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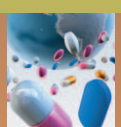

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March 2016

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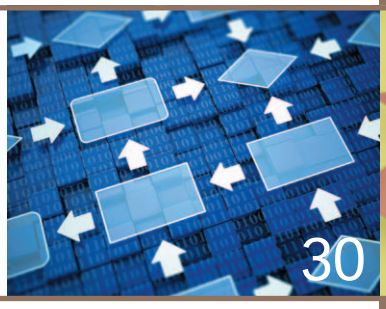

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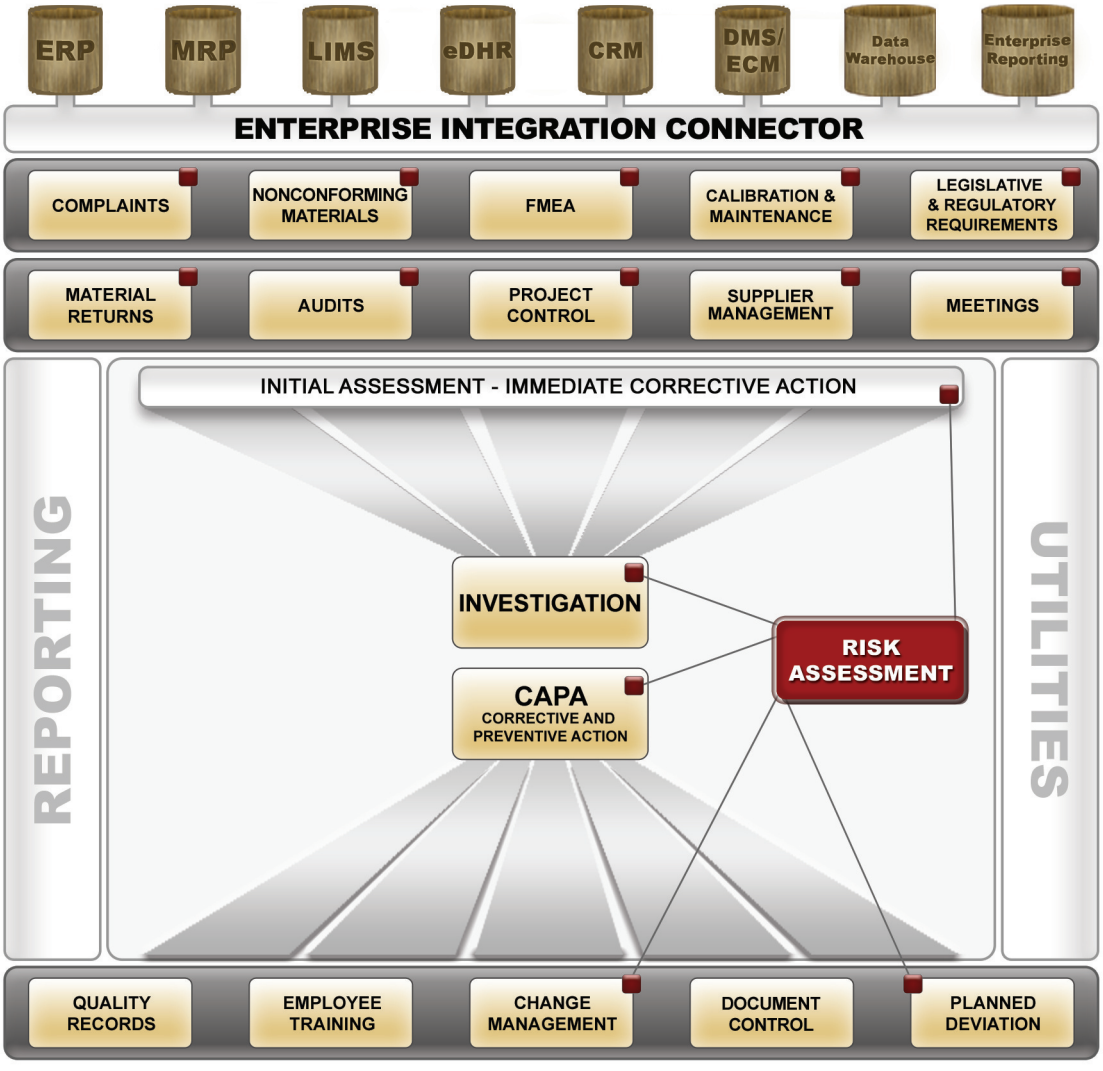

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Harnessing the Potential of Smart Glasses

Just as emails can be accessed anywhere on a computer or smart phone, pharmaceutical manufacturing process data can now be made accessible remotely through new network solutions. Remote access is not just limited to data on a screen. Smart glasses have moved beyond a consumer novelty to a business tool that can be particularly valuable. One of the primary uses today in pharmaceutical manufacturing is telepresence, by which remote personnel can literally see what an on-site person is viewing and can perform remote troubleshooting or maintenance, for example.

The smart glasses concept was popularized by the Google Glass for consumers, but companies such as Epson, Vuzix, and Osterhout Design Group also produce smart glasses and are designing them for enterprise applications, including manufacturing settings. Software applications are crucial to making smart glasses useful. Software provider Pristine, for example, focuses on "virtualizing the expert," by which an operator in a plant can wear smart glasses and be connected to the expert in another plant or an office.

Apprentice Field Suite, which uses smart glasses and other mobility technology to improve processes for its pharmaceutical and biotechnology clients, designed three technology modules specifically for pharmaceutical manufacturing and R&D. The Tandem module allows an engineer to have a "telepresence" for remote troubleshooting. The Gauge module can alert operators to the condition of equipment and capture data from gauges. A Manuals component can be used to display information in the glasses, allowing the users' hands to remain free to perform operations.

Software provider Vital Enterprises sees the main advantage of smart glasses in manufacturing as allowing hands-free operation with access to information and remote collaborators. Ash Eldritch, cofounder and chief science officer of Vital Enterprises, notes that the gains are largest for geographically distributed teams who can benefit from telepresence and for cases where there are long process checklists, such as in technology transfer procedures.

Smart glass technology has only been around for a few years, and experts note there is still relatively little knowledge about the potential benefits. Even so, the technology continues to get smarter. "Smart glasses are advancing in 'contextual awareness'—rather than the operator telling the glasses what checklist is needed, for example, the glasses will leverage the sensors in the industrial internet of things (IIoT) to sense where the user is standing, who they are, and what task needs to be performed," says Eldritch. "The convergence of IIoT and augmented reality will be the next step forward from where the technology is now, as a head-mounted display. In 5 to 10 years, smart glasses will be able to project digital imagery directly onto physical objects, meshing digital information seamlessly and intuitively into the world around us," he predicts.

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Pharma Outsourcing Market Expands

The pharma outsourcing market starts 2016 with expansions, acquisitions, and new offerings.

Susan Haigney

Pharmaceutical and biopharmaceutical companies will continue to use outsourcing services, especially drug manufacturing, due to cost concerns and mergers and acquisitions, according to a market survey of drug manufacturers by ISR Reports. The survey showed that the top five activities that drug companies outsource are drug product manufacturing, packaging and labeling, distribution, small-molecule manufacturing, and holding and storage, according to Kate Hammeke of ISR Reports (1).

The ISR survey suggests that the majority of companies are outsourcing their small-molecule manufacturing. ISR's 2016 small-molecule outsourcing survey also showed that other popular outsourced activities include packaging and labeling, distribution, and holding and storage. Respondents to ISR's survey indicated resources, an increased product demand, cost, and mergers and acquisitions as some of the reasons small-molecule companies outsource these activities.

For large-molecule companies, distribution was the number one outsourced activity indicated by ISR's survey, with packaging and labeling coming second. Cost was the number one reason large-molecule companies indicated as the reason for outsourcing.

Service providers are expanding their services and capabilities to keep up with the high demand. The following are some examples of the growth the outsourcing industry is experiencing.

Company developments, expansions, and acquisitions

The first few months of 2016 have seen an array of investments, expansions, and acquisitions in the pharmaceutical outsourcing market. Outsourcing companies appear to be looking to the early-phase development and clinical trial markets to increase their portfolios.

Catalent Pharma Solutions announced on 2 Feb. 2016 (2) an investment of €4.2 million (US$4.6 million) to expand its Singapore clinical supply facility by building GMP space for secondary packaging. The investment doubles the ambient storage space and quadruples cold-storage capacity, the company reports. The site provides clinical supply services including project and supply-chain management, comparator sourcing, clinical label printing, secondary packaging, clinical storage, import/export management, importer of record service, and returns and destruction management services. It has served as a regional hub for studies in Australia, Singapore, Korea, Hong Kong, and other countries in Southeast Asia.

Onyx Scientific, a UK-based CRO and small-scale API manufacturer, has announced an investment in an additional site located adjacent to its existing facility in North-East England to increase its laboratory facilities, GMP suites, and storage of GMP materials (3). In addition, the company has recruited several more chemists to support clients' pre-clinical, development, and early-stage API manufacturing projects. In 2015, the company grew its GMP space following an increase in demand for its small-scale API manufacturing services.

Vetter announced on 28 Jan. 2016 that the company's Schuetzenstrasse multi-functional building in Ravensburg, Germany, has been completed on schedule and departments critical to its operation have started to move in (4). The €29 million (US$32 million) investment is part of a €300 million (US$331 million) total investment strategy announced by the company in September 2015 for further development to its manufacturing sites.

The continued demand by large and small customers for enhanced drug development services, as well as the need for ever-more future-oriented sophisticated IT systems to protect their data, created the need for the new facility, the company reported in a press statement.

Recipharm, a Sweden-based contract development and manufacturing organization (CDMO), plans to invest €40 million ($44.4 million) over the next three years in solutions for serialization processes, the company said in a 10 Feb., 2016 press release (5). The decision came just days after the European Medicines Agency (EMA) announced plans to implement packaging safety features as part of the Falsified Medicines Directive (Directive 2011/62/EU) (FMD), adopted in July 2011. The serialization of licensed drug products will be a legal requirement for companies in the EU starting in 2019.

Recipharm currently provides serialized products in Turkey, Korea, and China. The company has established a global steering committee that will work with clients in Europe to ensure they plan and implement changes that comply with pending regulatory requirements for drug serialization.

In February, Recipharm AB also announced (6) that it agreed to acquire Italian CDMO, Mitim Srl,

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which specializes in the filling of injectable beta lactam products, for €$68.4 million (SEK 640 million). Mitim's product portfolio includes beta lactams in dry sterile powder for injectable solutions, tablets, and oral suspensions. Other products include injectable sterile solutions, oral solids and liquids, and semi-solids. The manufacturing site has five production lines; the company completed an investment in a production line for injectable beta lactams in March 2015. Mitim employs approximately 250 people.

PBOA expands membership

The Pharma & Biopharma Outsourcing Association (PBOA), founded in 2014, has been advocating for the pharma outsourcing industry as the global market changes and expands. "We're focused on working on the reauthorization of the Generic Drug User Fee Amendment (GDUFA), while keeping an eye on FDA's Quality Metrics initiative, and helping make sure that CMO/CDMOs [contract manufacturing organizations/contract development and manufacturing organizations] are prepared for track-and-track/serialization regulations as they roll out in the US and the EU in the next few years," says PBOA President Gil Roth.

In February 2016, PBOA expanded its membership (7). IDT Biologika and Ei SolutionWorks joined the PBOA as general members; 3M Drug Delivery Systems (DDS) joined as a sustaining member. Diego Romeu, manufacturing and supply chain director at 3M DDS, was also voted to a three-year term on the board of trustees, along with Rajan Puri, director of business development at Therapure, and Lee Karras, CEO of Halo Pharmaceutical.

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Tackling Regulatory Challenges of EU's Variations Framework

The EU is striving to reduce the costs and administrative burden facing pharmaceutical manufacturers when complying with variations regulations for keeping authorization dossiers up to date.

The European Union's medicines licensing agencies have committed themselves in a strategy document in December 2015 (1) to ease the regulatory burden on the pharmaceutical industry by being more efficient in their control of pharmaceuticals throughout product lifecycles. This pledge has been raising the hope of the generic medicines industry. One of the generic medicines industry's priorities is the reduction of the costs and administrative difficulties that occur when complying with variations regulations for keeping authorization dossiers up to date.

Problems with variations rules were a major topic at an annual regulatory and scientific regulatory affairs conference in London in January 2016, which was organized by the European Generic and Biosimilar medicines Association (EGA). Approximately a third of the 200 participants were regulators with most of the remainder from the industry.

As the EU's pharmaceuticals regulations have been tightened up in recent years, the submissions on variations to regulatory agencies—comprising the London-based European Medicines Agency at the centre and a network of national agencies in the EU's 28 member states—have increased substantially. As a result, variations have been taking up a rising proportion of the pharmaceutical industry's regulatory costs.

Variations requirements

Pharmaceutical producers and importers are required to provide regulators with even more information about changes to their medicines, such as modifications to manufacturing processes, improvements or extensions to formulations, and even minor additions such as alterations to names and addresses. The industry is seeing many of the variations requirements as being the imposition of an unfair weight of responsibility on their shoulders.

The current regulatory requirements are laid down by an EU legislation (2) approved in 2008, which came into force in August 2013. The aim was to provide clearer rules by dividing the variations into four main categories. Two of these are type IA, which have "minimal or no impact at all" on the quality, safety, or efficacy of medicines and type II, which can have a "significant impact." An "extension" category covers changes to an active substance or the strength, pharmaceutical form, and route of administration of a medicine. Type IB variations are changes that are neither minor, major, nor an extension.

Although the legislation's main objective was to simplify rules on the notification and approval of variations, a series of guidelines have had to be issued to clarify their application. At the same time, new EU pharmacovigilance legislation (3) was introduced, which brought in additional requirements for information of variations in the quality, safety, and efficacy of medicines after their launch on the market. This new legislation also had to be clarified by guidelines, the latest of which was issued in the form of a questions and answers document (4) in January 2016.

"Guidance covering matters that should be clearly described in legislation has increased the regulatory work load of the industry," Susana Pereira, a principal regulatory affairs officer at Teva Pharmaceutical Industries, told the conference (5). An increasing proportion of variations are now related to details about the production, origin, and composition of APIs. This follows the migration of API manufacture out of Europe and North America to China and India, which has considerably complicated the supply chains for active substances, mainly used in generic medicines. At the same time, rules on good manufacturing practice (GMP) have been made stricter and broader while GMP inspections of API facilities have become more rigorous. A lot of additional variations information is being generated by the more stringent application of GMP.

API changes and GMP rules

The average number of variations per marketing authorization per year had increased by 45% in the five years leading up to 2014 (5), the equivalent to one additional variation per authorization. Variations in APIs are a major factor behind this increase. Up to 60% of quality variations submitted by marketing authorization holders (MAHs) are now related to API changes, said Pereira (5). New interpretation of regulatory data requirements had led to rises of up to 300% in the variations related to the API supply chain, with a high proportion relating to GMP matters, she added (5).

With the addition of stricter GMP rules and the new requirements under the pharmacovigilance legislation, "variations have become a mechanism to implement new legal obligations," Pereira claimed. The result was rises in regulatory costs covering the maintenance of a product's lifecycle to a level that is higher than the authorization costs for the marketing of the medicine. "This imbalance can lead to the withdrawal of a medicine from the market, particularly

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if the cost of maintenance is higher than the product's profit," she warned (5). Instead of taking a drug off the market, a company may delay process improvements or hold back other changes that would reduce the medicine's cost.

Companies are also choosing carefully the regulatory authorities to which they are submitting variations, particularly because of differences in the fees they charge. These costs can range from zero to up to €1400 ($1544) for type IA variations; up to €1500 ($1654) for type IB; and up to €18,000 ($19,852) for type II, Pereira said. "The current system doesn't create incentives for [national licensing authorities] to implement cost-effective mechanisms," she added.

Companies are choosing carefully the regulatory authorities to which they are submitting variations.

Other speakers pointed out how certain aspects of API manufacture were increasing the requirements for variations information, often as a result of the interpretation of regulations made in guidelines. Marieke van Dalen, global regulatory specialist at Aspen Oss B.V., a Dutch API producer, said that a recent trend was a requirement for information on starting and even pre-starting materials, even including the names and addresses of the suppliers. This information was passed to the MAH before being added to the authorization dossier. Some authorities also wanted information on the analytical methods used in the validation of the starting materials and their intermediates.

Joseph Bondin, executive director, quality operations, at the generic-drug producer Actavis, gave examples of how much information had to be provided when an outsourced API manufacture introduced intermediates from new producers with new testing sites. In one example, details of as many as 12 additional players in the API supply chain had to be submitted because of changes in the suppliers of intermediates. As a result of new regulatory interpretations of the information requirements on API intermediates, he warned that there could be a two- to three-fold increase in the total number of variations, which in 2015 averaged just under three variations per marketing authorization per year (6).

"This increase seems contradictory to several EU policies," he said. "[These policies include] have effective and fit regulatory systems that foster supply-chain resilience to prevent temporary supply disruptions." In addition, it would seem to refute the value of the systems adopted by pharmaceutical companies themselves to validate the quality of intermediates, even though these could be based on quality guidelines proposed by the International Conference on Harmonization (ICH).

Recommendations for improvements

In a regulatory efficiency report (7) published in September 2015, the EGA recommended a series of specific improvements to the EU regulatory system on variations. These recommendations include reliance on the new database system of Identification of Medical Products (IDMP) to make the API supply chain more transparent. It proposed that API information should be limited to details about the final API manufacturer. Information on other involved sites, such as intermediate producers, would be managed through the drug manufacturers quality systems and regulators' GMP inspections.

Much greater use, as a source of required variations data, could be made of the central European inventory of information on medicines and active substances, which is being set up under the EU's pharmacovigilance legislation. Under article 57 of the law, companies have to provide up-to-date post-marketing information on their products relating to quality, safety, and efficacy (3).

Regulators at the conference reiterated their commitment to making regulatory compliance easier and less costly for the pharmaceutical industry, particularly for the generic-drug sector. Noel Wathion, the EMA's deputy executive director, stressed that the article 57 database and the implementation of IDMP would be used to improve the cost-effectiveness of regulations for generic and biosimilar medicines within the EU's regulatory network. The regulators, however, were unable to make pledges about specific measures, particularly on the vexed issue of variations. This issue seems likely to remain a matter of grievance among generic-drug companies for some time.

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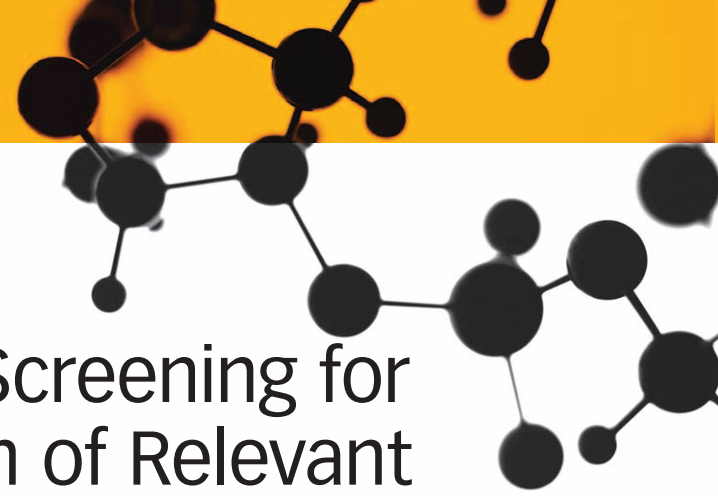

Polymorph Screening for Identification of Relevant Crystalline Forms

Gauging the adequate level and type of screening is the challenge.

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

Solid-dosage drugs remain the preferred dosage form due to ease of administration and typically lower manufacturing costs compared to parenteral and other dosage forms. Many of the properties of a chemical relate directly to its physical form, and solid compounds can adopt numerous different crystalline forms (e.g., polymorphs, solvates, and hydrates) and non-crystalline (e.g., mesophases or amorphous) forms. Extensive screening must be completed to identify the different potential stable and meta-stable forms that an API may adopt during manufacturing of the drug substance and drug product, packaging, storage, and within the body. Potentially stable salts and cocrystals of the API may also be evaluated. In addition to the skills and knowledge required to conduct and evaluate the large quantities of structure data generated during polymorph screening projects, the ability to design appropriate screening studies has a direct impact on their success.

Why polymorph screening

Toxicology, efficacy, and stability are important criteria when selecting an appropriate candidate for the development of a solid-dosage drug. "These properties can vary depending on the physical structure of the API. It is necessary to understand the physical properties of each potential solid form and the relationship between these different forms in order to identify the candidates with the greatest likelihood of success," says Brett Cowans, director of materials science for SSCI (Solid State Chemical Information), a division of AMRI.

The chances of selecting the best candidate improve considerably the earlier these factors are known. "The challenge for companies is to balance the cost of development and risk of selecting the wrong solid form. Ideally, this balance will include understanding the true physical properties of the selected candidate compound, including polymorphism, and how these properties will affect the API manufacturing and drug product efficacy and stability for each form, as well as the intellectual property position for the formulated drug," Cowans observes.

Many forms to identify

From a technical point of view, the main challenge of polymorph screening is to identify all crystalline forms relevant and potentially crucial to development. Solid forms may, for example, be observed in the presence or absence of certain impurities in the final isolation step of the API, upon storage of its intended dosage form, or *in vivo* when administered orally, according to Patricia Andres, director of particle engineering for SSCI. "The screening of such forms typically requires a rational design of experiments often not amenable to high-throughput screening, and the unambiguous identification of new phases necessitates the preparation of pure phases in sufficient quantities for characterization," she notes.

Andres cautions, however, that while thorough and targeted screening will considerably reduce the chances that a new critical form is discovered later in development, it is not possible to know without a doubt that all relevant forms have been found. She cites ritonavir as a classic example of a crystalline form not discovered during development. The product was developed using a form designated as Form I, which was later found to be metastable with respect to a new form exhibiting considerably lower solubility and rendering the initially developed drug product bio-unavailable.

Achieving the right balance

"The ability to gauge the level and type of screening that is adequate based on considerations of development phase, dosage form, physicochemical and biological properties of the compound, and regulatory requirements is paramount," Andres asserts. Risks associated with the discovery of a new crystalline form at a later phase of development must be weighed against the possibility of the compound failing in development. This risk assessment requires both experience of solid-state issues that can affect the performance of the drug substance and drug product and intimate knowledge of the drug substance and drug-product processes.

Another practical challenge in polymorph screening, according to Marco Gil, a general manager

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with Hovione, is to identify processes for isolation of different forms that can be scaled in a robust manner to yield the selected polymorphs (or cocrystals).

Fit-for-purpose approach

Polymorph screening is a complicated process that involves many individual experiments and significant data analysis. Significant resources have been invested in efforts to accelerate the process. The dream of displacing rational experimental design in pharmaceutical form screening (e.g., salts, cocrystals, and polymorphs) with high-throughput screening was pursued for about a decade by mid-sized and large pharmaceutical companies, as well as material science contract research organizations (CRO), according to Jon Selbo, director of preformulation with SSCI. "Significant internal resources were dedicated to developing home-built screening instruments and/or purchasing equipment and software to implement this new strategy," he says.

The justification for high-throughput screening was that significant improvement in identification of otherwise unknown forms could be more easily obtained by conducting large arrays of experiments in parallel. In most cases, however, this strategy failed for both identification of new forms and desired forms for development. "In general, crystallization quality was poor, there was a lack of experimental diversity (regardless of significant increases in solvents used in crystallization attempts), the analytical results were inadequate, and analyzing the large quantities of poor quality data generated in the experiments often proved difficult," Selbo observes. In addition, polymorphs identified using high-throughput screening must be considered as general lead compounds and must be thoroughly assessed, including evaluation of their pharmacokinetics, solubility, and other properties, according to Gil.

The driver for large-scale screening in early development has, for the most part, also disappeared with the new molecular entities failing more often today due to efficacy and toxicity issues rather than biopharmaceutics properties. "Only a few larger pharmaceutical companies and small CROs continue to employ high-throughput screening as a first pass strategy," says Selbo.

What is important, according to Cowans, is how the results of high-throughput screening can contribute to better understanding of the properties of potential solid-form candidates. "As a screening tool, high-throughput technology provides a platform to evaluate the potential for crystallizing new solid forms under certain conditions, albeit with some limitations. The information obtained solely from high-throughput technology is not sufficient to select a solid-form candidate for development, however," he says. Consequently, rational experimental design with fit-for-purpose screening strategies based on rational screening or mixed screening approaches have become the norm for the industry, according to Selbo.

Large-scale screening is still employed as a part of intellectual property (IP) strategies for later-stage programs where there is more certainty of compound survival. "High-throughput screening is today an essential technology for mapping polymorphic forms, generating IP, and broadening the protected space in terms of polymorphs, and helping to avoid surprises as much as possible in advanced development phases," Gil comments. For these programs, mixed screening services with rational, mid-, and high-throughput screens may be employed in an attempt to cover all bases, according to Cowans.

Sharp patterns

With respect to advances in technology for polymorph screening, Cowans points to improvements in x-ray powder diffraction (XRPD), which he refers to as the "quintessential tool for distinguishing different crystalline forms." Most importantly, current-generation instruments are capable of providing the sharp, high-quality patterns that are necessary for identifying whether a material exists as a single crystalline phase and are amenable to indexing algorithms.

The combination of indexing software and advanced XRPD technology improves the ability to identify crystalline phases or mixtures, increases screening efficiency, and provides critical information about the various crystalline forms obtained, according to Cowans. SSCI has developed and patented its own indexing software specifically targeting organic molecules and integrated this tool into its routine screening activities.

Another important advance for polymorph screening is the reduction in the quantity of API required for analytical techniques (e.g., XRPD), according to Gil. Automation has also increased the efficiency of these analyses and accelerated sample pre-characterization. **PTE**

Emerging Analytical Technologies Advance Biopharma Development

New technologies must meet the speed, sensitivity, and safety demands of emerging bio/pharmaceutics.

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

Although just a few decades old, the biopharmaceutical industry has evolved significantly since its inception. Many candidate biologics today—antibodies and antibody fragments, highly potent antibody-drug conjugates (ADCs), virus-like particles, cell- and gene-based therapies, etc.—are different from the first simple, recombinant proteins. Manufacturers have been continuously challenged to develop analytical methods for timely and accurate determination of the chemical, physical, and therapeutic properties of these different actives, as well as potential contaminants throughout the production process, from raw material selection to process analysis, formulation development, and release testing.

The introduction of biosimilars and the move toward continuous processing are creating the need for more rapid and sensitive analytical techniques. The advent of quality by design (QbD) has further increased the importance of analytical methods/technologies within a manufacturing environment, according to Fiona Greer, global director of biopharma services development at SGS Life Science Services.

Newer versions of traditional methodologies, such as capillary isoelectric focusing (cIEF) versus IEF gels, peptide mapping with liquid chromatography–tandem mass spectrometry (LC/MS/MS), and high-performance LC (HPLC) are available today. Notably, mass spectrometry-based methods and next-generation sequencing technologies are addressing the need for greater sensitivity in less time. Automation and high-throughput technologies are also having an impact. As the industry introduces more complex and increasingly potent molecular formats with novel, highly potent product-related impurities, however, ongoing advances will be required.

Many sensitive mass spec methods

For product characterization, the most appropriate techniques will depend on the class of molecule: protein, glycoprotein, pegylated, ADC, vaccine, etc. "Improvements in biopharmaceutical mass spectrometry in the past 10 years—in sensitivity, dynamic range, resolution, mass accuracy, and user-friendliness—have dramatically improved our ability to get detailed protein molecular information," says Byron Kneller, director of analytical/formulation development with CMC Biologics.

The continued development and deployment of LC/MS-based applications are having a significant impact on both the characterization and quality testing of biopharmaceuticals, particularly for recombinant proteins and monoclonal antibodies, agrees Mike Garrett, senior director of global marketing for BioReliance. "While in the past these methods were reserved for early research into the structure of these molecules, today, methods are being developed that bring this technology closer to the quality control lab," he observes. Access to more sensitive and detailed characterization data is allowing manufacturers to better understand and more carefully control the molecular structures of their products during the manufacturing process. Garrett also notes that LC/MS has enabled finer control of bioprocess optimization, allowing for correlation of process changes to both molecular structure and yield.

Dan Ward

Some of the most recent advances in product characterization techniques have, according to Greer, been developed in response to challenges encountered with biotherapeutic products and their post-translational modifications (PTMs). Glycosylation analysis in particular has been advanced significantly with the advent of high-resolution mass spectrometry and the use of hydrophilic interaction liquid chromatography (HILIC) columns for glycans. "Introduction of the quadrupole orthogonal acceleration time-of-flight (Q-ToF) geometry and the increased resolving power of MS now allow the direct determination of the monoisotopic mass of antibody heavy chains including modifications such as deamidation," Greer explains. Kneller adds that current-generation Q-ToF and Orbitrap instruments allow for high-resolution intact mass and peptide mapping measurements for both characterization and process-development support, and current software continues to make data processing easier and faster.

State-of-the-art MS instruments with markedly increased sensitivity are also providing profound insights into the impurity profiles of biotherapeutics and allowing the identification of previously unknown host-cell contaminants, according to Harald Wegele, head of analytical development and quality control in Europe for Roche. "Sensitive assessment of specific host-cell proteins (HCPs) and other contaminants provides crucial guidance for the development of impurity depleting process steps, which ultimately helps to warrant a maximum of product safety," he states. Additional developments such as sequential window acquisition of all theoretical mass spectra (SWATH) and parallel reaction monitoring are improving the quantitative assessment of process-related impurities.

Greer also expects wider adoption of numerous other MS-based analytical techniques, including ion mobility-MS, capillary electrophoresis-MS (CE–MS), and hydrogen-deuterium exchange-MS (HDX–MS). Wegele adds that size-exclusion chromatography (SEC) coupled to native MS already provides—particularly for novel antibody formats like bispecifics—a fast and easy means for gaining unachieved levels of information on, for example, the size-variant distribution of biotherapeutic, as early as at the onset of clinical development. He also points to 2D–HPLC as providing a convenient and accurate method for characterizing single product peaks, side products, and excipients.

Advances in bioassays have also made potency testing easier, faster, and more reproducible.

More rapid analyses

There is tremendous pressure on biopharmaceutical companies to get products to the market more quickly and at lower cost without compromising safety. Manufacturers are consequently looking for alternatives to conventional cell-based analytical methods. Newer personalized treatments such as cell-based therapies, in fact, require more rapid release testing because they do not have long-term stability and must be administered to patients soon after they are produced. Manufacturers are also moving to continuous processing, which requires process analytical technology (PAT) that provides real-time process monitoring data.

Several newer testing methods have been developed and are in the process of being implemented by the biopharmaceutical industry, largely in cooperation with regulatory agencies such as the US Food and Drug Administration (FDA). Improvements in real-time, quantitative polymerase chain reaction (qPCR)-based methods have allowed for broader detection of known potential contaminants with improved speed and accuracy, according to Garrett. Newer nucleic acid detection technologies, such as next-generation sequencing, are also being applied to the quality control testing lab. "Importantly, these technologies will allow manufacturers to test their biopharmaceutical products for both known and unknown adventitious contaminants," Garrett says.

Advances in bioassays have also made potency testing easier, faster, and more reproducible, according to Kneller. "The broader availability of reporter-gene assays (e.g., for antibody-dependent cell-mediated cytotoxicity [ADCC]) testing has decreased the difficulty of implementing some potency assays, while access to soluble enzyme-linked immunosorbent assay (ELISA) formats and ready-to-use analytical cell banks has decreased both the time needed for potency assays and assay variability," he explains. Wegele adds that novel LC-, cell-, and surface plasmon resonance (SPR)-based assay formats are facilitating the assessment of the impact of PTMs on antibody/bispecific antibody Fc (crystallizable fragment) effector functionality, including pharamacokinetic (PK) properties (e.g., via FcRn [neonatal Fc receptor] affinity chromatography). The Fc region of a therapeutic antibody interacts with receptors on various types of cells and is involved in immune-mediated effector functions, such as ADCC and complement-dependent cytotoxicity (CDC). It is therefore potentially important in determining drug safety and efficacy and must be fully characterized.

Advances in chromatography methods are also enabling more rapid analyses, according to Kneller. "The increased use of ultra high-pressure liquid chromatography (UHPLC) systems and sub-2 µm columns has enabled more rapid, higher-resolution chromatographic assays, which has decreased testing time for many release methods," he comments.

Gaining throughput

Implementation of high-throughput (HTP) methods and expanding use of automation are additional avenues the biopharmaceutical industry is pursuing to achieve more rapid testing. The challenge has been to reduce testing times without loss of accuracy, precision, specificity, sensitivity, and robustness. Several successes have been achieved to date, however.

Microfluidic capillary electrophoresis (MCE) has, according to Wegele, become a central pillar for product quality analytics during clone selection and bioprocess development due to its ease of sample preparation, robustness, and unrivaled high-throughput capability. "This HTP method is indispensable for meeting the steadily growing demand for the shortest possible sample turnover time and enhanced time efficiency in present-day biologics development," he says.

Automated high-throughput quantification of process-related impurities (e.g., HCPs and Protein A), titer, and fermentation broth supplements such as insulin, LongR3, etc., via electrochemiluminescence immunoassay (ECLIA) is also now used at Roche to support process development, process characterization/process validation studies, manufacturing, and in-process control/release testing, according to Wegele. "This technology is high-throughput-compatible and greatly reduces hands-on time. As a result, it enables novel insights for bioprocess development in near real-time and facilitates the assessment of process-related impurities depletion," he says.

Higher-throughput screens for formulation development coupled with the use of design-of-experiment (DoE) tools have also enabled faster, more comprehensive screening of many formulation conditions and excipients and decreased the time required for formulation optimization, according to Kneller. Often, combinations of light-scattering, intrinsic and extrinsic fluorescence, and calorimetry are used to rapidly deliver information on protein stability in many excipient combinations.

Methods for emerging biologics

Recent years have seen growing interest in newer types of biologic actives. Significant numbers of antibody-based treatments have been commercialized, and many more, including those based on antibody fragments and ADCs, are in advanced stages of development. Successful initial studies with cell- and gene-based therapies are attracting interest in these therapies, many of which are now in clinical trials. While many of the analyses required to characterize these different classes of biologic drug substances are the same, their characterization does in many cases require different analytical techniques.

Often, combinations of light-scattering, intrinsic and extrinsic fluorescence, and calorimetry are used to rapidly deliver information on protein stability in many excipient combinations.

For newer antibody formats, both Garrett and Wegele note that LC/MS is a relatively fast method for gaining high levels of information on the size-variant distribution of biotherapeutics at early development stages. CE is also providing deeper insights into the structure of these molecules, according to Garrett. "Use of these techniques has led to numerous improvements in the manufacturing of antibodies and antibody fragments, particularly when considering the variables that can now be investigated and controlled as part of the manufacturing development process," he asserts.

For cell-based therapies, Garrett notes that the development and adoption of rapid, molecular-based testing methods for both process and product safety will enable cell therapy products to be manufactured in the timeframes necessary to both manipulate patient-derived cells and then deliver them safely. The development of methods for assessing the safety of the viral backbones used to produce gene therapies has also kept pace with their advancement into the clinic. "Virology-based tests have been refined such that they now provide information on the specific properties and quality of vector backbones, which is crucial for ensuring the safety of these advanced therapeutics," Garrett states. He also notes that molecular methods such as next-generation sequencing are being employed to investigate the identity, purity, and stability of virus-based gene therapies.

Biosimilar solutions

Full analytical characterization of branded biotherapeutics and potential biosimilar products is fundamental to the development of biosimilars, and the pathway for analytical method development for biosimilars is somewhat different from that of novel biotherapeutics, according to Jun Lu, director of analytical development for Catalent Pharma Solutions. "Both release and characterization methods are required at the very early stage of biosimilar development, because the reference product from multiple lots must be extensively characterized to establish the target product profile," he says. More specifically, analytics are essential to defining the critical quality attributes (CQAs) that form the quality target product profile (QTPP).

Demonstration of similarities between the biosimilar and reference product through side-by-side comparison (i.e., physical, biological, and chemical characterization) is required before progressing into the clinic, according to Greer. Matching of the amino acid sequence and PTMs of the reference product determined by using LC/MS/MS and other protein characterization methods must be performed as a clone selection criterion, because upstream and downstream development has minimal impacts on changing these CQAs, adds Lu.

Use of orthogonal methods for biosimilar assessment is also emphasized by regulators, because subtle differences between a biosimilar and the reference product may be difficult to detect using only one analytical method. FDA in particular has introduced the concept of "fingerprint-like" analyses, according to Greer. "This approach entails the use of a carefully selected portfolio of characterization techniques for primary and higher-order structure, together with biological and potency assays producing data that, when combined, add up to more than the sum of the parts," she says.

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For instance, Lu notes that for analysis of high-molecular-weight (HMW) species, which present a high-risk safety concern, supplementing SEC with analytical ultracentrifugation (AUC) is strongly recommended. For the determination of higher-order structure, a combination of at least two techniques from a list including circular dichroism (CD), Fourier-transform infrared (FTIR), differential scanning calorimetry (DSC), and HDX–MS can be used to potentially elucidate any detailed structure differences. Garrett adds that advanced cell-based potency assays are important for determining whether the *in-vitro* effects of biosimilars are similar to the originator molecule. Greer observes, however, that the link between higher order structure and biological activity remains to be explored. She does note, though, that several techniques are emerging from research backgrounds to address these questions, such as HDX–MS and 2D-nuclear magnetic resonance (NMR) imaging.

Statistical analysis of analytical data for the determination of biosimilarity is also required by FDA to ensure confidence in the data. One consequence, according to Lu, has been the replacement of imaging methods such as sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and IEF gels with CE–SDS and cIEF, respectively, which allows greater analysis of the data output.

More work to do

Despite the numerous advances in MS, CE, next-generation sequencing, and other rapid assays, further developments are still needed. Adoption of many new analytical technologies takes time given the need for extensive confirmation and validation of performance. Many of these newer methods are gaining acceptance further down the development pathway and closer to quality control, but are not yet widely used. Regulators are, however, starting to explore the potential advantages these technologies can provide, according to Garrett.

One specific issue for Kneller is HCP quantitation, which for early clinical work is typically performed using commercially-available ELISA kits, but then requires transition to costly custom assays later in development. "This transition can be difficult if kits do not provide adequate coverage of all HCPs potentially present in the product. Orthogonal approaches to HCP quantitation (e.g., mass spectrometry) are not yet feasible or widely-adopted, however," he notes. Wegele points to the need for tools that enable the assessment of the criticality (e.g., safety, immunogenicity, PK, potency) of various product-related impurities/CQAs (e.g., HMW species, dimers, fragments, PTMs, charge variants, etc.) to identify control strategies that make sense and do not lead to excess testing burdens.

Despite the numerous advances in analytical technologies, further developments are still needed.

Reed Harris, senior staff scientist in Pharma Technical Development at Genentech, would like to see more effective methods for identifying the causes of excipient degradation, which may be due to trace-level impurities that are below current detection capabilities. He also points to the need for better resolution of higher-molecular-weight species using SEC. SEC aggregate resolution is needed because there is growing evidence that antibody aggregates are not as immunogenic as originally believed, and further work is necessary to establish the true patient risks for different aggregate types. "Current SEC columns resolve monomers from dimers, but do not resolve different dimer types or multimers such as trimers, tetramers, etc., very effectively," he says. Furthermore, he notes that while CE–SDS is an advance over SDS–PAGE, further improvements are needed. The presence of SDS makes it difficult to analyze CE–SDS peaks with mass spectrometry, and therefore, most peak assignments are performed by spiking forms prepared using other methods into samples, which is time consuming.

Particle analysis is another issue for Wegele. He notes that currently available methods are mostly insufficient for precise and robust assessment of subvisible particles, particularly translucent proteinaceous particles and particles with diameters less than approximately 2 µm. Roche has developed a modified light-obscuration sensor that monitors the signal width rather than length, leading to improved detection of very small subvisible particles, reduction of artifacts during the analysis of low concentrations of translucent protein particles, and higher counting accuracy compared to flow imaging microscopy and standard light obscuration measurements.

Other ongoing needs, according to Wegele, include replacement of cell-based potency assays with novel, cell-free assay formats in the quality control environment; methods for the evaluation of the impact of combined administration of biotherapeutics; and more automated testing solutions to cope with the steadily increasing sample load of ever more complex biologics and next-generation biologics, which are often highly potent therapeutics with novel, highly potent product-related impurities. "It is important to address novel and critical product-related side products (e.g., immune-cell-activating side products acting at the crossroads of immunology and oncology) to ensure maximum patient safety and guarantee efficacy," he asserts.

Finally, Harris notes that the industry is struggling to balance the needs for comprehensive testing, including testing to account for unexpected events, and more rapid product development. "Risk-based (i.e., QbD) test strategies will lead to a reduced set of tests, but it is also necessary to include tests that detect variation outside of process models. The two approaches present a fundamental conflict," he states.

Indeed, biopharmaceutical manufacturers remain challenged to increase the speed and accuracy of product development while still ensuring safety in the face of more rigorous regulatory scrutiny, novel biologic molecules, and evolving manufacturing strategies. "All of these factors are adding complexity to analytical testing programs," Garrett concludes. **PTE**

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Statistical Tools to Aid in the Assessment of Critical Process Parameters

Ke Wang, Nathan D. Ide, Olivier Dirat, Ann K. Subashi, Nicholas M. Thomson, Kim E. Vukovinsky, and Timothy J. Watson

There are many different approaches for assessing process parameter criticality, and assessing which process parameters have a significant impact on critical quality attributes (CQAs) is a particular challenge. Including an unimportant process parameter as a critical process parameter (CPP) in a control strategy can be detrimental. The authors present a statistical approach to determine when a statistically significant relationship between a process parameter and a CQA is large enough to make a practically meaningful impact (i.e., practical significance).

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The assessment of critical quality attributes (CQAs) and the control of critical process parameters (CPPs) that affect these attributes are important components of the overall control strategy for drug substance and drug product manufacturing. There are many different approaches for assessing process parameter criticality, and statistics can play an important role in these evaluations. One particular challenge involves assessing when a relationship between a process parameter and a CQA represents a significant impact on that CQA. Assessing impact based solely on statistical significance (p-value) is not appropriate, because statistical significance does not take into account the strength of the relationship relative to the relevant quality requirements and can lead to the inclusion of relatively unimportant process parameters as critical elements of the control strategy. Including these unimportant process parameters as CPPs is undesirable as it effectively dilutes the focus on process parameters that are truly important for ensuring product quality. The excessive assignment of criticality to unimportant process parameters can also place an unnecessary burden on manufacturing operations.

This article introduces a statistical approach to help determine when a statistically significant relationship between a process parameter and a CQA is large enough to make a practical meaningful impact (i.e., practical significance). The assessment of practical significance can then be used to determine if a parameter has a significant impact on a CQA, thus helping to assess the criticality of process parameters. The described statistical methodology is intended to provide a consistent framework for discussions on process parameter criticality and should be used to support but not replace scientific judgment.

The statistical approach that has been developed takes into account the process risk (Z score) and the parameter effect size (20% rule). This article discusses some background on criticality assessments, the motivation behind the development of a new strategy for these assessments, and examples of the implementation of this approach.

Background on criticality assessments

The control of CQAs, critical material attributes (CMAs), and CPPs is an integral component of the overall control strategy

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for drug substance and drug product manufacturing. The International Council on Harmonization (ICH) Q8(R2) (1) provides the following definitions:

- CQA is defined as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
- CPP is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

ICH Q11 (2) states that: "A control strategy should ensure that each drug substance CQA is within the appropriate range, limit, or distribution to assure drug substance quality. The drug substance specification is one part of a total control strategy and not all CQAs need to be included in the drug substance specification. CQAs can be (i) included on the specification and confirmed through testing the final drug substance, or (ii) included on the specification and confirmed through upstream controls (e.g., as in real-time release testing [RTRT]), or (iii) not included on the specification but ensured through upstream controls."

In addition, ICH Q11 states that: "Impurities are an important class of potential drug substance CQAs because of their potential impact on drug product safety. For chemical entities, impurities can include organic impurities (including potentially mutagenic impurities), inorganic impurities (e.g., metal residues), and residual solvents."

The term CMA is not defined in the glossary of ICH Q8, but ICH Q11 clarifies that material attributes can be intermediate, reagent, solvent, or starting material attributes. It is appropriate to use the term CMA for any of the starting material or intermediate attributes that have an impact on a drug substance CQA (particularly in the case where a specific CQA/impurity in the drug substance is derived from a different chemical species upstream).

Based on the above definitions and ICH Q8/Q11 guidance, the criticality of process parameters should be assessed for their impact on the CQAs and CMAs. Upstream/intermediate specifications can include quality attributes that are not part of the control strategy for CQAs but are included for monitoring and trending purposes only.

Figure 1: Decision tree for assessment of process parameter criticality. CQA is critical quality attribute.

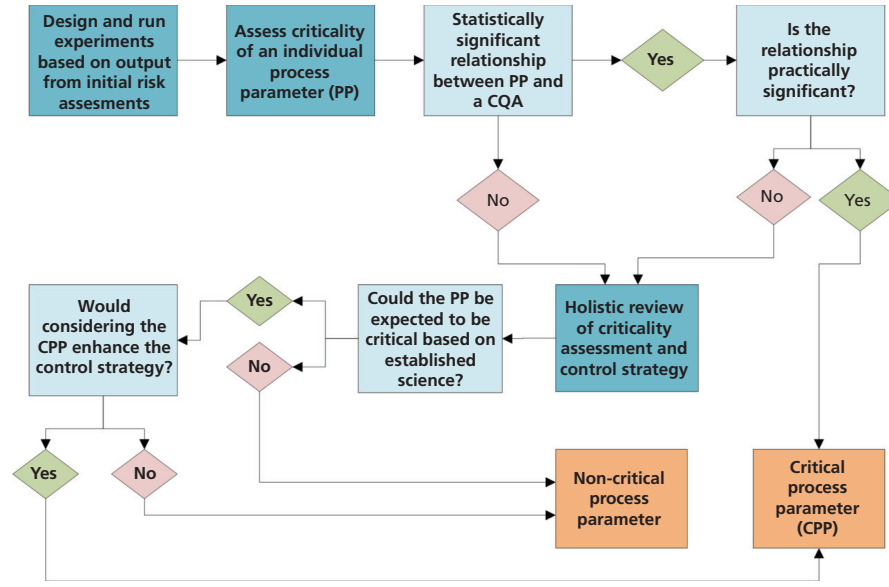

Figure 2: Illustration of statistical significance and practical significance. The green and blue lines represent two statistically significant relationships between a process parameter and a response. The red dashed line indicates the acceptable limit for this response. The relationship represented by the blue line is practically significant, but the relationship represented by the green line is not, because the effect size is small and all of the results are far below the limit.

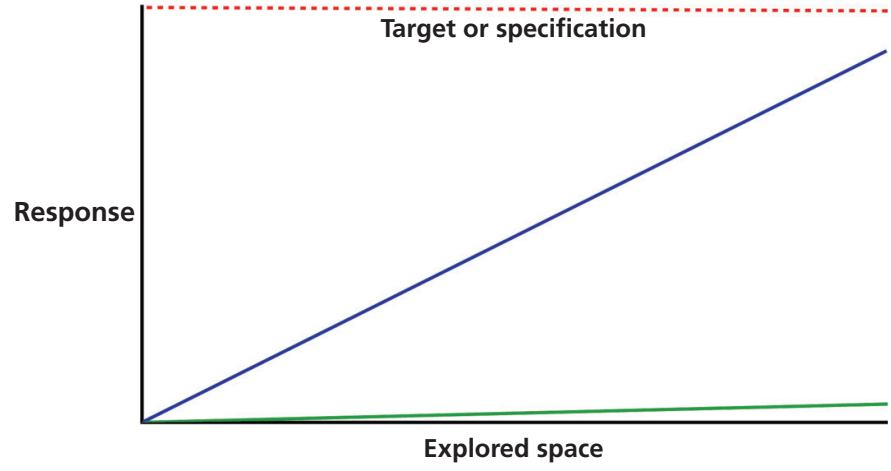

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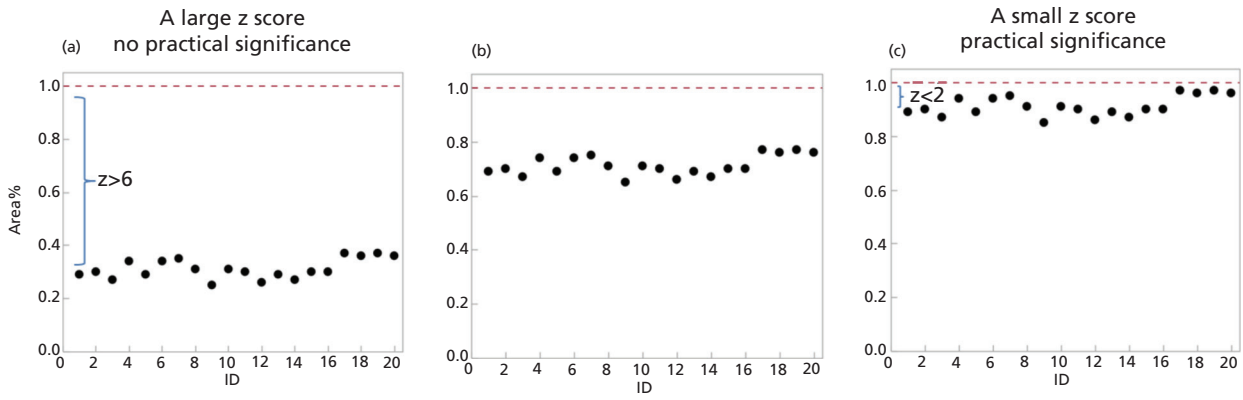
Figure 3: Illustration of the Z score concept.



Assessment of process parameter criticality

Process parameter criticality can be evaluated using risk assessments, experimental investigation, or a combination of these two approaches. The determination that parameters are critical or non-critical by risk assessment is relatively straightforward—if established science, knowledge, or data clearly indicates that a parameter will or will not have a significant impact on a CQA, criticality can be assigned. For many parameters, however, the risk assessment will indicate that experimental investigation is required to assess criticality (3).

In cases where data are available from multivariate and/or univariate design of experiments (DoEs), these data can be used to help assess process parameter criticality (see **Figure 1**). The first question to consider is whether a parameter has a statistically significant relationship to a CQA. If so, the practical significance of this relationship should be assessed. If the parameter is considered to have a practically significant relationship to a CQA, then the parameter should be considered critical. If the parameter is determined to not have a statistically significant relationship to a CQA, or it is determined to have a statistically significant, but not a practically significant relationship to a CQA, the team should still review the control strategy holistically, prior to assessing the parameter as non-critical. In this review of the control strategy, the team should evaluate the established science related to this process parameter and consider whether promotion of the parameter to critical would be beneficial to the overall control strategy. Promotion of a parameter from non-critical to critical during this final review process would not be expected to be a common occurrence.

Statistical approach for practical significance

Using statistical significance as the definition of practical significance is not appropriate, because statistical significance does not take into account the strength of the relationship relative to the relevant quality requirements. An appropriate statistical evaluation of practical significance can take into account the risk of failing a limit/specification and the parameter effect size. For example, the green and blue lines in **Figure 2** represent two statistically significant relationships between a process parameter and a response. The acceptable limit for this response is indicated by the red dashed line. The relationship represented by the blue line is practically significant, but the relationship represented by the green line is not, because the effect size is small and all of the results are far below the limit. Therefore, the severity resulting from a parameter effect needs to be considered for CPP assessment just as it is contemplated in evaluating quality attribute criticality (3).

A statistical approach has been developed to help determine when a statistically significant relationship between a process parameter and a CQA can be defined as a practically significant relationship. This approach uses two statistical tools (Z score and 20% rule). The concept behind the first tool, the Z score, is shown in **Figure 3**. Each plot represents the data points from a 20-run multivariate DoE (five parameters included in the study) with an impurity (Area %) on the y-axis and the experiment number on the x-axis. Variability present in the data could come from different sources, including intentional changes in parameters, analytical variability, and the natural variability (i.e., random noise) inherent in the process. If there is too much variability in the data that is not explained by the intentional variation of parameters, the variability should be addressed before proceeding with this analysis.

In **Figure 3**, the limit for this impurity is indicated by the red dashed line. The data points in (a) are tight and far away from the target, suggesting a low-risk process. Moving any parameter over its experimental range is not going to significantly elevate the risk of failing versus this limit; it is reasonable to conclude that no parameter is practically significant. By contrast, data points in (c) are very close to the limit, therefore, even though the relative variability in the data is the same as in (a), the process is at higher risk. In this case, any statistically significant parameter should be considered practically significant. Data points in (b) are neither far from nor close to the limit. In these cases, the second statistical tool (20% rule) is needed to quantify the individual parameter effect size. This effect size, calculated using the statistical model, can be used to assess practical significance.

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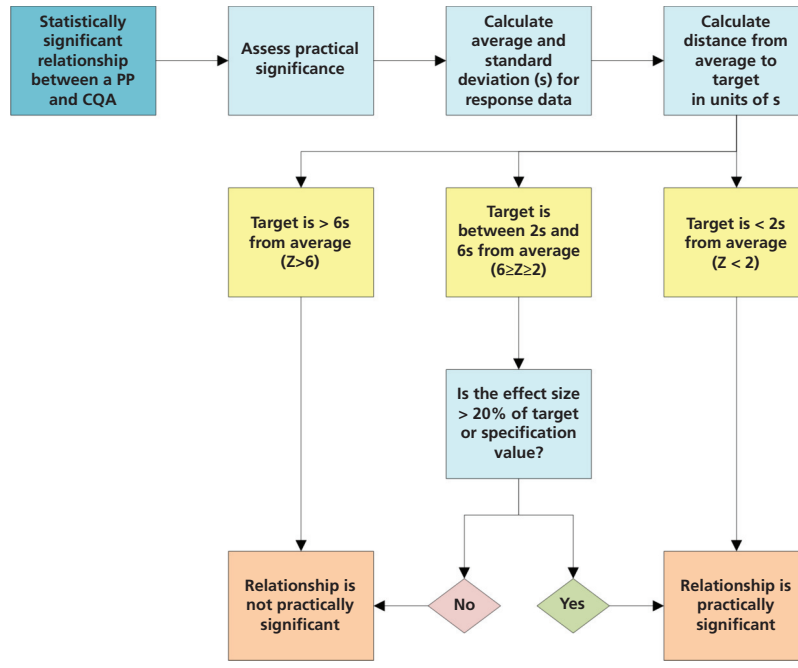
Figure 4: Decision tree for practical significance. PP is process parameter. CQA is critical quality attribute.



As introduced conceptually in **Figure 3**, the distance between the data and the limit plays an important role in process risk evaluation, and the Z score can be used to measure this distance. If $\bar{x}$ and s are the average and standard deviation of the data respectively, and U is the upper limit of the specification, the Z score can be calculated using **Equation 1**:

$$Z = (U - \bar{x})/s \qquad \text{[Eq. 1]}$$

The Z score evaluates how close the entire dataset is to the limit, without focusing on any individual parameter effects. The value for Z effectively indicates how far the data is from the limit/specification; a large Z score indicates that the data are far from the limit/specification, while a small Z score indicates that the data are close to the limit/specification. Conceptually, the Z score is similar to a process capability index (Cpk)(4); a large Z score indicates a low-risk process and a small Z Score indicates a high-risk process.

In this approach, Z score values of two and six are used as the cut-off values for assessing practical significance. In cases where a Z score is larger than six, as illustrated conceptually in **Figure 3(a)**, there are no practically significant parameters. In cases where a Z score is less than two as illustrated conceptually in **Figure 3(c)**, it is generally appropriate to conclude that every statistically significant parameter is practically significant. If a Z score is between two and six, as illustrated conceptually in **Figure 3(b)**, the individual effect size of statistically significant parameters needs to be quantified and compared to the limit/specification. Here, 20% of the limit/specification range (20% rule) is chosen as the threshold for practical significance. If a parameter effect size is greater than 20% of the limit/specification range, it should be considered practically significant. If the parameter effect size is less than 20% of the limit/specification range, then it is not practically significant. The selection of 20% as the threshold for practical significance is similar to the conventional criteria (0.2–0.3) for a small effect size, using Cohan's d (5). This procedure for assessing practical significance is outlined in **Figure 4.** The described approach allows for the rapid and consistent assessment of process parameter criticality.

For simplicity, the above discussion of Z scores is focused on one-sided, upper-limit specifications (U). It is worth noting that the approach can be easily extended to one-sided, lower-limit specifications and also to two-sided specifications.

Examples

Two examples are included to illustrate the implementation of the described approach. The first example shows the criticality assessment for six crystallization process parameters in a drug substance intermediate step. The studied parameters were seed temperature, temperature ramp rate 1, temperature ramp 1 end temperature, temperature ramp rate 2, temperature ramp 2 end temperature, and seed loading. These parameters were incorporated into a 26-2 fractional factorial with four replicates, at the target conditions, for a total of 20 experiments. Shown in **Figure 5** are the bar charts for one process-related impurity (impurity 1) with a limit of not more than 1.0% at the intermediate step. This impurity is a CMA, as it tracks forward to an impurity (CQA) in the drug substance. The limit was set based on downstream fate and purge data. Statistical analysis revealed that ramp rate 1 and seed loading had statistically significant relationships with impurity 1. Given the calculated average

Figure 5: Bar chart for impurity 1 (y-axis) in Example 1 design of experiment (DoE) (x-axis). Black dashed line is the average of impurity 1 and red dashed line is the target. Z = 18.

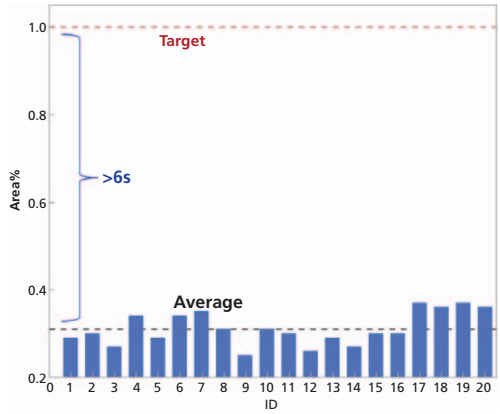
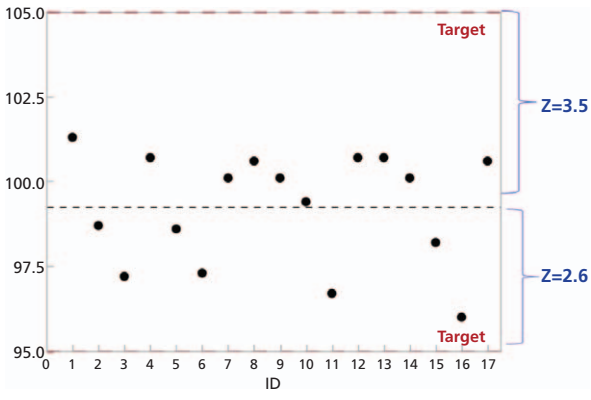


Figure 6: Scatter plot of tablet assay (y-axis) in Example 2 design of experiment (DoE) (x-axis). Black dashed line is the average of tablet assay and red dashed lines represent the two-sided specification. Z1 = 3.5 and Z2 = 2.6.



(0.31%), the standard deviation (0.037%), and the limit of 1.0%, a Z score of 18 is obtained. The Z score of 18 is greater than six, and therefore none of the studied parameters have a practically significant relationship with impurity 1.

A second example is shown in **Figure 6**. This example is based on a measurement of tablet assay, in a 17-run experimental study for a drug product process, with a two-sided specification of 95%–105%. The study was designed to explore the impact of excipients (magnesium stearate quantity, dicalcium phosphate [DCP] source) and process parameters (Comil shear force, pre-blending) on tablet assay. Statistical analysis revealed a significant interaction between DCP source and Comil shear force. The fitted regression model is shown in **Equation 2** as follows:

$$\text{Assay\%} = 99.18 - 0.78 \bullet \textit{ComilShearForce} - 0.70 \bullet \text{DCP} - 0.90 \bullet \textit{ComilShearForce} * \textit{DCP} \quad \text{[Eq. 2]}$$

For a two-sided specification, two Z scores are calculated, and the lower of the two values is used to assess practical significance. Given the calculated average (99.24%) and standard deviation (1.64%) for tablet assay, the upper limit and lower limit had Z scores of 3.5 and 2.6, respectively. Both Z scores require additional assessment via the 20% rule to quantify individual parameter effect sizes. For a model with a significant interaction between two parameters, each calculated parameter effect needs to take into account both the main effect and the interaction effect. The statistical model in **Equation 2** predicts that the maximum change in assay is 3.36% for Comil shear force and 3.20% for DCP. Given the specification range of 10% (105%–95%) for tablet assay, the 20% threshold is 2.0%. As both effect sizes are greater than 2.0%, Comil shear force and DCP are practically significant.

Summary

In general, it is expected that the evaluation of practical significance presented in the two examples discussed would encompass all relevant experiments that assess a given parameter (i.e., the entire explored range). Given the expectation that criticality assessments should be performed by evaluating effects across the entire explored range, boundaries of the explored ranges should be set in a pragmatic fashion. These explored ranges need to effectively support the development of process understanding and the need for usable ranges in manufacturing, while avoiding unnecessary expansion of the investigation into ranges that would never be considered for manufacturing.

Conclusion

Process parameter criticality can be determined using risk assessments, experimental investigation, established science, or a combination of these approaches. The proposed statistical methodology is intended to provide guidance and a common language to facilitate discussions on process parameter criticality. Criticality is assessed by determining when a statistically significant relationship should be considered a practically significant relationship, which is then used to aid the overall criticality assessment.

Acknowledgements

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Building Consensus for E&L Testing Standards

Standardized testing protocols are crucial for acceptance of single-use systems.

Rita Peters

Single-use systems (SUS) featuring plastic components and materials are widely used in bio/pharmaceutical development and clinical-trial material manufacturing, and are expected to become more common in commercial manufacturing. Drug manufacturers and contract manufacturers favour SUS for the benefits of fast changeover, reduced cross contamination, and manufacturing system flexibility.

Concern about the potential for contaminants from the plastic materials interacting with the drug, unacceptable extractables data, and a lack of standards for evaluating SUS materials could, however, slow adoption.

Nearly three-quarters of biopharmaceutical manufacturers surveyed for the 2015 BioPlan Associates industry study (1) identified extractables and leachables as a concern that may limit further use of SUS. The only greater concern was breakage of bags and loss of production material. Concerns about extractables and leachables have been steady during recent years, partially due to the increased use of disposables and increased awareness of the uncertainties about related regulatory issues, according to the report.

Good manufacturing practices in both Europe and the United States require that manufacturing equipment must be constructed so the surfaces that contact components, in-process materials, or drug products must not affect the safety, identity, strength, quality, or purity of the drug product (2–3). Therefore, bio/pharma and contract manufacturers must—using scientific- and risk-based approaches—test the materials and surfaces that come in direct or indirect contact with the API, ingredients, and drug product to demonstrate equipment and process suitability for regulatory filings.

Extractables studies identify chemicals that migrate from a material when exposed to a solvent at an elevated temperature, generating a worst-case test for contaminants. The data are used to assess toxicities of the extracted chemicals and to assess the potential for leachables—compounds that migrate into a specific drug product or process under normal conditions during the drug product's lifecycle.

Some suppliers of manufacturing components and packaging materials provide extractables data that can be used for preliminary screening and risk assessment; however, the information often is not available or sufficient. A complex supply chain, where different parts of an SUS technology may be manufactured or processed by multiple subcontractors at multiple locations, adds uncertainty to the quality and completeness of the data.

In the BioPlan study, more than 80% of the respondents "agreed" or "strongly agreed" that vendors of SUS should generate and validate extractables and leachables data. The study authors concluded that drug owners believe SUS vendors need to do more testing and analysis of materials used in SUS devices, or they are not comfortable dealing with extractables and leachables issues and defer to suppliers for the testing (1).

The cost of acquiring data was also considered. Nearly one-third of the respondents said they would not pay SUS suppliers more for extractables and leachables data; 22% said they would pay up to 25% more. The estimated average upcharge was 13.4%. The study authors attributed the drug manufacturers' price sensitivity to SUS-supplier upcharges for data to general cost-consciousness, increased knowledge about regulatory issues, a better assessment of developing the data internally, and an increasing number of contract service providers offering testing services of extractables and leachables.

Willingness to pay a markup for data has largely stabilized, the study concludes, although a growing number of drug owners are willing to do their own testing for early-phase development, where data requirements are less stringent.

Industry efforts

The lack of sufficient extractables data from suppliers of SUS has spurred activity for standardized testing protocols for these technologies. Representatives of drug manufacturers, testing laboratories, SUS manufacturers and suppliers, independent consultants, and regulatory authorities have participated in discussions, authored position papers, proposed best practices and standards, and developed databases. Often, the proposals conflict on key points; however, the groups are reporting efforts to build consensus.

The Product Quality Research Institute (PQRI), a collaborative effort of US Food and Drug Association's Center for Drug Evaluation and Research (CDER), industry, and academia, has published several documents including safety thresholds and best practices for extractables and leachables in orally inhaled and nasal products (4), and a similar publication for parenterals and ophthalmic drug products (5).

Bio/pharma and medical-device companies formed the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium to compile toxicological data on leachables and extractables to study their

USP updates standards for packaging plastics

The US Pharmacopeial Convention (USP) will publish a revision to the *United States Pharmacopia Chapter* <661> on Plastic Containers in May 2016, renaming the chapter Plastic Packaging Systems and their Materials of Construction. New General Chapter <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems describes scientific practices for accomplishing an extractables assessment. New General Chapter <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems outlines a framework for the design, justification, and implementation of assessments for drug-product leachables derived from pharmaceutical packaging and delivery systems. General Chapter <1664.1> addresses specific considerations for leachables in metered-dose inhalers, nasal sprays, dry-powder inhalers and inhalation solutions, suspension, and sprays.

impact on drug product packaging, delivery, and manufacturing systems. As of October 2015, the consortium had developed a database of nearly 400 compounds listing chemical, chronic toxicity, mutagenicity/carcinogenicity, reproductive/developmental toxicity, and absorption, distribution, metabolism, and excretion information (6).

An ELSIE materials working group also piloted an extraction study protocol on polyethylene and polyvinyl chloride that included extraction solvents, extraction techniques, and a range of analytical techniques. The study investigated whether a reduced number of extraction techniques or a reduced number of solvents could be used to obtain information useful for material selection, regardless of product type (7).

Trade associations, including the Parenteral Drug Association and the International Society of Pharmaceutical Engineers, also have been active in sponsoring presentations and publishing papers about extractables and leachables testing.

Proposals and consensus

The Bio-Process Systems Alliance (BPSA), a corporate member trade association of component suppliers, systems integrators, users, and testing laboratories, has published recommended practices for extractables and leachables testing and has initiated efforts to standardize testing procedures for other aspects of SUS materials (8).

The BioPhorum Operations Group (BPOG), which represents the drug-owner segment of the industry, defined a standardized extractables testing protocol for SUS manufacturing systems that covers methods for extractables testing studies, including sample preparation, extraction conditions, and reporting data. The authors, members of the BPOG extractables working group, wrote that a testing protocol, with agreed-upon test methods, would establish common expectations among suppliers, users, and regulators on the type of testing data to be generated. The enhanced data would help users compare components from different suppliers, would assist suppliers in selecting materials that end users need, and would help in controlling product variability (9).

Following publication of the BPOG paper, BPSA published a perspective article noting a difference of opinions among end-user companies, suppliers, testing laboratories, and standards-writing bodies that must be resolved to achieve a full industry consensus standard (10).

Representatives of BPSA and BPOG are participating in an ASTM International working group developing practice documents for extractables studies. The extractables test solutions practice will define a standard method to create extraction samples from single-use bioprocess systems using model bioprocess extraction solutions. Data generated from these studies could be used to make risk-based decisions about the potential impact on the API or drug product and the selection of equipment or components. Analysis of extractables test solution will be covered in a separate practice (11).

ASTM is also developing a practice for testing of leachables for single-use materials that contact APIs, intermediates, or the final drug product. The studies are designed to provide a leachables profile based on testing methodology comparable to extractables studies (12).

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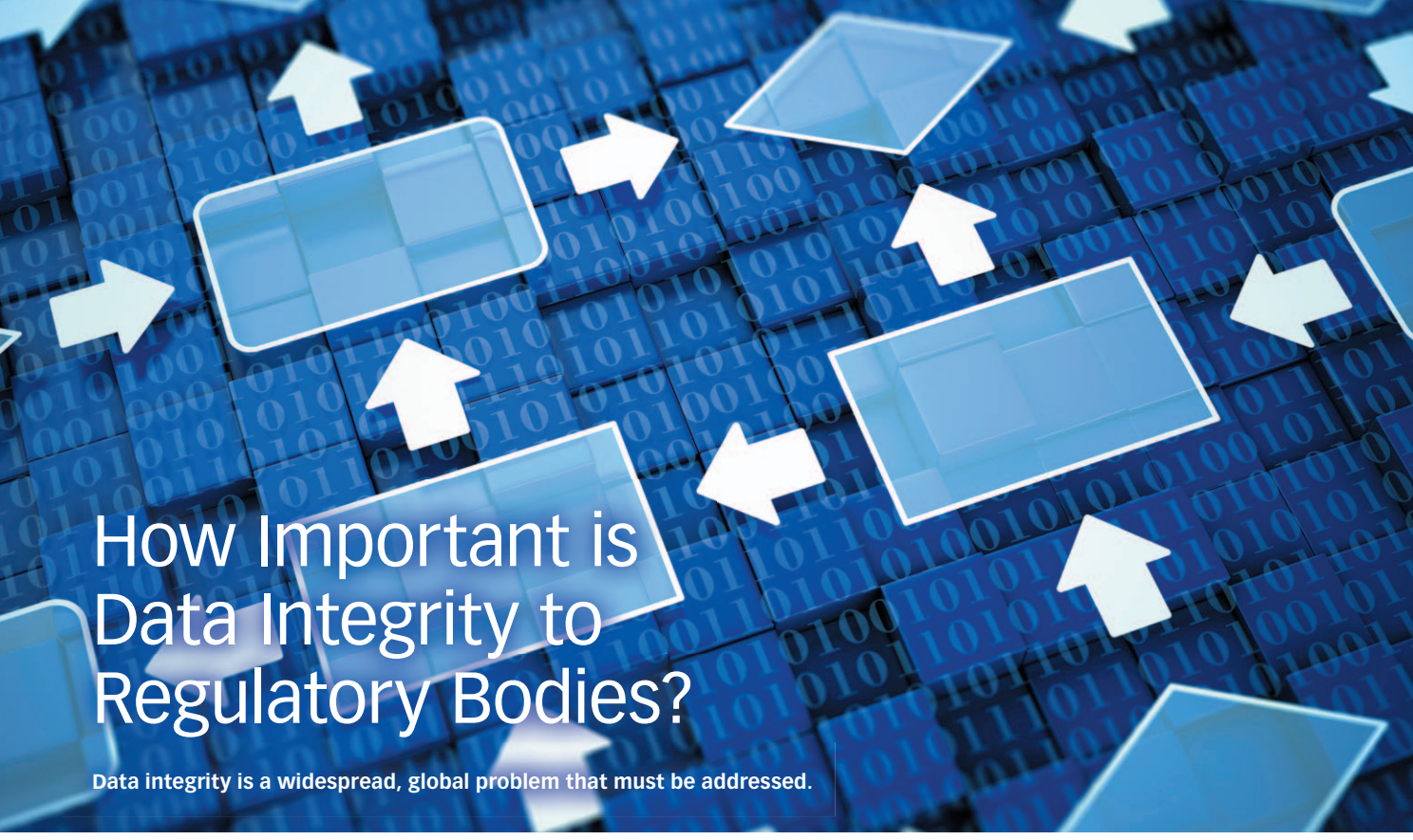

How Important is Data Integrity to Regulatory Bodies?

Data integrity is a widespread, global problem that must be addressed.

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Data integrity is a major regulatory topic in GMP-regulated laboratories. The problem is widespread, as cases of non-compliance have also been observed in laboratories regulated by good laboratory practice (GLP) and good clinical practice (GCP), not just GMP. Non-compliances from the European Medicines Agency (EMA) or warning letters from the US Food and Drug Administration (FDA) show examples from companies in the United States, Canada, the United Kingdom, and Italy, as well as China and India. So, it is not just a problem for Asia—it is a global issue.

The non-compliances are not confined to falsification and fraud. In fact, in the majority of labs, the main data integrity issues concern poor data management, which account for 95% of non-compliance cases; only 5% are a result of falsification or fraud. Problems arise from basic errors such as relying on paper as raw data and failing to protect electronic records, rather than deliberate manipulation of data. It is the latter, however, that gets the major headlines. In July 2014, FDA issued a stern warning that data integrity was a key focus of its enforcement efforts (1).

Regulatory guidance on data integrity

In January 2015, the UK Medicines and Healthcare products Regulatory Agency (MHRA) went further and issued *Guidance for Industry on Data Integrity* (revised in March 2015) (2). This guidance consists of descriptions, definitions, and expectations based around those definitions, which include raw data, original records, file structures, and audit trail. The regulatory expectations presented in this guidance are useful. However, the definitions are simply presented as a shopping list; a diagram explaining and linking key definitions would be more beneficial.

The guidance presents data integrity as the extent to which all data are "complete, consistent, and accurate" throughout the data lifecycle, which covers the period from data acquisition through to interpretation, reporting, and archiving and then destruction after the record retention period. There are similarities in the US regulations; a 20-year-old FDA definition of data integrity describes the degree to which a collection of data is complete, consistent, and accurate (3).

In European GMP regulations, documentation constitutes a key part of quality assurance and, therefore, compliance with GMP (4). An organization must have good documentation, follow standard operating procedures (SOPs), and demonstrate compliance with the applicable regulations. Several requirements focus on data integrity for computerized systems (5). If critical data are entered into a data system, a second check is required, which can either be a second person or can be automated using the computer system itself.

In the US, the regulations for laboratory records focus on the concept of complete data (6).

A review of data integrity warning letters reveals several citations for failure to have complete data including a failure to have a complete procedure (7), a failure to fully document the work that is carried out (8), or being selective in reporting data (e.g., using test samples to "check" if an instrument is working correctly) (9). Complete data includes the actual observation, which can be visual or by computerized

Table I: Good Automated Manufacturing Practice (GAMP) criteria for data integrity—ALCOA+.

ALCOA Term	Criteria	Definition
A	Attributable	Who performed the action and when? If a record is changed, who did it and why? Link to the source data.
L	Legible	Data must be recorded permanently in a durable medium and be readable.
C	Contemporaneous	The data should be recorded at the time the work is performed and date/time stamps should follow in order.
O	Original	The information must be the original record or a certified true copy.
A	Accurate	No errors or editing performed without documented amendments.
+	Complete	All data including any test, repeat, or reanalysis performed on the sample.
+	Consistent	Consistent generation of records and application of date time stamps in the expected sequence.
+	Enduring	Data should be recorded on controlled worksheets, in laboratory notebooks or in validated electronic systems.
+	Available	Data needs to be available and accessible for review, audit, or inspection over the lifetime of the record.

In European GMP regulations, documentation constitutes a key part of quality assurance and, therefore, compliance with GMP.

system. Contextual metadata, which puts the data or result in context, is also required. Examples of metadata include operator ID, units of measurement, sample information, identity, batch number, instrument suitability, and readiness. Audit trail events are also part of the metadata. If a hybrid system or a fully electronic system is used, FDA and European regulatory agencies require companies to review and evaluate audit trail events to see if data have been manipulated without authorization.

FDA guidance comprises a list of commonly asked questions and answers that are crucial for maintaining data integrity (10). Detailed explanations are given for:

- Why paper records from a hybrid system should not be defined as raw data—instead it should be the underlying electronic records; Although the reasoning focuses on chromatography, it is applicable to any computerized system.
- Why sharing of user identities in a computerized system is not allowed—as it makes it impossible to attribute the work carried out to a single individual.
- Why actual samples should not be used as system suitability tests to see whether a batch passes or not. FDA warning letters reveal many citations for this transgression.

Data integrity criteria

The criteria for data integrity are defined by the acronyms ALCOA and ALCOA+. ALCOA, which stands for attributable, legible, contemporaneous, original, and accurate, was developed by an FDA GMP inspector in the late 1980s. ALCOA has been used in many areas that are regulated both by FDA and other regulatory agencies worldwide. In 2010, EMA published a paper on electronic source data for clinical records, in which another four requirements relating to electronic data were added: complete, consistent, enduring, and available (11). The Good Automated Manufacturing Practice (GAMP) Data Integrity Special Interest Group (SIG) now refers to ALCOA+, which includes the nine attributes or criteria for data integrity (see **Table I**).

Inspection trends

In the past, an inspector would review piles of paper; to view a computer system, he would be shown print-outs of the screen. Now, the focus is on the computerized systems and the electronic records within; the paper output is secondary. Inspectors will focus on the electronic records, looking at how they were generated and manipulated within the application. In the light of these changes, consideration needs to be given to the person who will manage the system during an inspection. How is the system configured to protect the electronic records? Are electronic signatures being used in the application, ensuring that the configuration of the application is documented and reflects the settings within the software?

Annex 11 now requires audit trail entries to be reviewed, and FDA considers these entries as part of the complete data. Many findings of non-compliance during inspection have been discovered by looking at audit trail entries, therefore, an approach to reviewing audit trail events is needed. Citations have noted when audit trails were been turned off, the audit trail had not been reviewed, or user identities were shared, which is not allowed under the regulations. Additional citations can be found in the September 2014 issue of *LCGC* (12).

The ten compliance commandments

The 10 compliance commandments for computerized laboratory systems described in **Table II** should be considered (12).

Where should the electronic data transfer begin?

Let's consider preparation of standards by way of example. In an analytical lab, standards are usually prepared using an analytical balance. The actual weight is typically printed on a strip printer and pasted into a lab journal. Afterwards,

Table II: The 10 compliance commandments.

	Commandment	Comment
1	Management is responsible.	Management must take the lead in making certain that the integrity of data in the lab is managed and maintained.
2	Use a networked system, ideally with a database.	Stand-alone systems should not be used in a regulated environment.
3	Document the system configuration and manage all changes to it.	You must document and ensure the configuration protects the records.
4	Work electronically and use electronic signatures.	Try to work electronically wherever possible. The advantage is that the data are maintained within the system. Don't use a hybrid because you have two incompatible formats (worst possible situation).
5	Allocate each user a unique identity and use adequate password strength.	Ensure that you have unique user identities, so that you can attribute the work to a single individual.
6	Separate roles to avoid conflict of interest.	Separate the roles within any computerized system. Typically "Admin" should only be accessible by IT or a small group of people, not standard laboratory workers. Exception if there are only 1–2 users (in which case it is necessary to share the roles).
7	Define methods that can and cannot be adjusted.	Consider which methods within a system can actually be changed and which cannot.
8	Have a standard operating procedure for data manipulation.	For chromatography data systems, a standard operating procedure (SOP) for both automatic and manual integration is necessary.
9	Ensure staff are trained and competent.	The need for an SOP is clear, but do people understand it and are they competent to use it? Ensure the people are trained, both in data integrity and the instrumental techniques they are using.
10	Carry out effective self-inspections or internal audits.	Make certain that internal audits don't just focus on paper. Instead, they should go deeper and look at things within the computerized system.

Capturing the data at the point of origin and transferring the data electronically throughout the whole workflow is a much lower risk approach and reduces the risk of errors during the early stages of a process.

the standards are widely used for analytical methods, such as high-performance liquid chromatography (HPLC), gas chromatography (GC), titration, etc. Data management and documentation for analytical instruments are usually managed by dedicated software or a laboratory information management system (LIMS). This procedure is currently allowed by regulatory bodies, which state that print-outs representing original data for simple devices (such as balances) are acceptable (2) but is not the case for more complex devices. Nevertheless, it is important that reference standards are accurate and traceable because they represent the starting point of many analyses. Warning letters have cited "no details available on the preparation of standards or solutions, especially of analytical reference standards" (13, 14). Independent of process, it is important to ensure that all the data are available.

This then begs the question: Where should the electronic transfer begin? In the process described above, there is a gap in the data transfer between the "simple instrument" (the balance) and the "complex instrument" (e.g., the HPLC). Clearly, this is not recommended because it introduces an additional level of risk; it is obvious why no gaps should occur.

Capturing the data at the point of origin and transferring the data electronically throughout the whole workflow is a much lower risk approach and reduces the risk of errors during the early stages of a process, giving additional confidence in the compliance of a workflow or laboratory.

What data should be transferred?

The next question then becomes: What data need to be transferred? It is essential to associate results with metadata to build context around the values collected. Although integrating even a simple instrument can be tricky, the advantages of an integrated solution are obvious. When electronic data transfer starts from the beginning of the process, each piece of information needs to be input only once for it to be available throughout the whole system. This allows seamless movement of data and other information from the start of a process to the end, without the need for manual effort, such as manual transcription, creating an efficient work environment.

This transfer of data is achievable using a laboratory execution system (LES), such as LabX, which enables a variety of instruments to be directly connected (balances, titrators, density meters, refractometers, thermal analysis instruments, and pH meters). Useful features such as SOP-user guidance on the instrument terminal, automatic results capture in a database, and real-time data access support traceability of data and compliance with the GAMP data integrity criteria in ALCOA+.

As regulators continue to tighten their inspection approaches, it is crucial for managers and scientists

in regulated GXP laboratories to understand these criteria for data integrity and to assess and improve laboratory data management processes to ensure compliance with current regulations. Only after all these points have been addressed can data integrity truly be achieved.

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Gaining Insight from Process Control Data

Integrated data and cloud-based solutions can be used for process optimization.

Jennifer Markarian

In the past, process control data were used simply to control the process. With the explosion of data collection and analysis capabilities, however, data can be harnessed to do much more. *Pharmaceutical Technology Europe* spoke with Dr. Hartmut Klocker, vice-president of the Pharma Market Development Board at Siemens, about how data from process control systems can be used to optimize manufacturing processes.

Integrating data

PTE: What can be accomplished by more effectively using process control data?

Klocker: In the past, process control data were collected in the distributed control system archives and dedicated plant information systems, and their only purposes were to control the process and visualize the status of the process in real-time and historically. Today, however, pharma companies try to gain additional information by bringing together all different types of data from many sources including control systems, programmable logic controllers (PLCs), analyzers, building management systems, and laboratories.

The analysis of key performance indicators (KPIs) using all these data will open new insights into manufacturing processes and provide the basis for process optimization while keeping the quality within tight specifications. In addition, new technologies, such as continuous processes for tablet manufacturing or the production of personalized medicine, would not work without integrating process and analyzer data and even parameters of the scheduling and planning tools. In the future, the industry will focus on using process data to predict the end-product quality and thus the expected therapeutic effect using model predictive control.

Some data generated within PLCs, smart sensors, and complex analyzers are not collected and not used at all. Collecting these data, transferring them to a database, and applying tools to generate valuable information out of the pile of data are key challenges. A cloud solution may provide sufficient storage capacity and calculation power. The data analysis can then be performed by the customer or even outsourced to the suppliers of the automation systems or the machine manufacturers by giving them access to the relevant cloud data. An example, available today, is equipment monitoring, with the purpose of getting a better understanding of the condition of the machines and the overall production process. Data could be then used for energy management and condition-based maintenance.

PTE: How can data from different sources be integrated and presented to users?

Klocker: Data integration platforms are key to bringing together these data. The networking capabilities of devices are increasing steadily in line with the general industry trends of digitalization. Key technologies that allow this integration are the open standards OLE for Process Control, Unified Architecture (OPC UA) and OPC Analyzer-Device Integration (OPC UA ADI), which is for complex analyzers with large quantities of multivariate data.

Cloud technologies can provide a basis for such data platforms. Different experts can then be granted access to a subset of these data to provide data analytical services. For example, equipment experts can be shown data for predictive maintenance, and process engineers can be shown data to support continuous process improvement. In addition, the common problem of overloading plant operators with control data that are not directly relevant to monitor the process can be avoided. Data can be hidden on the operators' screens but transferred into the cloud, where other experts can look at various issues, such as machine health and performance or the relationship between climate and process quality parameters. The traditional operator screens will change, and instead of colourful graphics of process flow diagrams, process parameters and alarm messages with more focused views will prevail. The intent is to give a fast and clear picture of what is really going on, while hiding irrelevant details. Another tool is

Opening art image courtesy of Siemens

smart-phone apps that can be used to present the information needed to deal with specific tasks.

PTE: What are the security concerns with storing data in the cloud?

Klocker: Cyber-attacks are a challenge that is mentioned in every industry, especially when storing process data and accessing it broadly. To create the highest level of security, it is important to modernize and integrate the automation environment, with security built natively into the system from the field-level up. Siemens uses a 'defense-in-depth' concept that covers plant and network security as well as system integrity.

Using data

PTE: How can the collected data be used for determining KPIs, such as overall equipment effectiveness (OEE)?

Klocker: KPIs, such as OEE and others, must use the whole range of data sources from automation systems, planning tools, building management systems, and laboratory management. There are two principal methods for achieving this. The first strategy is to collect all data in one large database and apply the KPI calculations to this database. This strategy is straightforward as long as the intelligent device can be easily integrated into the plant information database using an open communication standard. In the alternative strategy, the data are not copied into a database, but accessed from all the distributed databases on request. The databases accessed might be plant information systems and historical data from control systems, recipe-control systems, enterprise resource planning data, and others. Intelligent caching of data to allow quick access using internet browsers is important. The advantage of this concept is to avoid copying of the original data, which might make the proof of data consistency (according to GMP regulations) cumbersome.

PTE: What are some best practices for using process data to control the manufacturing process?

Klocker: Critical quality attributes (CQAs) determine the final product quality and are the basis for predicting therapeutic effect. Today, many CQAs can be measured in-line/on-line by applying process analytical technology (PAT). Data collected from experiments using the in-line/on-line measurement of the CQAs in the different unit operations of a production chain are the basis for process data modelling. Correlation of the data provides a basis for understanding the process and determining the critical process parameter (CPP) settings to obtain the right quality. Furthermore, the application of PAT, combined with model predictive control in the process control system, allows us to adapt CPP settings dynamically and produce within specification all the time.

A good example of the need to combine data from several sources is personalized medicine, which is of increasing importance to the pharmaceutical industry. The same principles in terms of manufacturing, quality control, and release of the drug apply to personalized medicine as to conventional drugs, but instead of large batches of active ingredients, a batch size becomes the drug product for a single patient. Without tight data integration and a fully paperless production process, manufacturing costs would exceed any acceptable limit. To overcome this challenge, process automation data and data from the laboratory information system have to be shared with the information technology (IT) systems for batch recording, reviewing, and releasing. Furthermore, scheduling systems are a key part aligning all production steps and ensuring planning principles like first-in/first-out prioritization rules. Extensive integration of these data sources by IT and automation systems will allow production costs to be lowered by at least an order of magnitude.

Another case that presents some challenges is transforming a batch pharmaceutical process into a continuous process. A continuous process requires a robust process design and continual monitoring, typically using online analyzers. Multivariate analyzer data and other process parameters from simple sensors must be combined and treated by statistical engines to give the operators a clear view of the process so that they can ensure that the process always stays within the quality boundaries. In the next generation of continuous production processes, it will become important to use these quality parameters to automatically adjust the process, thus closing the loop. The core of such an advanced process-control system is a data platform handling a large quantity of multivariate and univariate data in real time and applying statistical methods like principle component analysis. The easy integration of multivariate analyzer data (e.g., spectral data) following open standards is an important requirement. An equally important feature is the real-time integration to the control system for adjusting the set-point dynamically. Advanced process control methods, especially model predictive control strategies, can add the benefit of controlling the overall quality at the lowest variance within the lower and upper limits. **PTE**

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Redefining Pharma Agility

Supply-chain success is measured by how effectively new medications reach patients, and how swiftly manufacturers can react to internal and external changes.

Agnes Shanley

In the past decade, there was a movement within the pharmaceutical industry to benchmark drug manufacturers' performance against that of manufacturers in other industries, to improve such areas as process robustness, speed and consistency, and to reduce waste (1). Proponents of lean manufacturing urged pharmaceutical companies to adopt best practices from other industries.

Thought leaders began to look more closely at manufacturing, as well as such standard industry benchmarks as changeover times and inventory turns, and asked whether pharmaceutical companies could improve performance and become more agile. To see how closely the industry has been examining its approach to inventory management and supply chain agility, *Pharmaceutical Technology Europe* asked Lora Cecere, founder of Supply Chain Insights, for her opinion on progress.

"Pharma is stuck in the mud," notes Cecere, who writes the Supply Chain Shaman blog (2) and has more than 40 years of experience managing major corporate supply chains, consulting, and analyzing industrial performance.

As a 2012 Supply Chain Insights report (3) noted, pharma is immature, compared to other industries, in its supply-chain management practices. It still has higher operating margins, but faces more complexity, commoditization, and globalization than it did in the past. Mergers and acquisitions have also had an impact, Cecere says. Today, most pharmaceutical companies still generally take a conservative, functional approach to their supply chains, and focus more on the demand cycle than on channel data, says Cecere, who suggests that more industry executives follow the advice of supply-chain expert Carol Ptak, a partner at the Demand Driven Institute. In a blog post on *SupplyChainInsights.com* (4), Ptak suggests that companies focus, first, on return on investment and cash flow, and secondarily on profit and loss, so that they can sense changes in demand and adapt planning and production dynamically.

Cecere and her collaborators have developed a supply chain index to measure how individual companies and industries are improving their supply chain agility. Considering such big issues as overall growth, profitability and complexity, the index tracks industries' and companies' improvement by averaging metrics over different time periods.

Each industry is analyzed individually, based on its unique characteristics, but then companies are ranked, with those that have made the greatest gains recognized as "Supply Chains to Admire" (5) within those industries, based on improvements in inventory turns, return on capital investment, and operating margins.

Companies in industries with lower operating margins tend to manage their supply chains better

Dieter Spannknebel/getty Images

Continuous Manufacturing of Pharmaceuticals: Scale-up of a Hot Melt Extrusion Process

LIVE WEBCAST Thursday, April 14, 2016 at 8 am PDT | 11 am EDT | 4 pm BST | 5 pm CEST

Register for free at www.pharmtech.com/pt/hot_melt

EVENT OVERVIEW:

The use of hot melt extrusion (HME) for formulating active pharmaceutical ingredients with low solubility continues to advance as interest in continuous manufacturing increases. An understanding of the variable process parameters that have a significant impact on the final pharmaceutical product is necessary to successfully manage an HME process when using twin-screw extrusion. In this webcast, experts will discuss residence time, mechanical-energy consumption, and other critical parameters, as well as their effects on a scientific approach to process scale-up.

Key Learning Objectives:

- How HME parameters affect final solid dosage forms
- How to scale-up a continuous process from research to production while minimizing process optimization
- How to optimize parameters to meet product quality

Who Should Attend:

- Scientists, engineers and specialists in formulation research, process development and production; scientists actively using twin-screw extruders in the pharmaceutical industry who want to learn a systematic approach to HME process scale-up.

Presenter:

DIRK LEISTER
Technical Marketing, Pharmaceutical Extrusion Applications
Thermo Fisher Scientific
Karlsruhe, Germany

Moderator:

RITA PETERS
Editorial Director
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Table I: Supply chain rankings (2011–2014), pharma and biopharma vs. Apple, Inc. (data from *Supply Chain Insights*).

Company and ranking for its industry (2006–2014 vs. 2009–2014)	Growth (%)	Operating margin	Inventory turns	Return on capital (%)	Revenue per employee ($/year)
Apple (16, 16)	0.32	0.31	136.6	25	2,077,891
Novartis (1, 1)	0.01	0.30	8.44	11	436,307
Biogen Idec (2, 6)	0.20	0.36	14.55	21	1,115,679
Merck (3,8)	-0.02	0.16	7.22	11	556,423
Teva (4, 2)	0.06	0.14	4	7	444,822
Novo Nordisk (5,5)	0.10	0.37	8.16	60	412,580
Abbott Labs (6,3)	0.10	0.12	8.11	10	297,141
Eli Lilly (7,7)	-0.04	0.21	8.40	18	585,537

Source: Supply Chains to Admire, 2015, excerpted with permission. Biogen-Idec was listed on the Supply Chains to Admire list for 2015, representing the pharmaceutical industry. Apple was not on the list and was ranked 16 on the consumer electronics list, but is included for comparison. The full report may be accessed via *Supply Chain Insight's* community site, www.beetfusion.com.

than those with higher margins, so Cecere was surprised to find that generic pharmaceutical manufacturers were not more agile than Big Pharma. In 2015, no generic or over-the-counter drug companies made the cut, while Biogen-Idec was the sole pharmaceutical company to make the list of 26 Supply Chains to Admire.

Biogen-Idec listed on the 2015 "Supply Chains to Admire" List

Biogen-Idec improved its overall supply chain index ranking from 6 (when considering the period from 2006 to 2014), to 2 (when considering 2009 to 2014), the study found. The company increased return on capital from 13% to 21%, respectively, during these same time intervals, and inventory turns, respectively, from 9.99 to 14.55. **Table I** shows performance for the seven top-ranking pharmaceutical companies from 2011 through 2014, comparing them with metrics for a manufacturer from a different industry: Apple, Inc.

If traditional supply chain management is not a top priority, how is the industry becoming more agile, and what metrics best reflect its progress? *Pharmaceutical Technology Europe* asked Greg Anthos, senior managing consultant at Tunnell Consulting, for his thoughts. Anthos says that pharmaceutical manufacturers are focusing more of their attention upstream, to improve the research and development process, and, in particular, the way they handle clinical trials.

More pharmaceutical manufacturers are moving to adaptive trial designs, he says, and a growing number of them are working to be able to bring life-saving products to market under accelerated approval in Phase II. This is a major feat, considering the Phase III failure rate for new drugs (6).

At a time when some commodity generics continue to be in short supply, the emphasis is not on reducing inventories but on ensuring adequate supplies, Anthos says. Companies are also addressing the challenges brought by mergers and acquisitions, which can temporarily distract staff, at all levels, from operational and agility goals. McKinsey analysts argue for the need for greater CEO involvement, standardized processes, and greater communication and feedback, the hallmarks of any good lean or operational excellence program, when a merger or acquisition is underway (7).

The following are some opinions on agile manufacturing that Anthos shared in an interview with *Pharmaceutical Technology Europe*.

Fear of stockouts and tendency to play it safe with inventory

PTE: It was one of Tunnell's analysts who first drew industry's attention to pharma's inventory turns, compared to those in other industries, as a measure of its agility. Why is it that the industry appears to have made so little progress in improving its performance in this area?

Anthos (Tunnell Consulting): Not a lot has changed if you analyze the industry based on the classic supply-chain measures. Some manufacturers are probably carrying well over a year's worth of inventory. Today, however, supply chain agility has to mean getting medicines to the patient more reliably and efficiently.

You'll see some progress in inventory management, but it has not been the primary focus. Today, the industry's first goal is ensuring supply to market so that there will not be any stockouts. A growing number of processes, especially in biotech, can be complex and fickle, so there is a tendency to play it safe with inventory. In the end, pharma companies will be measured based on ensuring supply, but also on revenue and profitability and cash flow, so inventory turns are largely issues for manufacturing departments, the CFO, and the guys in the warehouse.

PTE: So how is agility being defined in pharma today?

Anthos (Tunnell Consulting): Agility is much more about, in the short term, getting new products to market quickly. It's about launching adaptive trials for breakthrough medications and having a sufficiently strong foundation to be able to launch a new product based on Phase II data.

In addition, agility means adapting immediately to changes in the market. These can be changes in demand, for example, when a competitor fails to get approval for a new drug and drops out of the market. But agility also means reacting to changes in internal processes or challenges within the company that must be overcome.

In the end, agility is getting to market faster and better managing the supply chain, and overcoming, more dynamically, any issues, whether external or internal, that have disrupted the supply chain. It's all about being more responsive to change.

The downsized challenge: doing more with less

PTE: How can companies be agile when they are dealing with more, and more complex processes, as well as with reductions in staff and resources?

Anthos (Tunnell Consulting): As I see it, the most progressive companies are focusing on three areas:

- **Increasing risk assessments, on both the supply chain and the enterprise.** They are becoming more proactive about determining the risks that are out there, prioritizing them, and ensuring that their resources are focused more effectively to address them.
- **Thinking through potential future changes as they develop any new product,** i.e., how the process could be simplified to improve robustness and process understanding. They are also taking steps to simplify their supply chains.
- **Ensuring the potential of their processes to address future changes.** Recently, I had a conversation with someone at a pharmaceutical company who had been in discussions with FDA [the US Food and Drug Administration] regarding process changes. He told me that a number of people within FDA have become frustrated by the fact that they are spending most of their time addressing process changes (e.g., changes that incorporate the use of more up-to-date equipment, or even simple changes in the location of manufacture).

As a result, less of their time is being spent on their primary mission: ensuring that safe and efficacious medicines get to the public. For drug developers and manufacturers today, the key question is: How do we develop new products so that, in the future, no or only minimal regulatory changes will be required, except maybe filing for new drug approval in a new geographical market. It's a great stretch concept, but it takes a fair amount of work to get to a point where you can think about, and address, all the issues involved.

Certainly some of FDA's and the industry's early work with quality by design (QbD) had that goal in mind. The idea was to better understand your product performance ranges and the design space, file for approval in a wider range that would allow you to make adjustments in that range.

Today, complexity, both of the products and of the regulatory landscape, has boxed us in. Significant numbers of supplements must now be filed for individual products. That's a challenge that the industry still has to surmount if it is to develop more robust supply chains and more robust processes.

PTE: How are manufacturers doing this?

Anthos (Tunnell Consulting): It requires figuring out design choices. For example, a company might choose to launch a new process using a stable platform that is already fairly well understood and characterized, and that has already been scaled up. It also means doing more of the classic QbD work, such as design of experiments (DoE) to really understand how the product behaves, where it works well, and what the process' fault lines are. Simplification is key, so you lean out the process to reduce unnecessary complexity.

PTE: But how can companies do that effectively with biologics, and how can they do it when they are also rushing to get product to market faster?

Anthos (Tunnell Consulting): With biologics, there is inherent complexity, so the key is designing in better controls or at least monitoring each process so that you better understand its behaviour. It's not easy. The industry is trying to move forward with greater process understanding while trying to get new products to market faster. These are competing forces.

PTE: How can all of this be done when international mergers are going on and day-to-day conditions are in such constant shift?

Anthos (Tunnell Consulting): Mergers distract staff. It's not only a question of pondering who will get to keep his or her job, but such questions as which processes to follow, whether in manufacturing or development. You want to create the best lean practices that are most effective, but you're often in a rush to meet some cost reduction synergy or regulatory target that a large consulting firm has told you to meet.

As a result, many companies reduce staff before they've figured out how to simplify and improve their processes.

Knowledge management is another major issue, because mergers and acquisitions drive a significant amount of employee turnover, both planned and unplanned. Knowledge often resides in individuals, rather than within the organization, and that jeopardizes business continuity. The way to avoid that is by understanding that you want to harmonize processes first, and engaging the folks who are already in the process of doing that to come up with the best work practices.

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Flexibility vs. Right-Sizing: Determining the Right Facility Size

Choosing the right facility size requires tailoring the design for current needs as well as anticipating the future.

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Right-sizing implies operational effectiveness and efficiency. Since the 1980s, the phrase has been used in management circles as a euphemism for layoffs, but in facility design, right-sizing can be a euphemism for minimal cost. Flexibility, on the other hand, is about having the capacity to adapt to future changes quickly and easily. Flexibility, however, typically requires an investment in infrastructure. At their most extreme, these two ideas are at opposite ends of a facility-design continuum.

Anticipating the future

The idea of "right-sizing," when applied to design, is to create an optimal facility. An example is found in the best practice recommendation of designing for actual equipment loads instead of the traditional method of estimated loads (1). Without the data of real loads, the practice of estimating results in oversized systems that increase energy and operational cost. But at what point is the glove's fit tailored too tight? Experience has established that—in the pharmaceutical industry—change is inevitable, making flexibility a necessary facility consideration. When building a facility, it is wise to build in some accommodation for future modifications. Anticipating the future can be daunting, but experience proves that it is prudent to try.

To effectively tailor a design for current needs, while at the same time planning for future potential, the different types of change that may occur must be considered. The most obvious potential change is increasing the manufacturing capacity to meet demand for the current drug portfolio. This change will require more and/or larger equipment of the same type as already exists. Another consideration is how new products will be introduced to the facility. Over the long haul, the ability of a facility to adapt to changing market and business conditions ensures its value far into the future. Inevitably, this ability will require more than just adding similar equipment, and new and different technologies will need to be accommodated.

Making space

In all cases, at a minimum, drug manufacturing facility owners need to allow for additional space. Planning for more space can be as simple as laying out a facility so that the manufacturing area has a direction in which to expand, such as into a warehouse or to the exterior into a future building addition. Key to effective growth, however, is having a strategy for internal circulation, with a sound way for materials and personnel to access the future area. Because continuity is harder to achieve if it has not been planned, a good place to start is ensuring that the current manufacturing circulation (i.e., the flow of materials and personnel) can be extended directly into the future area. While the exact use of the future space may be unknown, the need to get personnel and materials in and out in a way that is operationally effective and compliant is certain.

Over time, the drive for greater manufacturing efficiencies and capabilities leads to new equipment. All equipment has a limited useful lifespan. In addition, drug reformulation can demand additional or modified equipment, and new products and their processes may be added to an existing portfolio. A facility design should allow for the removal of existing equipment and the installation of new models. Dimensional clearances and movement pathways need to be integrated into the design. Without such a mindful approach, equipment may become inaccessible, and changes may require major interruption of ongoing operations.

Planning for utilities and services

Planning for additional space and new equipment is relatively easy to implement. A greater challenge, with greater cost burden, is planning for future utilities and services. Again, smart strategies need to be applied. Near-term flexibility can be provided by a thoughtful approach to system distribution. For example, service mains can be installed and sized so that local distribution can be easily added in the future. If judiciously done, this oversizing of a system can, for little upfront cost, provide for relatively easy and efficient growth in the future. In some situations, however, extending the current system may not be the right approach. If not, a strategy for future utilities still needs to be developed. One strategy is to plan a pathway and space for new mains and distribution to be installed later. Another strategy is to make a decision to develop a separate system in the future. In any case, it is better to build in a strategy at the beginning than to be without options later.

The greatest cost potential is in the generation of overall utility capacity, which is typically a longer-term consideration related to an expanded manufacturing footprint. Using modular equipment that can provide phased growth is a strategy that has found much success. Admittedly, this will not work for all systems, but it can work for many. Such an approach enables spending only what is required and delaying future capital expenditures until they are actually needed. Another option is purchasing extra capacity up-front by way of oversized equipment, thus anticipating the future need for increased capacity. You can ignore this possibility by rationalizing, "if we are that successful, we'll deal with it then," or you can develop a strategy that affords flexibility and a relatively quick and easy response when needed.

Conclusion

Right-sizing is more than responding to the immediate, foreseeable requirements of a facility. To optimize a design, there needs to be a prudent investigation of the potential for growth. With right-sizing, as the phrase implies, one size does not fit all. An approach needs to be crafted appropriate for the situation and the potentials that exist for a facility. Right-sizing is about finding value, the sweet spot where design, management, and operational considerations are balanced and deliver a quality facility for an appropriate cost. Finding the "right size," involves the creation of an efficient design with an appropriate amount of flexibility.

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Designing a Biomanufacturing Facility Incorporating Single-Use Technologies

Asking the right questions is crucial.

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The benefits of adopting single-use technologies in the production of biopharmaceuticals, such as lower capital investment and increased flexibility, are now well documented and widely recognized in the industry. But when building a new facility based on single-use technologies, or incorporating single-use into an existing facility, how do companies ensure they fully realize the benefits?

Facility design is a complex, multi-faceted, multi-step process, and early decisions can cause unforeseen limitations as the project progresses or, later, when further development of the facility is required. Asking the right questions at the outset and having the depth of experience and knowledge to understand the consequences of the answers are vital to establishing the right specifications during the design phase.

Identifying a partner or partners to support the design and build of a facility and the process that sits within it is the first key decision. Traditionally, an architectural and engineering firm and one, or possibly multiple, single-use process-equipment supply partners are selected. Working with a single external point of contact can help drive efficiencies in project-management and delivery. To be successful, however, the lead partner will need an understanding of biomanufacturing facility design, engineering, qualification, and validation, as well as the operational aspects of combining process hardware, single-use consumables, and automation platforms.

Overall, there are four sets of requirements to consider: product(s) to be made, process technologies, facility design, and supporting services. In each case, a series of questions will help identify objectives, design specifications, and potential constraints.

Considering the product

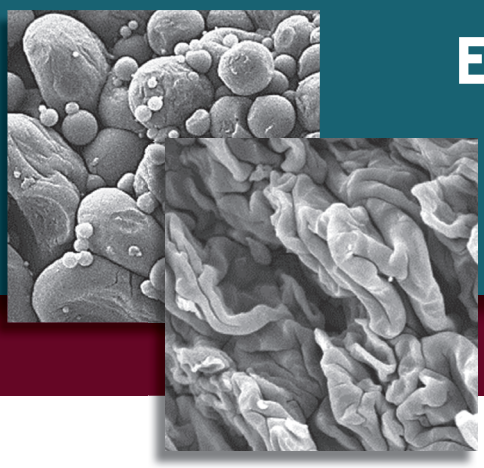
Product class. The first element that defines any biopharmaceutical manufacturing facility is the product itself. Will the facility be manufacturing monoclonal antibodies, recombinant proteins, vaccines, antibody-drug conjugates, or fragment antibodies? Also, will the products be mammalian cell-derived or microbial cell-derived? While these questions are most pertinent for the selection of the bioprocessing technologies required, they are also important for the design of the facility itself.

The promise of flexibility and simplification are often major deciding factors for choosing single-use technology. Removing the need for cleaning and sanitization, for example, means that switching between one product and another becomes quicker and easier. One way to take advantage of this flexibility is by making the facility multi-purpose (i.e., the manufacture of two or more products) to drive greater facility utilization. Deciding between a single- or multi-product facility impacts facility design considerations. Factors such as avoiding cross-contamination between products and ensuring that process-specific equipment can be moved around efficiently or housed nearby for rapid changeover need to be built into the design.

Regulations. With the plethora of regulatory guidelines and associated compliance requirements to adhere to when building a facility, it must be clear whether the product is for research and development purposes (pre-clinical), clinical trials, or commercial scale, as this will define the relevant GMP requirements. Also, if producing at commercial scale, which regulatory standard is needed? Is the product approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the China FDA, Brazil's National Health Surveillance Agency (ANVISA), or other agencies? In some cases, local requirements go beyond global ones. For example, Chinese fire regulations demand a greater level of fire resistance than is typical globally, and in countries such as Korea and Japan earthquake-proofing measures may have to be implemented.

Capacity. To define the necessary capacity of the facility, the primary question is how many batches per product per year are needed? However, this number has not always been defined when the facility design stage is reached. Alternatively, it should be possible to consider what quantity (in kilograms) of the bulk API needs to be produced for each product within the facility per year to meet clinical trial or commercial market requirements, and then work back to the number of batches.

For example, one can consider 2 x 2000-L bioreactors running a typical 14-day incubation



Engineering the Mechanical Properties of Amorphous Spray-Dried Dispersions

ON-DEMAND WEBCAST

Originally aired Feb. 23, 2016

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EVENT OVERVIEW:

Drug candidates with low oral absorption potential in the crystalline state are frequently converted to the amorphous form to increase solubility, prevent precipitation, and increase dissolution rate, thereby improving the extent of absorption and bioavailability. Spray drying drug from a solution containing an amphiphilic polymer is one of the most common and scalable methods used to achieve these enabling properties. The resulting powder contains the amorphous drug molecularly suspended or solubilized within the polymer matrix. Typical crystalline drug properties, often unfavorable for downstream processing, are masked by the amorphous state of the drug and matrix polymer. In addition, unlike many crystalline drug substances, spray-dried dispersion (SDD) particles are tunable, even within the spray drying process. Given this tunability, SDD composition and physical properties can be co-optimized for absorption potential, physical and chemical-state stability, mechanical and powder flow properties, and spray drying throughput. This is a departure from traditional development, where drug substance and drug product are progressed somewhat independently, with drug substance form and morphology often changing during the development and scaling processes. This often results in constraining the oral dosage formulation and process to overcome undesirable crystalline drug properties.

In this webinar, experts will discuss:

- How particle engineering by spray drying can be used to co-optimize several facets of SDD development with a specific focus on optimization of SDD mechanical properties
- Reduction of SDD tableting scale up risks and pill burden through identification of the primary mechanismof compaction and rational formulation design
- Development case studies highlighting SDDs whose primary mechanism of compaction is plastic flow versus brittle fracture.

Key Learning Objectives:

- The mechanical properties of SDDs can be tuned by changing the degree of atomization and drying rate in the spray dryer.
- A review of typical SDD mechanical properties, including stress stain behaviors, and how these can be exploited to optimize tableting.
- Engineering SDD particles provides opportunities to reduce pill burden by maximizing SDD loading in the dosage form through rational excipient selection and SDD physical property design.

Who Should Attend:

- Large pharma, mid-size pharma, biotech companies
- Product development group leaders and formulators, technical, and engineering positions involved in scale-up and manufacturing of oral solid dosage forms

Presenter

Aaron Goodwin, Ph.D.
Principal Investigator, Research & Development
Bend Research
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Moderator

Rita Peters
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For questions, contact Daniel Graves at daniel.graves@advanstar.com

Figure 1: An example of a production process from cell culture to bulk drug substance.

period staggered a week apart, which equates to one batch produced each week. A typical batch at 2 g/L with a 70% overall yield in downstream processing and a 95% production success rate will therefore yield 138 kg/yr in total. The final yield here is determined by the product titer of the production bioreactor, combined with the efficiency of the downstream purification steps, both of which will be driven by the details of the bioprocess itself.

Selecting process technologies

The next step is to drill down into the discrete unit operations of the biomanufacturing workflow. If the production process is already defined, it should be listed out, but if not, then the contracted partner may be able to provide an equipment list with flexible process capability. **Figure 1** shows an example of a production process from cell culture to bulk drug substance.

Starting with upstream, the status of the cell line and whether the process should be batch, fed-batch, or perfusion needs to be decided. Details about the nature of the process also need to be captured, including the bio-safety level and lengths of culture time for the seed and production bioreactors.

Moving to downstream, the overall yield of the purification process from post-cell culture harvest through to purified bulk API should be provided, along with an estimate of the step yield of each unit operation. If chromatography columns are used in the process flow, also specify the column volume and diameter required along with the desired number of cycles for each step.

Many single-use consumable supply partners now offer large customized system designs that can be tailored exactly to a specific workflow. Having an all-encompassing single-use system for a unit operation may seem to be the most efficient option. However, manufacturing a large single-use system comes with challenges. Packaging size and transportation integrity, sterility validation, component supply, handling and staging, installation, and operational use can all become more difficult and lead to greater risk levels. In some cases, defining and selecting smaller and simpler single-use systems to function in a modular workflow can be beneficial for minimizing risks.

Another important consideration in selecting single-use consumables is ensuring the supply chain is robust. Switching out any element of a validated process requires significant additional work. Therefore, make sure the supply partner has a proven track record, a materials policy in place, transparency on how they work with raw material suppliers, and a proactive communication programme, and that they can provide examples of how they have dealt with previous situations of raw material changes. Also check the robustness of the qualification and validation package supplied, and make sure it meets all relevant regulatory requirements.

Breaking new ground or renovating?

The crucial point in designing a new facility is whether it will be a brownfield/renovation or a greenfield site. If it is brownfield, then designers and engineers will need to know if the footprint is fixed and whether there are any restrictions on the space, such as floor strength, ceiling height, or door and elevator sizes. When thinking about the layout, are there existing personnel, product, or material flows already in place? Also, is there existing support infrastructure, such as utilities, warehousing, or laboratory space, that can be accessed? If possible, plans for future plant expansion at the site, or at other sites, should be taken into account, particularly if they will have an impact on the product requirements of the facility being built now.

If it is a greenfield site, then there is increased flexibility in what can be built. However, sourcing an engineering firm with the relevant experience for a stick-built biopharmaceutical facility design can be challenging in some parts of the world. In response to this, another option that has emerged is the modular facility, made from standardized prebuilt units delivered to the greenfield site. This approach can have benefits in ensuring consistent standards of quality and reduction of time to first batch. This modular approach to building allows site excavation to run in parallel with module construction and validation of unit operations to begin offsite.

For those on a brownfield site or those building a new facility adjacent to an existing one, any current centralized automation platform for data archiving and process monitoring may need to be linked to the new facility. In other cases, a standalone automation platform will be appropriate.

Finally, the need for any additional support functions or buildings should be decided (e.g., fill and finish building, a black utility generation building, a warehouse, quality control [QC] laboratories, or a waste treatment plant).

The needs here can sometimes run counter to expectations. For example, when embarking on a first foray into single-use, many presume that the removal of the hard piping and utilities needed for clean in place of stainless steel will result in a reduced footprint requirement. What is not always anticipated is the warehousing requirements for the stock of single-use consumables, which also need to be unpacked and prepared in a staging area. While having adjacent

FIGURE IS COURTESY OF GE HEALTHCARE

warehousing on a site may fulfill this need, more efficient tracking, set-up, and speed of changeover will be achieved if some consumables staging and storage sits within the facility itself, in close proximity to, or as part of the cleanroom environment. In total, the footprint is likely to be reduced in switching from stainless steel to single-use, but the change is not always as significant as expected.

When adding a single-use train to complement existing stainless-steel production facilities, the flexibility of single-use can help reduce the need for additional utilities. In one case, when designers and engineers looked at which existing underutilized utilities could be shared with a new single-use setup, it turned out to be a significant amount. For example, the flexibility of single-use meant that single-use unit operations requiring a water supply could be scheduled for the downtime or periods of low water consumption of the stainless-steel process. The reduced consumption of utilities required to operate the single-use process allowed for easier integration of additional capacity into the existing infrastructure of a production site.

Safety and time considerations

The ability of operators to safely work with biologic and potentially hazardous materials at any stage during the process is a key facility design consideration. Knowing where to place biosafety cabinets, if aseptic connections are required, and knowing any special design modifications to the single-use system (e.g., extra clamps, material selection, handling of highly toxic excipients) is vital.

Next, if known, specify the buffer and media requirements of each unit operation step in the production process, including whether any solutions require special handling (e.g., 70% ethanol), if steps are time-constrained (e.g., a highly-labile product that must be processed in a specified period), or if temperatures other than room temperature are required (e.g., temperature-sensitive media for upstream or cold purification processing).

The buffer preparation schedule for downstream purification can have a significant impact on facility design. Whether it is just-in-time preparation, one day in advance of use, or before any purification is started, will influence how much space is required for buffer storage or whether a system of built-in piping is required.

Planning for the future

Facility design is a multifaceted, interlocking web of needs, wants, and risks, and it must be properly managed from the outset to accommodate and account for all requests. Management includes being able to step back and take a holistic view. The prime driver and desired outcome, whether it is shortest time to market, lowest overall cost, or capital preservation, will significantly direct the decisions made at all stages of the design and building process.

For example, for a small biotech that was particularly concerned about reducing capital expenditure, the ultimate recommendation was to buy-in ready-made buffer and media in single-use liquid delivery bags. The overall scale and output of the facility was relatively low, and therefore the additional infrastructure required for in-house preparation was not going to drive significant savings in the longer term. This change in processing methodology minimized both footprint and utility needs.

Another element to consider at this point is how much "future flexibility" to account for during the design and build phase. Do you want to allow for the possibility of adding more production bioreactors to expand manufacturing capacity? Do you want to add 10% more communication drops for the integration of future equipment? The balance to be struck is between too much and not enough.

One reason such flexibility is important is that future manufacturing needs are always uncertain. Factors such as increased productivity and titre, coupled with increased market competition due to products coming off patent, has led to some stainless-steel facilities becoming underutilized and ending up shut down or sold.

The facility itself is only the beginning. Operational training will be required, as a minimum, but many supply partners can offer a much wider range of services. Validation requires significant experience and know-how and has the potential to consume significant internal resources. Outsourcing this element to an experienced partner can be a cost-effective option.

Ultimately, of course, budget is a crucial factor, along with when production needs to commence. But these should be considered alongside a close appraisal of the experience and depth of knowledge of the team that will be delivering the project. By mapping skills against requirements, it is possible to identify key attributes external partners need to have to make a project a success, first time. PTE

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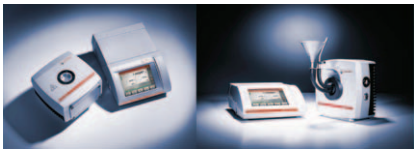

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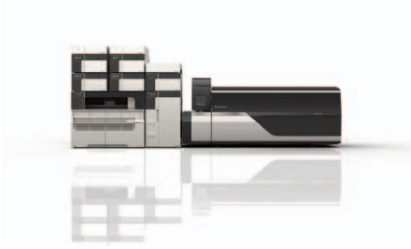

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Phase-Appropriate GMP

Siegfried Schmitt, principal consultant, PAREXEL, discusses the regulatory requirements for cGMPs in the different phases of drug development and manufacture.

Q: Our company covers the entire lifecycle for our drugs, from R&D through clinical trials to commercial product. The quality management system covers good clinical practice (GCP) and current good manufacturing practice (cGMP). In a recent client audit, we received an observation: "You do not apply the same level of cGMP to clinical-trial material manufacture as you apply to commercial product." Is this a new regulatory expectation?

A: It is not a regulatory expectation to apply the same level of cGMP to investigational new drug (IND) and marketed products. Although it is correct that you need to apply cGMP to all your clinical-trial supplies (referred to as investigational medicinal products [IMP] in the European Union [EU] and IND in the United States) and to commercial operations, the level of cGMP differs. The reasons for this are practical constraints as well as regulatory requirements. Under the US Food and Drug Administration (FDA) regulations, the manufacture of most INDs used in Phase I clinical trials is exempt from cGMPs (1) (i.e., 21 *Code of Federal Regulations* Part 211 is not applicable). For INDs for clinical Phases II and III and for commercial product, cGMP applies (2, 3).

In the EU, the relevant regulations are in *EudraLex* Vol. 4, Part I (drug product) and Part II (drug substance/API), and IMPs are covered specifically in Annex 13 "Manufacture of Investigational Medicinal Products," which was last updated in 2010 (4). *EudraLex*, and any laws and regulations laid down by EU member states, are based on Commission Directive 2003/94/EC, which applies to both IMP and marketed products (5).

Paragraph 17 in Annex 13 summarizes the differences in cGMP for IMP and marketed product: "Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilizing processes should be of the same standard as for products authorized for marketing."

Though these guidances are useful, they will not necessarily answer all questions. The common adage supported by the majority of regulatory agencies is to apply a scientifically sound risk-based approach to compliance. More information can be found in several publications, including a widely publicized technical report by the Parenteral Drug Association (6).

The regulators do understand that product and process knowledge will continue to grow during the lifecycle from clinical Phase I to launch and beyond. With increased understanding, companies can and need to apply more controls and move towards a fully validated process. You may wish to discuss the observation with the auditor in light of the regulations and guidance documents mentioned above.

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