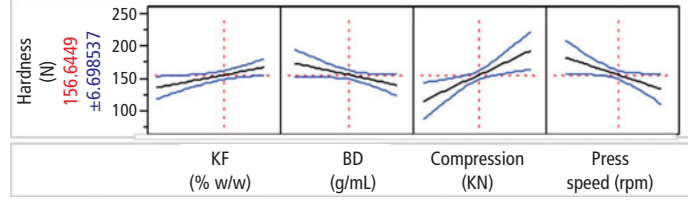
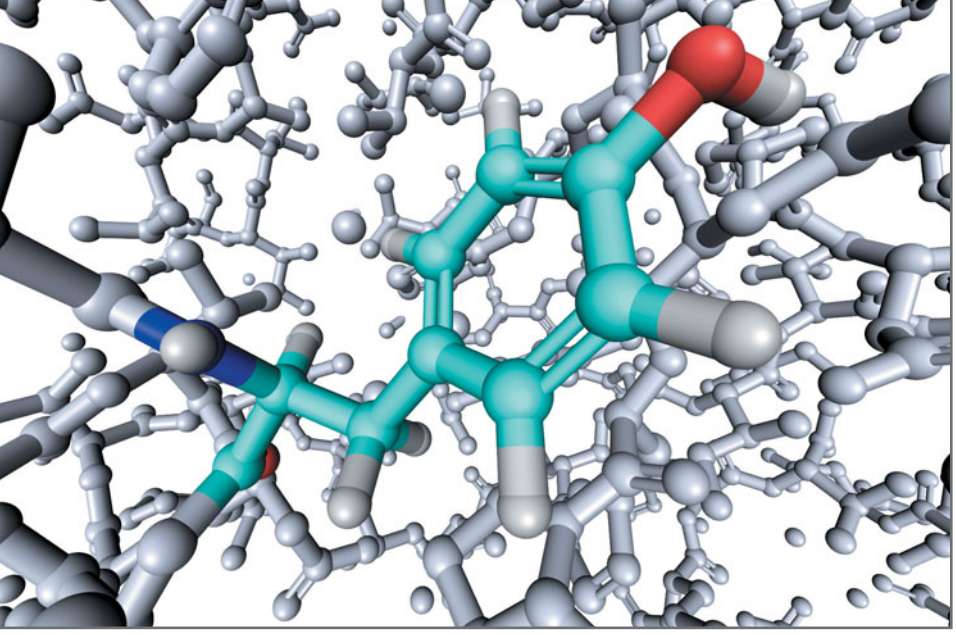


Figure 9: Design of experiments (screening phase). Modeling relationships between critical quality attributes (tablet hardness) and different potentially critical process parameters (final dosage form process). KF is the residual moisture of the bulk powder by Karl-Fischer (% w/w); BD is the bulk density of the product (g/mL).



To view the on-demand *Pharmaceutical Technology* webcast, "Optimising Quality by Design in Bulk Powders and Solid Dosage Forms," go to www.PharmTech.com/bulk. The webcast provides insight on how to apply QbD by learning how to define critical quality attributes, implement risk assessment, optimise process development, develop a design space, perform criticality analysis and execute a control strategy with reference to two case-studies involving bulk powders and solid dosage forms.



Advancing API Synthesis

Commercial-scale amide formation and an improved process route for a tetracycline derivative are some recent developments.

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

Process chemists in the fine-chemicals and pharmaceutical industries are tasked with developing optimal routes for manufacturing pharmaceutical intermediates and APIs. Among their challenges, they must develop approaches to improve yield, purity, stereoselectivity and solid-state properties for a given API while optimising production economics as a product moves from development to commercial scale. Some interesting recent developments include commercial-scale amide formation and an improved process route for a tetracycline derivative.

Commercial-scale amide formation

It is well known that amide-formation chemistry can be inefficient and warrants further investigation. This issue has been addressed in the chemical literature, most recently in a study by the American Chemical Society Green Chemistry Institute Roundtable that is particularly relevant to pharmaceutical synthesis (1). The study found that, out of a random selection of drug candidates, amide-bond formation was used in the synthesis of 84% percent of drug candidates.

The only theoretical by-product of amide formation is water, but examples of this type of reaction are incredibly rare, according to Barrie Rhodes, director of technology development for the CMO Aesica. "Frequently," he says, "commercial-scale amide syntheses for pharmaceutical manufacture require overly complex stoichiometric coupling agents or reagents."

Aesica has set as goals the reduction of this complexity in conventional amide syntheses and the development of more sustainable (green) chemical transformations that are practical on a commercial scale. In the pursuit of those goals, the company has partnered with the University of Nottingham for the commercial development of alternative methods in amide-bond synthesis. The partnership's aim is to revolutionise traditional amide-formation techniques by generating alternative methods for amide-bond formation that will be more eco-friendly and chemically versatile, according to Rhodes.

The new approach should be commercially available to Aesica customers later in 2013. The company is actively seeking commercial opportunities to work with potential compounds that could benefit from the novel technology. "We envisage this new development helping pharmaceutical companies that encounter problems with amide synthesis, and due to the utilisation of more sustainable reagents, production costs will be lowered while chemical yields will be increased," Rhodes notes.

The initial chemistry was developed in 2005 by Simon Woodward, professor of synthetic organic chemistry at the University of Nottingham in the United Kingdom. The coupling reagent of interest is DABAL-Me3, which is an adduct of trimethylaluminum and DABCO (1,4-diazabicyclo[2.2.2]octane). Unlike trimethylaluminum which is very pyrophoric, DABAL-Me3 is a free-flowing solid that can be handled in air (2). In addition to its use in amide-bond formation (3), DABAL-Me3 has been used for the methylation of aldehydes and imines (4, 5), the methylation of aryl and vinyl halides (6), and conjugate additions to enones (7).

With respect to amide bond-formation, DABAL-Me3 can be used to generate amides from unactivated esters and amines that, with conventional routes, require the use of trimethylaluminum or diisobutylaluminum hydride (3). In addition, reactions with DABAL-Me3 tolerate various functional groups, including acetals, alcohols, alkenes, alkynes, ethers, nitriles, hindered esters and BOC groups. Stereocenters in non-peptidic species are not racemised. Importantly, the preparation of aromatic and aliphatic amides can generally be carried out in an air atmosphere. It should be noted that the rate of the reaction can be accelerated with the use of microwave irradiation, and products can be isolated in 51–99% yield in 8–16 minutes (8).

Preliminary studies on DABAL-Me3 at the university were undertaken using funds awarded by the Engineering and Physical Sciences Research Council (EPSRC) under the Research Development (Pathways to Impact) Funding Scheme. "Since realising the initial development of our coupling agent in 2005, one of our goals has been to see this novel technology used in larger-scale industrial environments," remarks Woodward. "We look forward to

collaborating with Aesica and seeing the full commercial potential of this novel technology in API manufacture," he adds.

The chemistry that Aesica is commercialising is more atom-efficient than some other types of amide-formation chemistry and offers a novel synthetic route to make amides from both esters and carboxylic acids, according to Rhodes. Some of the technology is in the very early stages of development and will likely be patentable, so Rhodes is unable to disclose any additional details. He does note that the chemistry is generally applicable and flexible in terms of its ability to prepare amides, and therefore, any API that either contains amide bonds or goes through an amide intermediate during its synthesis could benefit from this technology. In addition, Rhodes believes that the new amide production technology will enable cheaper and simpler routes to market for many compounds.

This partnership with the University of Nottingham is the Aesica Innovation Board's (AIB) fourth with an academic institution in less than six months, according to Rhodes. The AIB was established to help bridge the growing R&D gap by identifying early-stage technologies for development into commercial applications.

"The University of Nottingham is renowned for its excellence in chemistry research and has a strong background in green and sustainable chemistry. That, coupled with its interest in open innovation (in that risk and reward are shared) as a model, has been very beneficial. Effectively, the university has the expertise in terms of the technology while Aesica brings its expertise in terms of commercialisation and a global network in the pharmaceutical industry," Rhodes explains.

The partnership for the development of amide bond-formation chemistry is just the start of a hopefully long-term collaboration between Aesica and the university, according to Rhodes. The collaboration builds upon announced plans by the University of Nottingham to establish a Center of Excellence for Sustainable Chemistry, which will be partly funded by an investment from the Higher Education Funding Council for England UK Research Partnership Investment Fund. The Center aims to form creative partnerships with innovative companies to develop new chemical-based technologies that minimise environmental impact and are both energy and resource efficient, according to a university press release.

"As Aesica further enhances its innovation program, we will seek to develop new technologies, not only with the University of Nottingham, but with other academic institutions as well, in the fields of both API and formulated products manufacture," concludes Rhodes.

One of the hurdles that the researchers had to overcome in developing the large-scale synthesis of eravacycline was the sensitivity of the Michael–Dieckmann transformation to the reaction conditions.

Process-scale synthesis of tetracycline derivative

Tetracyclines comprise a group of antibiotics that are recognised as safe and effective and are thus commonly used to treat serious bacterial infections and other less severe conditions such as acne. Unfortunately, because tetracyclines are commonly used, many bacteria have developed resistance to the older versions of these drugs. Recent efforts have thus been directed at developing new tetracycline derivatives.

Scientists at Tetraphase Pharmaceuticals are overcoming this barrier by implementing a new synthetic route first reported by Myers in 2005 (9). This approach involves the coupling of a cyclohexenone intermediate that contains the key tetracycline functionalities with a second functionalised aromatic intermediate via a Michael-Dieckmann reaction, thus enabling the incorporation of a variety of different substituents at various positions in the tetracycline skeleton. Using this methodology, Magnus Ronn, vice-president of CMC at Tetraphase Pharmaceuticals and his colleagues at the company recently reported the successful preparation of eravacycline, a fully synthetic broad spectrum 7-fluorotetracycline in clinical development, in multihundred gram quantities (10). A summary of their work is presented below.

The advantage of this approach to the synthesis of tetracycline analogues is that a single key intermediate can be used to access a wide range of substituted tetracycline active pharmaceutical ingredients (APIs)," says Ronn. This key intermediate is a tricyclic cyclohexenone with three chiral centers (the synthesis of this compound was reported previously [11]). The enone is reacted with a suitably functionalised phenol bearing an ortho-carboxyphenyl group and a meta-methyl substituent. Other functionalities are included as needed to produce the desired tetracycline analogue.

This aromatic compound, referred to by the researchers as the lefthand piece (LHP), is deprotonated with a strong base to form a benzylic anion, which then undergoes diastereoselective 1,4-conjugate (Michael) addition to the enone moiety when added to the cyclohexenone. The ketone enolate that forms from this step undergoes a Dieckmann-type condensation with the phenyl ester to produce the protected tetracycline compound. To obtain the desired tetracycline analogue, this intermediate is subjected to subsequent silyl-ether cleavage and hydrogenolysis of the benzyl-protecting groups with concomitant reductive ring opening of the isoxazole (10). The LHP selected for the preparation of eravacycline is a benzyl-protected phenol with a fluorine atom and a dibenzylamine substituent. It was prepared from a commercially available starting material in seven steps, the synthesis of which will be published in the future (10).

One of the hurdles that the researchers had to overcome in developing the large-scale synthesis of eravacycline was the sensitivity of the Michael–Dieckmann transformation to the reaction conditions, according to Ronn. Not only the order of addition, but also the strength of the base was important for the two different deprotonation steps (10). Thus, the researchers reported that it was necessary to first deprotonate the LHP (1.04 equivalents of LHP is used) with lithium diisopropylamide (LDA, 1.13 equivalents) and then add the generated anion to a solution of the cyclohexenone and the weaker base lithium bistrimethylsilylamide (LiHMDS) at -70 °C. The desired adduct was isolated after workup and trituration with methanol in > 90% yield a 98% purity (using high-performance liquid chromatography), even on the 200-g scale (10).

Because both the deprotonation and the Michael–Dieckmann reaction should be performed at -70 °C, two cryogenic reactors are required. The researchers reported that attempts to eliminate one of those reactions by raising the temperature of the cyclohexenone solution to -20 °C led to increased production of impurities (10).

To obtain eravacycline, the first step after the Michael-Dieckmann reaction involved cleavage of the tert-butyl silyl (TBS) protecting group. Despite the issues associated with using hydrofluoric acid in commercial manufacturing, the researchers reported that this reagent gave better results than other investigated alternatives and it was thus selected for scale-up (10).

Reductive ring opening of the isoxazoline group and removal of the four benzyl groups using palladium on carbon(Pd/C)/hydrogen to give the 9-amino-7-fluoro-sancycline required extensive investigation by the researchers (10). A mixed solvent system of tetrahydrofuran (THF) in methanol (1:3) was required because of solubility issues. An acid additive was also needed to improve the rate of the hydrogenation reaction, but epimerisation at the C-4 position and reduction of undesired groups led to the formation of impurities, including one that was very difficult to separate from the desired product. The reaction was optimised using concentrated aqueous hydrochloric acid (HCl) because it is a stable reagent with a reliable concentration. The palladium on carbon was removed using Celite, and residual palladium was eliminated with the metal scavenger (SiliaBond DMT, Silicycle). The desired hydrochloride salt was precipitated from water/ethanol in approximately 80% yield and high purity (< 2% of the undesired impurities), even on a large scale (10).

We are continuing to improve the process for future larger-scale manufacturing and are also developing an isolation procedure that will be suitable for commercial production of eravacycline.

Next, the hydrochloride salt of the fully deprotected penultimate intermediate was coupled with the desired side chain to prepare eravacycline. The reaction was carried out in acetonitrile and water. To achieve complete conversion, several charges of the acid chloride were necessary. It was also found that adjustment of the pH from approximately 3 to approximately 7 after the second charge aided the complete dissolution of the starting material, allowing the reaction to go to completion. After the completion of the coupling, the pH of the reaction solution was brought to pH 6.8 to ensure hydrolysis of any over-acylated compounds to the desired tetracycline product.

Eravacycline was extracted using dichloromethane at pH 7.4. As an added benefit, the researchers found that the undesired C-4 epimer was partly removed in the aqueous layer and when the dichloromethane solution was dried with sodium sulfate prior to evaporation, thus increasing the purity of the tetracycline product (10). Finally, the bis-hydrochloride salt of eravacycline was prepared using an ethanol–methanol mixture containing an excess of hydrogen chloride and precipitated with addition of ethyl acetate.

"While some of the steps presented challenges, this overall route to eravacycline has enabled the production of sufficient quantities of the API for clinical testing. This tetracycline derivative has completed Phase II clinical studies and has been shown to be active against multidrug resistant bacteria and is therefore a candidate as a broad spectrum antibiotic for serious hospital infections. We are continuing to improve the process for future larger-scale manufacturing and are also developing an isolation procedure that will be suitable for commercial production of eravacycline," Ronn notes.

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The Basics of Measurement Uncertainty in Pharma Analysis

How good is a reportable value?

Christopher Burgess, PhD, is an analytical scientist at Burgess Analytical Consultancy Limited, 'Rose Rae,' The Lendings, Startforth, Barnard Castle, Co Durham, DL12 9AB, UK; +44 (0) 1833 637 446; chris@burgessconsultancy.com; www.burgessconsultancy.com.

All measurements are subject to error. When a reportable value is derived from a measurement or series of measurements, this value is only an estimate of the "true" value and has a range around it associated with how confident one is that the true value lies within it. Traditionally in the pharmaceutical industry, a range is selected corresponding to 95% confidence (1).

Reportable value data quality

The quality of a reportable value or an analytical result depends upon the size of the confidence interval. The smaller the confidence interval is, the more confident one is in relying on one's reportable value or analytical result. Unfortunately, also for historical reasons relating primarily to physical metrological considerations, the International Organisation on Standardisation (ISO) uses the term "measurement uncertainty" (MU) for the same concept (2).

One difference between the ISO MU approach and the International Conference on Harmonisation (ICH) Q2(R1) and *United States Pharmacopeia* (*USP*) approaches is that in the latter, the effects of imprecision and bias are considered separately (3). It should be noted, however, that the *USP* General Chapter <1225>, "Validation of Compendial Procedures," and related General Chapters <1224>, "Transfer of Analytical Procedures," and <1226>, "Verification of Compendial Procedures," are under revision at present (4–6).

USP General Chapter <1010>, Analytical Data—Interpretation and Treatment, clearly states that accuracy has a different meaning from ISO (7). The USP states, "In ISO, accuracy combines the concepts of unbiasedness (termed trueness) and precision," and *USP* further defines a conventional 95% confidence interval around the mean of

$$\bar{X} \pm t_{(0.05,\ n\text{-}1)} \frac{S}{\sqrt{n}}.$$

The term $\frac{S}{\sqrt{n}}$ is the standard error of the mean and is called the standard uncertainty in ISO.

$t_{(0.05,\ n\text{-}1)}$ is called the coverage factor.

$t_{(0.05,\ n\text{-}1)} \frac{S}{\sqrt{n}}$ is called the expanded uncertainty in ISO.

Another difference is the way in which the standard deviation (s) is calculated. The ISO approach is by means of a calculated error budget (8), whereas the ICH Q2(R1) relies upon information derived from an experimentally designed analytical trial (3). Theoretically, these two approaches should yield similar results. In practice, however, this is not always the case. ISO also uses a different nomenclature from ICH. What would usually be called the analytical measurement or result is called in ISO the measurand. This measurand is the particular quantity subject to measurement and is related to the measured analytical response function by means of an equation in the same way as an analytical result.

Concept of an error budget

The idea behind an error budget is that if all sources of error are known, it is possible to calculate an estimate of the uncertainty of the measurand or reportable value based upon converting all the errors to standard deviations and then combining the variances. If all the error processes are independent, then an error budget can be defined in five steps:

- Define all the process elements involved and their interrelationships
- Define the measurand in terms of these process elements
- Identify all error sources and group them as required
- Estimate their individual contributions and convert them to standard deviations and combine them to produce an overall estimate of standard deviation
- Estimate the overall uncertainty using an appropriate coverage factor as described previously.

Figure 1 shows the error budget process diagrammatically.

An example of a simple error budget for a standard solution. The error budget approach may seem rather daunting, but a simple example of the preparation of a standard solution will make things clearer. This example is a common task in the laboratory, but few calculate how good their standard solutions are.

The reference standard purchased has a certified purity of 99.46 ± 0.25. Approximately 100 mg of this reference standard is weighed, by difference, accurately using a five-place analytical balance. The

reference standard is dissolved in water and a solution is made up to the mark with water in a Grade A 100.0 mL capacity volumetric flask at ambient laboratory temperature. It is assumed that the laboratory temperature is controlled but may vary between 16 °C and 24 °C. The first step is to draw a flow diagram of the analytical process used to prepare the standard solution. This diagram is shown in **Figure 2**.

Identify the measurand. In this instance, the measurand (C) is the concentration of the reference material in the standard solution in mg l^{-1} and is defined by the equation:

$$C = \frac{mP}{V} 1000 \text{ mg} 1^{-1}$$

where m is the mass of reference material in mg. P is the purity as a mass fraction of the standard, and V is the volume of the volumetric flask in mL.

Identify the error sources. Based upon the analytical process flow (see **Figure 2),** one can now identify three main areas of error, namely, the reference stand itself, the weighing process and the solution and the final volume of the solution. It is helpful to use a Ishikawa diagram to aid the identification and grouping of error sources. For this example, the Ishikawa diagram is shown in **Figure 3.** In **Figure 3**, the possible sources of error are shown for each of the three groups. In this example, it is assumed that the reference standard is sufficiently homogeneous to ignore any error contribution and is freely and easily soluble in water.

Note that the volume of the solution has three distinct uncertainty components that need to be taken into account:

- The uncertainty in the marked calibration volume of the volumetric flask itself at 20 °C
- The difference between the calibration temperature of the flask and the temperature at which the solution was prepared
- The uncertainty associated with filling the flask to the calibration mark.

Not all error contributions are of equal importance. To find out which error contributions are of importance, however, it is essential to convert all errors to standard deviations (8).

Figure 1: Error budget process.

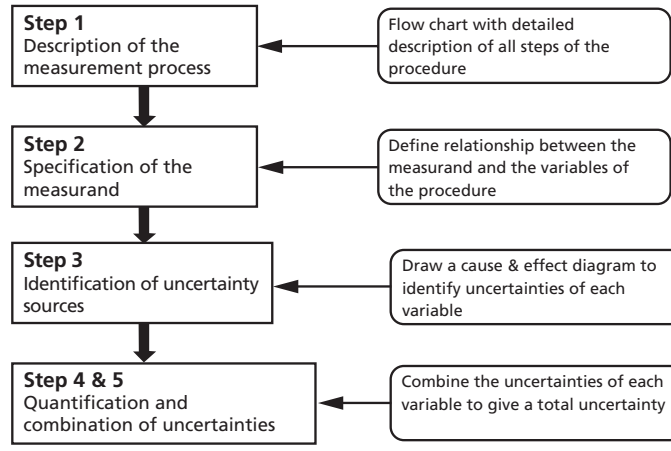
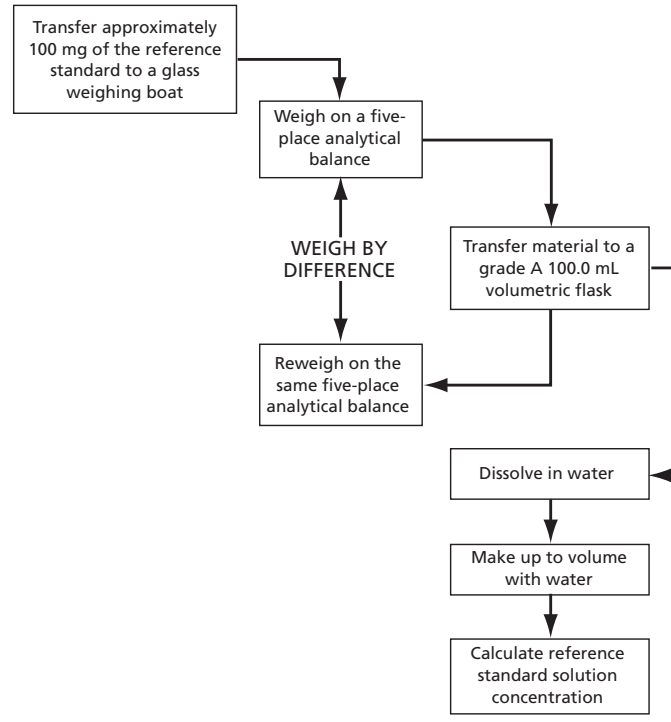


Figure 2: Analytical process flow for preparing the standard solution in the example.



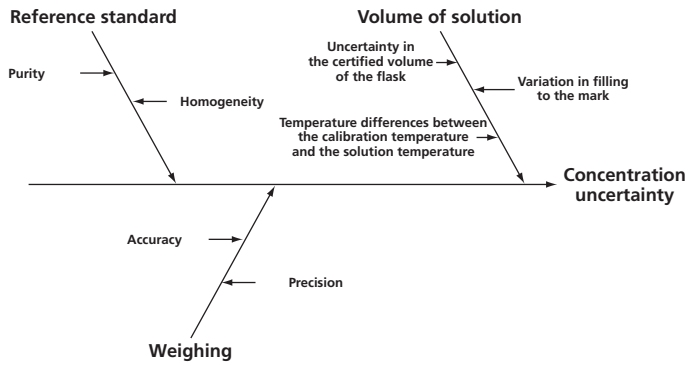
Processes to convert specifications, ranges and measurement data into a standard deviation. The easiest method to evaluate the standard deviation is by the statistical analysis of series of observations and assume the normal distribution. In the example, this method would be used in determining the uncertainty of filling the volumetric flask to the mark. This direct determination is known as a Type A uncertainty.

Type B uncertainties are derived from two approaches:

- Converting certificate ranges where there is no knowledge of the shape of the distribution so the rectangular distribution is assumed. For a range of ± a, the corresponding estimate for the standard deviation would be $a/\sqrt{3}$. In

All figures are courtesy of the author.

Figure 3: Ishikawa diagram for our analytical process.



the example, the uncertainty in the purity of ± 0.25 would be converted using the rectangular distribution.

- If it is more likely that the value lies closer to the central value, then the triangular distribution is assumed. For a range of ± a, the corresponding estimate for the standard deviation would be $a/\sqrt{6}$ In the example, the uncertainty in the grade A volumetric flask of ± 0.10 would be converted using the triangular distribution.

Uncertainty contributions in the example. Now we can proceed to quantify all the uncertainties in our analytical process in the following manner:

Reference standard uncertainty, u_P. Using the rectangular distribution we have:

$$u_P = \frac{0.0025}{\sqrt{3}} = 0.001443$$

Note that the purity and its uncertainty have been converted to mass fractions.

Weighing uncertainty, u_m. Using the balance manufacturer's data (Type A) we have:

$$u_m = 0.05 \text{ mg}$$

Note that our actual value of weighed material was 100.28mg.

Volumetric uncertainty (u_v). Here we have three different contributions to u_v:

The flask itself using the triangular distribution:

$$u_{vc} = \frac{0.10}{\sqrt{6}} = 0.04 \text{ mL}$$

The temperature effect assuming the coefficient of expansion of water of 0.00021 °C-1 and assuming the rectangular distribution:

$$\text{Volume variation} = \pm(100(4)(0.00021)) = \pm 0.084 \text{ mL}$$

$$u_{vT} = \frac{0.084}{\sqrt{3}} = 0.05 \text{ mL}$$

and the Type A uncertainty associated with the filling of the flask to the calibration mark. This was determined by the filling repeatability for $n=6$ assuming a normal distribution; u_{vr}=0.02 mL.

One can now combine these three standard deviations to arrive at the overall volumetric uncertainty

$$u_v = \sqrt{u_{vp}^2 + u_{vr}^2 + u_{vT}^2}$$
$$= \sqrt{(0.04)^2 + (0.02)^2 + (0.05)^2}$$
$$= 0.07 \text{ mL}$$

Finalising the error budget. Now that all uncertainties have been converted into standard deviations, they can be combined to produce an uncertainty for the measurand C as shown in **Table I** and using the variance combination equation:

$$\frac{u_c}{C} = \sqrt{\left(\frac{u_p}{P}\right)^2 + \left(\frac{u_m}{m}\right)^2 + \left(\frac{u_v}{V}\right)^2}$$
$$= \sqrt{(0.001443)^2 + (0.0005)^2 + (0.0007)^2}$$
$$= 0.00168$$

It is important to note that the uncertainty contribution from the reference standard is greater than either the weighing or the volumetric errors.

Expression of confidence: calculating the reportable value and its uncertainty. The concentration of the reference standard solution is directly available from the measurand equation,

$$C = \frac{mP}{V} 1000$$
$$= \frac{100.28(0.9946)}{100.0} 1000$$
$$= 997.4 \text{ mg1}^{-1}$$

The uncertainty in the measurand u_c and the expanded uncertainty U are now readily available.

$$u_c = 0.00168C$$
$$= 0.00168(997.4)$$
$$= 1.68mg$$
$$U = \pm ku_c$$
$$= \pm 2u_c$$
$$= \pm 3.36$$

Table I: Combined uncertainty for the measurand C.

Description	x	Value x	U_x		$\frac{u_x}{X}$	
Purity of reference standard	P	0.9946	U_P	0.001443	$\frac{u_P}{P}$	0.001443
Mass of the reference standard mg	m	100.28	U_m	0.05	$\frac{u_m}{m}$	0.0005
Volume in the flask ml	V	100.0	U_V	0.07	$\frac{u_v}{V}$	0.0007

The coverage factor of k=2 corresponds to a confidence of 95.45%.

Based upon this expanded uncertainty, we calculate that we have confidence that the standard solution uncertainty is approximately 0.34%.

Summary

This article covered some of the basics of error budgets and carried out a calculation of an expanded uncertainty for a standard solution. The expanded uncertainty is small (0.34%) and is dominated by the contribution from the reference standard itself. The more complex the analytical procedure, however, the more expanded uncertainties will build.

In regulated laboratories, such as the Official Medicines Control Laboratories in Europe, it is a prerequisite that analytical tests are performed under a properly functioning quality system, which means that:

- All balances and volumetric glassware are under regular control
- Official reference substances or in-house reference substances are properly qualified and stored
- Instruments are regularly calibrated
- Equipment is regularly requalified
- Laboratory technicians are (re-) qualified.

The uncertainties due to these sources are under control and are assumed to contribute little to the total uncertainty of the test result (9).

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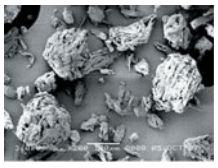

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Bischof + Klein's product range encompasses the entire range of flexible packaging – from traditional industrial packaging and consumer packaging to special films for technical applications – from 2-gramme portion packaging to flexible liquid liners for 1,200 litres.

Major products/services being exhibited

With our class 5 clean room production facilities in accordance with DIN EN ISO 14644-1 at rest, we offer low-germ and low-particle production of our packaging material, guaranteeing "safety via extremely pure quality".

This specifically includes:

- Single-wound and tubular films
- Open-mouth and side gusseted mitred sealed bags
- Bottle-shaped bags
- Multiple-ply bags (Two- or three ply bags)
- Laminated aluminium bags with three sealing seams
- Tyvek® / HDPE bags with three side seals, autoclavable
- HeaderBags with a Tyvek® strip
- Packaging with DMF

Tailored to customers' wishes, raw materials which are safe according to the FDA and LFGB can be used and specified for the material. All production and quality processes are oriented towards GMP.

Extrusion, printing and conversion machines are available in the completely encapsulated clean room to produce and develop these packaging materials. Our specially trained and motivated production teams are supported by our internal laboratory and testing facilities. The exclusive use of safe raw materials according to FDA and LMBG is equally a matter of course as GMP-friendly quality assurance at all levels.

On customer request CleanFlex® packaging could be additionally treated by a sterilisation process. The particle-low and sterilised packaging is therefore ready-to-use for high-purity processes.

B+K BISCHOF + KLEIN CleanFlex® Clean room packaging

Contact details

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Hall 4.1, Booth 41J56

Bosch Packaging Technology

Based in Waiblingen, Germany, and employing 5,000 associates, the Bosch Packaging Technology division is one of the leading suppliers of process and packaging technology. At over 30 locations in more than 15 countries worldwide, a highly-qualified workforce develops and produces complete solutions for the pharmaceuticals, food, and confectionery industries. These solutions are complemented by a comprehensive after-sales service portfolio. A global service and sales network provides customers with local points of contact

The product division Pharma is a leading provider of process technology and packaging solutions for the pharmaceutical industry. The portfolio includes single units, systems and complete solutions for process technology of sterile liquids and powder processing. It also comprises primary packaging for sterile fill&finish and solid dosage forms, secondary packaging

as well as inspection technology, qualification, validation and services.

Major products/services being exhibited

The two Bosch companies Hüttlin and Bosch Packaging Technology Ltd, formerly known as Manesty, offer part of the pharmaceutical process portfolio. Hüttlin's modular designed equipment for granulating, drying and coating ranges from single machines for laboratory applications to large production lines. From laboratory to production scale, the customized Manesty tablet presses and coaters offer highest quality and flexibility to the pharmaceutical industry. Bosch Packaging Technology offers pharmaceutical manufacturers a tailor-made consulting service for all laboratory requirements. Customers can rent operating laboratories equipped with the latest systems and machinery for pharmaceutical solids for research and on-site testing.

Bosch's products are on show on booth #41H30.

BOSCH Invented for life

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Hall 4.1, Booth 41H30

Catalent Pharma Solutions

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 over 75 years of experience, 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.™

Major products/services being exhibited

Catalent's OptiMelt™ hot melt extrusion enhances the bioavailability of poorly soluble APIs by producing an increased-energy form of the drug through a combination of the process and the chemical properties of the excipient. The resulting product, or extrudate, is then further processed and converted into a final dose form to achieve the desired final drug-delivery profile.

In addition to enhanced bioavailability, the continuous processing applied with OptiMelt allows for good process control and scaleability, plus the extrudate is versatile in its end use, allowing potential incorporation in controlled-release delivery formulations. The OptiMelt technology is also solvent-free and can incorporate taste masking.

Catalent has invested significantly in its OptiMelt hot melt extrusion capabilities, both in the US and Europe, to help provide additional options for bioavailability solutions, including an innovative open alliance model with BASF in this area.

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Hall 4.2, Booth 42FO3

CordenPharma

CordenPharma is your full-service CMO partner in the Contract Development & Manufacturing of oral, sterile, highly potent, cytotoxic, non-cytotoxic, and Beta-lactam antibiotic pharmaceutical **Drug Products, their Active Pharmaceutical Ingredients (APIs),** and associated **Packaging Services.**

Through acquisitions of multiple cGMP facilities across Europe and the US, CordenPharma is linking together a legacy of high-calibre scientists and capabilities to provide you with balanced outsourcing from R&D to Commercialization. Our facilities are fully-inspected by all relevant approval authorities such as the EMA, FDA, ANVISA and PMDA.

Major products/services being exhibited

API Contract Development & Manufacturing

- R&D Custom Synthesis & Scale-Up
  - Small molecules
  - Peptides
  - Synthetic Phospholipids
  - Conjugates
  - Carbohydrates
- Highly Potent APIs (SafeBridge Category 4, OEL ≤ 30 ng/m³)
- Large-scale API Contract Manufacturing
- Synthetic Peptide Production from multi-gram to ton quantities
- Sterile APIs
- CordenPharma Proprietary APIs & Building Blocks
  - >50 Generic APIs
  - Synthetic Phospholipids
  - AADs
  - Pseudoproline Dipeptides

Drug Product Contract Development & Manufacturing

- Highly Potent Formulations (Solid Forms)
- Cephalosporins & Penicillins (Oral & Sterile)
- Oncology Drug Products (Oral & Sterile)
- Parenterals
- Large Pre-Filled Syringes
- Two-Layer Tablets
- Packaging & Labeling
- Pack Serialisation

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Hall 3.1, Booth 31B32

Croda Europe Ltd

A FTSE 100 company, Croda is a global leader in speciality chemicals and has multiple manufacturing sites throughout the world; supplying ingredients into a wide range of industries, including the pharmaceutical industry, where performance and purity are paramount. Croda utilises an in-house proprietary flash chromatographic process to manufacture superior quality excipients for the global pharmaceutical industry. This process is called Super Refining™, which physically removes impurities without altering their fundamental structure.

Major products/services being exhibited

Croda offers a complete range of products for topical dosage forms as well as high purity multicompendial solvents, solubilisers and surfactants suitable for parenteral, oral, and ophthalmic formulations. Featured products include Super Refined™ ingredients: oils, oleic acid, oleyl alcohol, isopropyl myristate, PEGs, polysorbates and dimethyl isosorbide and also medical grade lanolins, poloxamers, GPI salts and omega 3 fatty acid concentrates.

CRODA Health Care

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http://www.croda.com/healthcare

Hall 6.1, Booth 61E59

DFE Pharma

DFE Pharma is a global leader in excipients. We develop, produce and market excipients for oral solid-dose and dry-powder formulations. Although the new "DFE Pharma" name is still young, our company's roots go back more than 100 years ago, formed from the merger of DMV International, Lactose New Zealand and DOMO-pharma. With over 100 years' experience DFE Pharma is a key global excipient player in the industry. We are on 'the pursuit of excipient excellence'.

Excellence is what guides us on our way to working together with our customers and in developing the best possible excipient solutions for them.

Through our international sales offices in Germany, the US, Singapore, India and Japan and our global network of over 100 distributors, our products can be found in over 100 different countries. Production locations in Germany, the Netherlands, New Zealand and India, are based on ISO 9001:2008, IPEC, PQG and cGMP and where applicable, ICH Q7.

Major products/services being exhibited

DFE Pharma has perhaps the most comprehensive excipient range in the market, covering MCC, Starch, Lactose, Inhalation Grade Lactose, and Superdisintegrants. Our range consists of well-known product brands such as Pharmatose, Primojel, SuperTab, Respitose and Pharmacel.

Through our newly introduced Pharmacel (MCC) products we now provide our customers with the synergy of the two most widely used diluents, lactose & MCC! Never before has any supplier been able to offer customer this combination.

DFE pharma

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Hall 6.1, Booth 61C51

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 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.

QUALITY ASSURANCE

Our quality system meets DS/EN ISO 9001 and ICH's cGMP Guide for Active Pharmaceutical Ingredients (ICH Q7). Uniform quality of finished products is ensured by our efficient quality control systems, computerised materials planning and rigorous laboratory quality control.

CUSTOMIZING QUATS

If the required product is not in the standard assortment, we can design customized products. Our flexible production process can meet customer demands for special chain length distribution and/or solutions of quats mixed in various ratios.

fef
a Novo Nordisk company

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Hall 6.2, Booth 62B48

Greiner Bio-One GmbH

Greiner Bio-One is specialised in the development, production and distribution of plastic laboratory products. The company is a technology partner for universities, hospitals, research institutes and the diagnostic, pharmaceutical and biotechnology industries as well.

Greiner Bio-One GmbH is a division of Greiner Bio-One International AG, based in Kremsmuenster (Austria). Today Greiner Bio-One International AG generates a turnover of 364 million euros. It has over 1,700 employees and operates globally with 24 subsidiaries and numerous distributors in more than 100 countries.

Major products/services being exhibited

Greiner Bio-One is a leading supplier of special products for cell cultures and microplates for high-throughput screening

and a developer of innovative biochips and sample collection systems. The company performs contract work from the pharmaceutical industry, the diagnostic and medical sectors. Greiner Bio-One uses injection moulding to produce a whole range of customised plastic platforms for the life-sciences sector and offers the complete product development and production process from the idea through to the finished product. The company produces small and large series, undertakes customer-specific branding and can call on production facilities in Europe, the USA and Asia.

greiner bio-one

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Hall 4.1, Booth 41H09

hameln pharmaceuticals gmbh

With over 60 years of experience hameln pharma is a well-established specialist for contract manufacturing of parenteral solutions and suspensions filled in ampoules and vials. In our cGMP certified state-of-the-art facility in Hameln more than 430 members of staff manufacture, test, package and ship pharmaceutical products to our customers serving healthcare markets worldwide.

The focus in everything we do lies on the product quality and safety – and therefore the well-being of the final patient. This makes us a valued business partner for many of the top pharmaceutical companies, renowned generic houses as well as start-up businesses from the biotech sector.

Major products/services being exhibited

Contract manufacturing of sterile liquids:

- Ampoules: 1ml - 30ml
- Vials: 2ml - 100ml
  - compounding
  - filling
  - visual inspection
  - labelling
  - packaging
  - analytical tests

Dossiers for various diluents:

- Wfl
- Sodium Chloride
- Calcium Chloride

Special abilities:
Handling of:

- Anaesthetics
- Suspensions
- Oxygen sensitive products
- Flammable liquids
- Cold chain products

hameln pharma

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Hall 4.2, Booth G32

HERMES PHARMA – a Division of Hermes Arzneimittel GmbH

HERMES PHARMA is the expert in developing and manufacturing user-friendly solid oral dosage forms - including effervescent and chewable tablets, lozenges, instant drinks and orally disintegrating granules. We offer customized solutions at every point along the pharmaceutical value chain, from new product development to market success. For more than 40 years, leading healthcare companies around the globe have been working with HERMES PHARMA to expand their product lines and grow their brands.

HERMES PHARMA is a division of Hermes Arzneimittel, a leading German provider of high-quality medicines marketed under its proprietary, well-established brands.

Major products/services being exhibited

Our customized services include

- New product design
- Formulation and analytical development
- Stability testing
- Registration procedures
- Manufacturing of laboratory, pilot and large-scale batches
- Quality control and batch release
- Packaging and delivery
- Regulatory support and lifecycle management

We specialize in user-friendly dosage forms which are easy to swallow, offer a variety of choice in terms of flavor and can be taken with or without water to suit individual preferences. And, in the case of solubles and effervescents, they dissolve easily and quickly leaving no residue or foam.

We have built up unique expertise in taste masking and flavoring. So even if the API is bitter or difficult to process, we know how to transform it into a dosage form your customers will like to take.

Interested in growing your brands through user-friendly dosage forms? Meet us at CPhI 2013.

HERMES PHARMA
Get the dose right™

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www.hermes-pharma.com

Hall 3.1, Booth 31E26

Hospira One 2 One™

Hospira's One 2 One™ business is a global leader in injectable product contract manufacturing. With more than 20 years of experience in biologics and small molecule fill and finish manufacturing, in-depth knowledge of the lyophilization process and expertise in multiple drug-delivery technologies, One 2 One™ is a reliable partner to help you achieve your development and commercialization goals. The complementary capabilities of its facilities in North America and Europe also make clinical trial and commercial product manufacturing more efficient, convenient and secure.

Major products/services being exhibited

One 2 One™ manufactures 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 a broad range of capabilities and experience with different types of molecules and processes:

- Biologics
- Small molecules
- Vaccines
- Cytotoxics
- Controlled Substances
- Highly potent compounds
- Aseptic Fill/Finish
- Development services
- Lyophilization
- Sterile Powder Filling
- Multilingual packaging and labeling
- Cold chain management

ONE 2 ONE™
Parenteral Contract Manufacturing Service of Hospira

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www.one2onecmo.com

Hall 4.2, Booth 42D31

ISOCHEM

Reliable, Flexible and Competitive

ISOCHEM operates 4 production sites, including 3 cGMP plants (FDA) and offers its renowned skills in multi-steps chemical synthesis. This includes the safe implementation of hazardous reactions like Phosgenation and Hydrogenation.

Through the acquisition of Wychem, which supplies intermediates in quantities ranging from 1 to 1000 kg to numerous industries, including the pharmaceutical industry, Isochem has significantly expanded its range of intermediates, particularly aromatic compounds, while Wychem's ''kilolab'' unit constitutes an additional resource for the development of Isochem intermediates.

Major products/services being exhibited

ISOCHEM offers a wide range of products including phosgene derivatives, functional intermediates and active ingredients.

ISOCHEM

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www.isochem.eu and
www.wychem.com

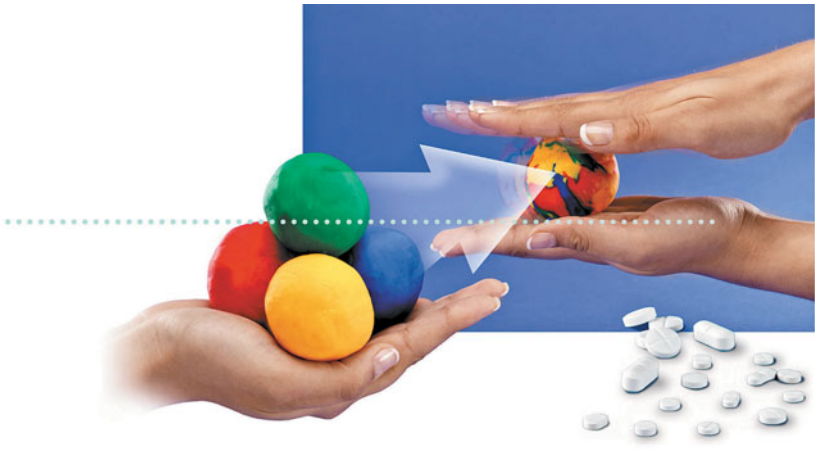
Hall 5.0, Booth 50D30

JRS Pharma GmbH & Co. KG

JRS Pharma is well known and valued worldwide - the most successful system partner for tabletting excipients and services, driving the pharmaceutical world with innovative excipients designed for Direct Compression.

Major products/services being exhibited

PROSOLV EASYtab – the all in one, ready-to-use composite - considered the biggest invention in its class and a major mile stone for significant cost cuttings in the industry!



JRS customers benefit from the extensive expertise offered in various fields by the JRS Pharma Family:

- VIVACOAT ready-to-use coating systems,
- CR0 and CMO for small molecules
- Biotech.

One partner offering multiple benefits - a win-win partnership at its best!

JRS PHARMA FAMILY

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Hall 6.1, Booth 61C59

Lonza

Lonza Custom Manufacturing has been helping pharmaceutical and biotech companies of all sizes improve and advance their products for over 30 years. APIs, HAPIs, conjugates, peptides, vaccines, plasmid DNA, recombinant proteins, Fabs, mAbs, and Cell Therapy are among the many services Lonza provides. We have the know-how and proven track record to handle almost any pharmaceutical or biotechnology challenge you may need.

From pre-clinical to commercial supply, Lonza's complete development services, industry-leading manufacturing processes and broad technology platform enable your product to reach its full potential.

Major products/services being exhibited

Lonza's Custom Development and Manufacturing Offering:

Innovative Technologies

- FlowPlate™ MicroReactors
- DuraSource™ Life Cycle Extension Services
- Easy Access™ Antibody Drug Conjugates
- Epibase™ Immunogenicity Services
- Light Path™ Custom Material Supply Services
- The GS Xceed™ Gene Expression System
- XS Microbial Expression Technologies™

Complete Process Development Services

- Process Development, Scale-up, Validation and Transfer
- Cell line Construction/Strain Design

Clinical through Commercial Manufacturing

- Mammalian
- Microbial
- Small Molecule APIs
- Cytotoxic and Highly Potent APIs
- Antibody Drug Conjugates
- Cell Therapy
- Viral Vaccines

Lonza

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Hall 6.2, Booth 62C01

MEGGLE Gruppe Wasserburg BG Excipients & Technology

Experts in Excipients

MEGGLE Excipients & Technology is a global leader in the manufacture of lactose for the pharmaceutical industry. Supporting supply chain security with manufacturing facilities in Europe and North America, MEGGLE offers a broad product portfolio of lactose excipients, co-processed technologies and excipient contract manufacturing.

MEGGLE is a pioneer in co-processing technologies that allow simple, robust formulation development and manufacture. Through co-processing, MEGGLE developed highly functional excipients possessing unique qualities for directly compressible immediate and sustained release pharmaceutical solid dosage forms.

As a family owned, German company, MEGGLE has proudly produced quality products for consumers and industry for four generations.

MEGGLE Excipients & Technologies serves the pharmaceutical and biotechnology markets with a global network of offices and authorized agents. As an innovator in co-processed technology, MEGGLE also provides contract manufacturing services to several other global excipient companies.

Our broad portfolio of products, multiple manufacturing locations, technical centers in major markets, and innovative technologies, make MEGGLE the preferred supplier and valued partner by large and small pharmaceutical product manufacturers.

MEGGLE Excipients & Technologies excipient products:

- Lactose monohydrate
- Anhydrous Lactose
- Co-Processed Excipients
- Lactose for Inhalation
- Lactose for lyophilization and parentral applications
- Custom lactose products

MEGGLE EXCIPIENTS & TECHNOLOGY

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Hall 3.1, Booth 31F54

OPTIMA pharma GmbH

Meeting highest requirements of the pharmaceutical sector - OPTIMA pharma

The concept offers an immensely diversified and innovative range of filling and packing machines for pharmaceutical products, e.g. sterile liquids and powders, non-sterile liquids and powders, pharmaceutical freeze-drying as well as isolation and containment technology.

Optima Pharma is your ideal partner – also for the efficient and precise realization of complex turnkey projects.

OPTIMA
EXCELLENCE IN PHARMA

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Hall 6, Booth E28

Pfizer CentreSource

Pfizer CentreSource (PCS) integrates Pfizer's world-class analytical, regulatory, technical support and production expertise to provide greater flexibility and help third-party customers work in accelerated timeframes. Key manufacturing assets include world-class bioprocessing facilities in the United States and Europe, as well as high-containment capabilities in Europe. PCS also offers specialty dosage form manufacturing and an array of active pharmaceutical ingredients and fine chemical intermediates.

Major products/services being exhibited

- High Containment solid oral dose processing
- Custom GMP fermentation and bioprocessing services
- Complex sterile manufacturing services
- Bulk Active Ingredients

PfizerCentreSource

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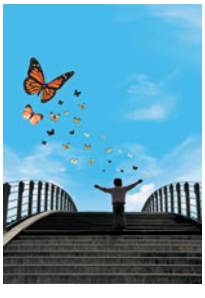
Hall 3.0, Booth 30D54

ROQUETTE



ROQUETTE: A GLOBAL SUPPLIER FOR GLOBAL NEEDS

Roquette is a long-established supplier of actives and excipients for the pharmaceutical and cosmetic industries. Our slogan "Simply formulate your wishes" points to the many services we offer our customers and to the strength of the support that we want to provide them.

ROQUETTE PHARMA SOLUTIONS

Our very wide range of excipients and actives has exceptional potential for meeting the needs of our customers, notably in the areas of:

- Injectables
- Tablets obtained by direct compression or wet granulation
- Film forming and film coating
- Syrups, suspensions, granules and sachets
- Orodispersible tablets
- OTC and nutraceuticals
- Toothpastes and mouthwashes

Roquette also offers on-site assistance for coating. More process insights: www.readilycoat.com.

Today, the direct scale-up of formulations is a new way to reduce drug development time and cost. To further strengthen this drive, Roquette provides a new compression modeling service. More information on: www.roquette-pharma.com/focus-on-innovation/roquettes-services/

Our Pharma Application Development Centers are also offering a new support model: "Boost your NutraPharma project". Manufacturers of nutraceutical and pharmaceutical products who want to get new products onto the market more quickly and reliably access a state-of-the-art laboratory with modern equipment & experienced application experts. For more information on this new service: www.roquette-pharma.com/2013/product-development-boost-your-nutrapharma-project

ROQUETTE
Offering the best of nature™

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Hall 6.1, Booth 61A70

Rovi Contract Manufacturing

Rovi Contract Manufacturing provides contract manufacturing of injectables and solid forms products. The services are carried out through our two manufacturing sites:

ROVI CM: specialist in filling and packaging of prefilled syringes and vials. Aseptic filling and/or terminal sterilization. All syringe formats available from 0.5ml to 20ml (filled from 0.2ml).

ROVI Alcala: one of the biggest FDA-approved plants for solid forms in Europe with a capacity of 3000 million tablets/ year. Dry granulation (roller compactor) and wet granulation (high shear and planetary mixers), compression presses, film coating, high speed and flexible packaging lines, testing and storage are available.
Both manufacturing sites belong to Laboratorios Farmacéuticos ROVI, S.A., a fully-integrated Spanish specialty pharmaceutical company engaged in the research, development, manufacturing and marketing of small molecules and biologic drugs. The company was founded in 1946 and the group is quoted on the Madrid Stock Exchange Market since 2007. The number of employees is approximately 915.

RoviCM
Rovi Contract Manufacturing
Rovi Alcala
Solid Forms Contract Manufacturing

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Hall 4.2, Booth 42L13

STERILINE s.r.l.

STERILINE ASEPTIC PROCESSING
STERILINE was established in 1989 for the purpose of producing automatic equipment for pharmaceutical companies.

STERILINE is currently one of the most successful European manufacturers and suppliers of process equipment in the pharmaceutical industry, worldwide.

STERILINE offers a wide range of high quality products which are specifically designed to meet the customer needs for high flexible applications.

STERILINE has meanwhile grown to be one of the most trusted equipment suppliers for the pharmaceutical industry, which supplies its equipment to the largest pharmaceutical companies worldwide.

Major products/services being exhibited

ASEPTIC FILLING LINES FOR PHARMACEUTICAL INDUSTRY
STERILINE offers a wide range of high quality pharmaceutical equipment specifically designed to meet customer needs.

STERILINE main products range from complete aseptic filling lines to combined lines for ampoules, vials, cartridges and syringes.

STERILINE lines can consist of:
- Washing machines
- Depyrogenating tunnels
- Filling machines
- Capping machines
- Isolator solutions
- Decontaminating machines

All STERILINE equipment is in compliance with CGMP, GAMP and 21 CFR Part 11 requirements

Steriline
ASEPTIC PROCESSING

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Hall 4.1, Booth 41J39

Tereos Alcools

Tereos Alcools is the dedicated company for marketing the pharmaceutical and traditional alcohols produced by Tereos France, the specialist for sugar beet processing in France. With five distilleries in the northern part of France, Tereos Alcools is the main player on the European ethanol market and is specially focused on the pharmaceutical industry.

Involved in the alcohol business for nearly a century, with a wealth of technical knowledge and the industrial capability of Tereos group, Tereos Alcools is a reliable partner for your ethanol supply.

Major products & services

Agricultural Alcohols

High qualities, sustainable and suitable for all applications, alcohols marketed by Tereos Alcools are from sugar beet grown in France.

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Multivariate Approaches for Powder Characterisation

John Yin, an applications specialist with Freeman Technology, discusses the importance of powder-characterisation techniques for optimising pharmaceutical product development and manufacturing processes.

Q. What advances in powder characterisation have been achieved in recent years?

A. In the past, much of the focus on powder characterisation has been at the single aspect level where one standard or number is expected to dictate 'good' or 'bad' once and for all. In reality, we rely on multiple techniques for explaining behavioural differences when being subjected to many processing conditions. While some information can be obtained with traditional methods, such as bulk-tapped density, flow through an orifice and angle of repose, these techniques are not at all representative of the conditions that powders see under process conditions and, therefore, are not able to provide process-relevant and differentiating information given the process technologies in use today in the pharmaceutical industry.

The multivariate approach for characterising powders has made it possible to gain much greater insights into how the combination of powder physical properties and external variables affect their behaviour. Dynamic testing for example, which measures the flow energy of a powder with respect to external conditions, such as aeration, flow rate and consolidation, is a newer technique enjoying considerable industrial uptake. Advances in shear testing are also improving both the precision and reproducibility of this important analytical method.

Q. What limitations remain with respect to powder-characterisation technology for the pharma industry? Why are these issues important?

A. One of the biggest limitations at this point is the lack of understanding of powder behaviour at the level needed to describe such behaviour mathematically or from an axiom perspective. There are so many variables, not just particle size and density, which are often perceived as the only critical factors that influence powder behaviour, but also the surface texture, particle shape, stiffness and porosity as well as external influences, such as air, moisture, consolidation stress and flow rate, which can all contribute to the picture. There is much work to be done in this area and it will be a steep learning curve. A second challenge is the need to make the pharmaceutical industry and other powder-processing industries (that share similar challenges) aware of the benefits of more comprehensive powder characterisation.

Q. What advances in powder-characterisation technology might be expected?

A. The adoption of continuous manufacturing for the production of solid dosage forms will have an impact on powder-characterisation technology. In addition, as the amount of data gathered on different powder systems increases, we will continue to gain more knowledge about powder properties and behaviour and be able to expand our insight into performance with respect to different processing conditions. **PTE**

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