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A Biologics Partisan Divide

Rita Peters

FDA and USP take sides in debate on biologic drug standards.

The May 2019 approval of Zolgensma, a gene therapy to treat spinal muscular atrophy, by FDA’s Center for Biologics Evaluation and Research was marked by sticker shock: a $2.1-million price tag for the drug, making it the most expensive drug approved to date (1). Patient-advocates noted the curative nature of the therapy was worth the price, and the drug company offered a phased-payment approach. Proponents cited it as another example of the high costs of drugs (2).

Meanwhile, a bipartisan effort by the Senate Health, Education, Labor and Pensions (HELP) committee has led to a contentious debate between FDA and standards-setting organization, the US Pharmacopeial Convention (USP). The committee voted 20–3 on June 26, 2019 to advance legislation designed to lower healthcare and drug costs; proposals include changes to patent policy, ending “surprises” in medical bills, increasing transparency in healthcare, and reducing roadblocks that delay generic drugs and biosimilars getting to market (3).

For example, Section 208 of the proposed legislation changes existing regulations so drug manufacturers cannot receive new chemical entity exclusivity for making small changes to existing drugs.

It is provisions in Section 207, however—designated as promoting biologic drug innovation—that are proving controversial, pitting FDA and USP in an exchange of policy statements. According to HELP committee documents, Section 207 is intended to prevent delays in the licensure of biosimilar and interchangeable products by excluding biological products subject to regulation under the Public Health Service Act from requirements to follow United States Pharmacopeia compendial standards. A similar provision to make biologics exempt from meeting USP standards was removed from the final 21st Century Cures Act of 2016 (4).

“A biological product is so inherently complex and variable that the established structure of the USP monograph standards process does not serve it well, and in fact, can impede technological progress or innovation,” noted Steven Kiozlowksi, director of the Office of Biotechnology Products in FDA’s Office of Pharmaceutical Quality in an interview published by FDA (5).

Due to the inherent differences in biological products, the “sameness” standard used in USP monographs for chemical-based drugs cannot apply to biologic drugs, FDA argues.

USP, backed by patient groups and pharmacists, argues that the elimination of required standards would harm patients. In a letter to the committee, USP noted the role standards play in providing quality benchmarks; supply chain security; reliability and predictability for drug product development, manufacturing, and distribution; and promote transparency and accountability that leads to patient trust (6).

“Essential to the framework that safeguards the quality and safety of medicines in the United States is the principle that public quality standards, required under the law, establish and articulate quality expectations for medicines, including biologics,” USP noted in the letter.

FDA has no legal authority to control the price of drugs. However, the agency notes it is “committed to facilitating increased competition in the market for prescription drugs through the approval of lower-cost, generic medicines” and “makes sure that safe and effective drugs are available to improve the health of consumers” (7).

That’s a lot of priorities to balance in today’s partisan environment.

References
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  - **David Churchward**, Expert GMDP Inspector, **MHRA**

- **Risk-Based Tools for Audit Trail Reviews in Manufacturing and Laboratories**
  - **John Grealis**, PhD, Regional Head Data Integrity, **Novartis**

- **Quality Culture: Milestones and Metrics in Support of Data Integrity**
  - **Ron Gunn**, COO, **Kaleo, Inc.**
  - **Gregory L. Tewalt**, PhD, Director Quality and Compliance, **Kaleo, Inc.**

The detailed agenda, including the full lineup of speakers, can be found at [pda.org/2019DIWorkshop](http://pda.org/2019DIWorkshop)

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FDA Revamps Biosimilar Quality Requirements

New guidance documents clarify production standards and processes for developing interchangeable biologic drugs.

As part of its ongoing support for the development and approval of competitive biotech therapies, FDA has updated and clarified standards and procedures for ensuring the quality and similarity of biosimilars. A new draft guidance recommends a process for developing comparative analytical assessment plans to demonstrate biosimilarity, with added details on procedures for conducting such assessments and for documenting quality in a range of production lots to make biosimilar development and production more predictable and efficient (1).

The new advisory replaces an earlier guidance on quality considerations for biosimilars issued in 2015 and updates a 2017 draft guidance on statistical approaches, both withdrawn later by FDA due to industry concerns and objections. This revised document presents strategies for conducting comparative analytical studies to assess biosimilarity to a reference product and for presenting scientific and technical information in the chemistry, manufacturing, and controls (CMC) section of biosimilar applications. There’s more detail on how comparative analytical assessments should cover key processes, including a product’s expression system, manufacturing process, physicochemical properties, functional activities, target binding, impurities, reference product and reference standards, finished drug product, and stability.

To address concerns about lot-to-lot variability, FDA advises biosimilar makers to include data from at least 10 reference product lots acquired over several years to fully assess reference product drift. Similarly, sponsors should assess 6–10 lots of the proposed biosimilar, including both investigational and commercial-scale lots, validation lots, and lots manufactured at difference scales. Additional sections clarify the submission of reference standards and data on functional activity to demonstrate any structural differences with a reference product. And FDA provides the usual caveat that it will consider alternative approaches from sponsors in analyzing and presenting requested data.

Support for interchangeables
FDA issued the revised quality assurance advisory soon after publication of a final guidance on developing interchangeable biosimilars, a much-anticipated and hotly debated option for manufacturers (2). That document updates a draft guidance from January 2017 that attracted voluminous comment from multiple stakeholders. The new version instructs manufacturers on conducting switching studies, which FDA says it usually will require to approve an interchangeable label. While some firms consider extensive switching studies unnecessary, FDA justifies this approach as important for demonstrating fully that safety and efficacy are not affected by changing treatment from brand to interchangeable, a finding that is considered important to gain the trust of physicians and patients in pharmacy-level switching.

Important for biosimilar makers, the new guidance supports the use of non-US-licensed comparator products to conduct tests and to produce the data needed to demonstrate interchangeability. Even though FDA wants data from bridging studies to foreign-made reference products, manufacturers still may benefit from leeway to obtain samples of biologics that often are less costly outside the United States and can help reduce the cost and time for developing interchangeable therapies. Sponsors developing interchangeable products may be eligible to gain a year of market exclusivity for being the first to develop such a copycat therapy.

The new guidance also appears less didactic by dropping the frequent use of terms such as “residual uncertainty” and “fingerprint-like” similarity between reference and interchangeable products, which were common in the earlier advisories. FDA here aims to set general standards and requirements for these therapies but notes, however, that the specific data and testing needed to document interchangeability may vary with the structural and functional complexity of the product and with clinical experience with the reference product. Sponsors may seek to justify an exemption from switching studies, and FDA says it will take a flexible approach.

Jill Wechsler
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Eye on insulin
In moving forward on standards for interchangeable products, FDA sets the stage for the development and approval of competitive insulin products, which are scheduled to transition to biologic status in March 2020. There is great anticipation that interchangeable insulin therapies will provide important alternatives to current costly diabetes treatments as multiple sponsors move into this field. These issues were discussed at an FDA public meeting in May on the future of biosimilar insulins, just days after the appearance of the interchangeable biologics guidance. As a relatively simple biotech product that has been available as a drug for 100 years (but ineligible for generic competition), manufacturers expect to be able to utilize a rather streamlined and straight-forward process for documenting similarity and interchangeability for these widely used therapies. Firms planning to produce competitive insulin therapies propose that FDA require data from only one, small immunogenicity study, as opposed to multiple switching studies, and that analytic characterization, bridging studies, and reliance on pharmacokinetic and pharmacodynamic data should provide ample support for interchangeable insulins.

FDA says it plans additional guidance on data needed on product container closure systems and delivery device constituent parts to support the presentation of a proposed interchangeable product. Of interest is how a biosimilar or interchangeable determination may be affected by delivery of insulin through a pump or over-the-counter device.

So far FDA has not approved any biosimilars as interchangeable, but this is expected to change with this added clarification of regulatory process and requirements. The rising price of insulin therapies has become one of the most contentious issues in the escalating drug pricing debate, with Congressional hearings generating multiple legislative proposals on this issue, many supporting the development of biosimilar and interchangeable products.

References
Cover Story: GMPs

Industry practice has changed radically over the past five decades. Can laws published in the 1960s still ensure pharmaceutical quality and safety today?

In the pharmaceutical industry, it often takes tragedy to lead to the passage of important laws. The Food, Drug, and Cosmetic (FD&C) Act of 1938, which established FDA’s authority over questions of drug safety in the United States, was passed after more than 100 people in 15 states died. The victims had ingested the first liquid form of sulfanilamide antibiotic, dissolved in a toxic—and at that point untested—solvent, diethylene glycol (1).

Current good manufacturing practices (cGMPs)—which set firm requirements for the safe manufacturing of finished drug products, and for plant and process design and operation—were passed in 1963 to update the FD&C Act. They came as a response to deaths caused by Winthrop Pharmaceutical’s failure to prevent cross-product batch contamination. The company had used two tableting machines within the same room, interchangeably, to manufacture antibiotic and anticonvulsant tablets. Lax controls led to the release of antibiotic tablets that had been contaminated by the anticonvulsant at two to three times the non-lethal dose; hundreds of people died or were hurt after taking the contaminated antibiotic (2–4).

Comprising the US 21 Code of Federal Regulations (CFR) Parts 210 and 211, and 212 for some radiopharmaceuticals, cGMPs aim to ensure that pharmaceutical processes and facilities are designed, monitored, and controlled properly; says Michael Kopcha, director of the Office of Pharmaceutical Quality (OPQ), at FDA’s Center for Drug Evaluation and Research (CDER). Unlike voluntary guidelines and best practices, cGMPs are the law and must be followed by drug manufacturers. Recently, FDA has extended cGMPs into dietary supplements and compounding.

The industry has undergone radical changes, however, since 1977. Instead of focusing on large-volume “blockbuster” drug markets, pharmaceutical manufacturers now juggle larger product portfolios with smaller, globally diverse markets. In addition, they source most APIs from India and China, and outsource more strategic operations to contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs).

At the same time, the industry has become far more complex with the growth of biopharmaceuticals, the shift from branded to generic pharmaceuticals, and the move to biosimilars and personalized medicine. “When cGMP came into effect, pharma companies were vertically integrated,” says Hedley Rees, managing consultant of PharmaFlow Ltd., based in the United Kingdom. “Quality systems were under the ownership of the companies developing and manufacturing the products, with a shared set of standard operating procedures and business objectives. The people working in the pharma companies all had skin in the game; they shared the pain and the rewards in the journey to regulatory approval,” he adds. The past four decades have seen supply...
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chain complexity increase by an order of magnitude, Rees says.

Keeping up with change
Should cGMPs be revisited and updated, given the fundamental changes that have taken place within the industry since they were published? Opinion on the subject is divided. At this point, FDA has no plans for any major revisions of US cGMPs. “We intend to continue modernizing or clarifying the regulations as needed to harmonize them with other FDA regulations and international cGMP standards, and to use guidance for industry as a primary way of developing and explaining our recommendations for complying with the statute and regulations,” says FDA’s OPQ Director Kopcha.

However, some within the industry believe that cGMPs need an overhaul. “The current cGMP regulations clearly need updating to reflect the current state of complexity in pharmaceuticals materials, processes, products, and supply chain,” says Ajaz Hussain, consultant, head of the National Institute of Pharmaceutical Technology and Education (NIPTE), and formerly head of FDA’s Office of Pharmaceutical Sciences at CDER.

“FDA’s periodic updates have been a bit like patches on software or add-ons to an existing building. It may take years, but cGMPs need to be modernized,” says consultant Emil Ciurczak, an early adopter of process analytical technology (PAT) and president of DoraMax Consultants.

The task would be Herculean, notes Hussain. “We have done all that we can to avoid having to do the update, with guidelines and guidelines. That has been the entire basis of the 21st century initiative,” he says.

One challenge is that FDA’s guidance documents, whether on PAT or process validation, only present suggestions and companies can—and often do—bypass them, as long as they meet legal product quality requirements. Some observers ask whether some suggested practices might need to become required ones if the industry is to develop a more scientific approach to manufacturing and quality control.

Industry observers pinpoint the need for more cGMP clarity in:

- Training and employee’s personal development
- Statistics and sampling
- Process validation.

Organization and personnel
Hussain believes that US 21 CFR 211 Part 11 Subpart B, which covers requirements for organization and personnel, should be a high priority target for cGMP clarification and updates. He points to recent FDA warning letters that refer to CFR 211, specifying deficiencies in production record review, batch record and maintenance data practices, training, and investigation of batch failures or other discrepancies.

Even though regulators may not explicitly refer to Subpart B in their citations, Hussain suggests, companies’ failure to follow its requirements is often the root cause of many, if not most of the cGMP problems that regulators do cite. “The cGMPs drafted in 1977 had called for adequate education, training, and experience. But when have we ever defined what ‘adequate’ means for people who work in cGMP, for the inspectors at FDA, for the reviewers at FDA? We have this fundamental flaw in the system,” Hussain says. “So how can we expect people who are not qualified for their jobs to do anything better? “Our attention needs to be focused on being objective,” he adds. Hussain sees professional development as the key to developing the type of managers needed to instill a “culture of quality” within the industry.

Inadequate management training and development may also have implications for the industry’s use of technology, says consultant Gary Ritchie. He uses digital records as an example. Like paper-based records, digital records are subject to the predicate rule; they must be retained for a set period of time after the drug expires. But digital records offer an immediate transparency that paper does not. “In some cases, companies are afraid to be stuck with electronic records that actually show how management made decisions when they processed something. You cannot erase the record,” he notes.

“The reality is that people are still working on paper in the 21st century digital world, because it is more flexible,” says Ritchie. “FDA has suggested that, in the future, it may not allow hybrid (i.e., paper-on-glass) systems, but until the science of manufacturing evolves, change won’t take place,” he says. “FDA wants to hold up as an example those companies that have moved to digital records, but there are still so many more facilities that use paper and whose practices remain stuck in the 1900s.”

Process validation practices
Another area where cGMPs could be shored up, observers say, is in process validation and delineating the expectation of statistically valid sampling and statistical process control. “That was the stated principle behind FDA’s process validation guidance in 2011,” says Hussain. As he notes, only a handful of Big Pharma companies appear to be using modern process validation principles correctly. “The rest are struggling, and haven’t even begun to use the concept for new, let alone legacy, products,” he says.

One problem pointed out by FDA compliance officer Grace McNally in a 2011 presentation is a failure to use the best statistical methods and validation principles. As she noted, “At times, compendial standards take on the character of statistical procedures … but, in all cases, statements about whether the compendial standard is met apply only to the units being tested”(8). Optimal production calls for meaningful in-process tests and for a statistically significant number of tests based on batch size of final dosage forms, Ciurczak says; companies may be following traditional practices, yet failing to meet the requirements set by cGMPs.

“Let’s say that a company tests 20 tablets out of two million. Even someone without a math background knows that’s not statistically significant,” Ciurczak says. He uses military standards as a contrasting example. “If you are manufacturing more than a half million units, the US Department of Defense says that you must run 25,000 tests. If a pharma company had to
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run 25,000 HPLC [high-performance liquid chromatography] tests, it would cost way too much and it wouldn’t show what was happening in the other 1.75 million.” Finally, there are the tests themselves, and whether they make sense given today’s manufacturing realities. “Friaub and disintegration tests are not meaningful, and they are simply not timely anymore,” says Ciurczak. “They may have been timely when you had a single-punch machine that was putting out 100 tablets an hour. They are not timely when you have a 36- or 40-punch machine that is putting out 100,000 or 200,000 tablets an hour,” he says.

**Getting past the three-batch rule**

FDA’s 2011 process validation guidance was supposed to mean the end of the “three batch” rule for product release but that concept is still alive and well at many companies, and sampling is still being handled in a rather primitive way at some facilities, says Ciurczak.

The problem with adherence to this practice is the fact that “any time you take selective samples, you’re guessing,” Ciurczak explains. If one could place hidden cameras in many oral solid-dosage form facilities today, he says, one might often see operators taking material from the top of the last drum, scooping it out and calling it representative of the entire last batch, instead of sampling every drum at different levels using different sample thieves.

One obvious solution would be to use PAT, but many manufacturers still aren’t, Ciurczak says. “With PAT, you have in-process tests and the potential of 100% analysis. There are online options that can automatically examine 100,000 tablets an hour, and there is zero excuse for not using them.” Ciurczak also sees a need for cGMPs to specify better calibration methods. “GMPs are based on 1950s technology, and they don’t stress raw material quality enough,” he says, at a time when most materials are being sourced from regions where regulatory practices are still evolving. For instance, cGMP practice still accepts the use of compendial testing, even though some older United States Pharmacopeia (USP) tests have proven to be fallible, as was seen during the heparin recall of 2007. “Spot and color tests for heavy metals might have been okay when pharmacists were making things in their back rooms and selling them locally, but now you’re sourcing materials from halfway across the world and the identity tests won’t show whether they are even useable,” says Ciurczak.

The biggest problem with cGMPs, Ciurczak says, is that they are “one size fits all.” FDA, however, cannot mandate the approaches that companies use to meet requirements. “Measurements, process release, and in-process measurements are not mandatory. PAT methods may reduce variability in commercial product, but how the manufacturer achieves required targets is up to them,” says Ritchie. However, he notes, when something tragic happens, it’s usually lawyers who point out that management knew that other options were available but chose not to use them. This may prove to be grounds for future liability and accusations of negligence, he suggests.

**Structural change needed**

Some believe the problem is much bigger than cGMPs alone, and requires that drug development and manufacturing, and the chemistry, manufacturing, and controls, and manufacturing functions become more closely connected. “These companies placed the end user of their products at the center and developed a value chain to deliver on their needs in terms of value for money. They achieved incredible improvements in quality by placing the responsibility for defects on the production operators, rather than a ‘quality function.’ The production operators were given the tools of statistical process control and they used them to great effect, achieving six-sigma quality levels (i.e., 3.4 defects per million opportunities),” he says. Amgen is one of a few biopharmaceutical and pharmaceutical manufacturers that has achieved this level of quality.

At the same time, Rees explains, forward-thinking manufacturers in other industries began to design for manufacture, as opposed to throwing processes "over the wall.” They adopted a collabora

tive approach, he says, in which design and production departments worked together to achieve the crucial balance between innovation and production feasibility and economics. “The results were transformational,” says Rees, who has commented on some of these issues in his new book, *Taming the Big Pharma Monster*, published in May 2019 (9). Rees sees the answer as going back to a simpler time, and to vertical integration. But one might ask: How can decades of industry change be reversed? For now, it remains to be seen if and how regulators will address the need to clarify industry’s interpretation of cGMPs. Hussain suggests breaking the problem down into smaller bites. “The cGMPs for nutritional supplements, compounding, and tobacco are still evolving. Perhaps the first order of business is to bring some sanity to the definition of adequate education, training, and experience, since the entire system rests on this foundation,” he says.

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5. FDA, “Pharmaceutical cGMPs for the Twenty-First Century: A Risk-Based Approach,” Report (September 2004), www.fda.gov/media/77391/download
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Indeed, the value of the global market for nanopharmaceutical drugs is estimated by market research firm BIS Research to be expanding at a compound annual growth rate of 8.1% and predicted to reach $79.3 billion by 2026 (1). Polymer and liposome drug carrier systems are the two sub-segments driving this growth.

Multiple areas of research

Pharmaceutical companies are always looking for opportunities to improve medicines for patients. Applying the use of nanoformulations to existing drugs based on previous learnings is one avenue for leveraging nanotechnology, but Pfizer is focused on developing nanoformulations and nanotechnology solutions that will ultimately enable the next generation of nanotherapeutics to be brought to cancer and other patients, according to Young-Ho Song, a research fellow at Pfizer Oncology. “We complete this work as early as the discovery phase in collaboration with our medicinal chemistry colleagues,” she notes.

Nanomedicine research is focused in two main areas, agrees Stephan T. Stern, acting deputy director of the Nanotechnology Characterization Lab, which is part of the Frederick National Laboratory for Cancer Research. One area involves reformulation of existing drugs or drug combinations to decrease toxicity and/or increase efficacy, or to develop competing formulations of existing marketed products (e.g., nanosimilars). The second research area involves the formulation of novel drugs, such as difficult-to-formulate new chemical entities, oligonucleotides, and vaccines. “Most pharmaceutical companies have nanotechnology formulation research groups that are involved in resurrecting drugs that are failing due to toxicity/efficacy/formulation issues,” he adds.

Parenteral and oral dosage forms

The most common dosage forms of nanomedicines on the market are intravenous liposomes (e.g., Doxil [Janssen], Onivyde [Ipsen Biopharm], Vyxeos [Jazz Pharmaceuticals]), intravenous polymerics (e.g., Genexol [Samyang Biopharm]), intravenous nanoemulsions (e.g., Dipyran, Intralipid), and oral nanocrystals (e.g., Rapamune [Pfizer], Tricor [AbbVie]), according to Stern. Generally, he observes that the formulation type is first chosen based on API liabilities. “The issue may be solubility, toxicity to off-target tissues, rapid metabolism, or poor distribution to target tissues. Once the liability is recognized, a series of formulations that could overcome the liability are identified and the optimum formulation and preparation method are chosen based on chemical compatibility of the API,” says Stern.

Many preparation methods

Choice of appropriate formulation type is dictated by the properties of the API. “Certain APIs are better suited to certain formulation, due to loading efficiency and stability,” Stern explains. “Amphiphilic weakly basic/acidic drugs, for instance, are suitable for active loading of nanoliposomes, while highly hydrophobic drugs are better suited to nanoemulsions, polymeric nanoparticles, and micelles,” he says. High-temperature techniques, such as microfluidizer homogenizing, are not ideal for thermally labile APIs.

Cynthia A. Challener is a contributing editor at Pharmaceutical Technology.
The formulation type will then determine the formulation method. Liposomes and emulsions are produced by solvent evaporation or thin-film hydration followed by extrusion/homogenization (microfluidizer), according to Stern. Polymeric nanoparticles and micelle formulations are generated by solvent evaporation, single/double emulsion, or precipitation techniques. Nanocrystals are generated by top-down techniques, such as milling and homogenization. Stern notes that bottom-up techniques (i.e., precipitation) are not currently used in the manufacture of nanocrystalline APIs.

**Pfizer’s nanopolymer approach**

Pfizer has been working with biodegradable polymeric nanoparticles for drug delivery. The most widely used processes for the production of these nanoparticles are nanoemulsion, in which the organic phase consists of water-immiscible solvents such as ethyl acetate or dichloromethane, and nanoprecipitation, in which the organic polymer-drug solution contains water-miscible solvents such as dimethyl sulfoxide, tetrahydrofuran, or acetonitrile, according to Song.

The polymeric nanoparticles developed by Pfizer are based on a biodegradable polyester polymer commonly used in dissolving stitches. Loaded nanoparticles are prepared by dissolving the polyester polymer, API, solvents, and excipients in an oil to form an emulsion. Thousands of pounds of pressure are applied to the emulsion, leading to the formation of nanosized droplets. The solvents are removed, and the droplets are hardened into polymeric nanoparticles encasing up to 10,000 API molecules. The surfaces of the nanoparticles are modified with antibodies that will bind to a specific cell type, such as a specific tumor cell. Once bound, the drug will diffuse out from the nanoparticles, slowly releasing and accumulating the API at the desirable target sites.

To date, the Pfizer researchers have investigated the application of their nanopolymeric technology for the development of drugs to treat various cancers and cardiovascular, inflammatory, and infectious diseases. “Our state-of-the-art nanoemulsion process and formulation approach have expanded the chemical space of compounds that can be formulated into our nanoformulations,” Song asserts.

**Overcoming challenges**

Despite their advantages, nanomedicines do face several challenges, including the lack of predictive preclinical models for safety/efficacy, problems with scale up, and an uncertain regulatory path, according to Stern. Song agrees that there are multiple hurdles that must be overcome before nanomedicines can become commercial products. “An individual’s perspective often determines what is the biggest challenge, and each medicine can present its own set of challenges. It takes a team effort, from discovery through approval, to address each challenge as it is presented,” she observes.

Advances in technology are helping, too. "Recent advances in nanodelivery formulation around oligonucleotides (siRNA, mRNA, and genetic materials) using lipid nanoparticle (LNP) nano-systems are breakthrough technologies,” according to Song. “These new approaches can help to convert a very difficult drug formulation challenge ultimately into a drug product,” she states.

Stern points to a gradual refinement in established platforms regarding improved stability, safety, and delivery as important evolutionary advances in nanomedicine. One example he highlights is the approval of Onpattro, a treatment of transthyretin-mediated amyloidosis and the first gene-delivery nanoliposome, which has been decades in the making. "With market approvals like this one, more venture funding will flow into nanotech, allowing for more research and advancement in the field,” Stern asserts.

Another way these challenges are being overcome, says Stern, is through the participation of contract research, development, and manufacturing organizations that are developing and expanding specialized capabilities at the lab to commercial scale and can assist with the scaleup of complex drug formulations. He also notes that as more nanomedicines reach the clinic and eventually the marketplace, a better understanding of which preclinical studies are useful and important is being realized. In addition, FDA and the European Medicines Agency are in the process of streamlining the regulatory approval process for complex drugs, including their generic/follow-on versions, which should expedite future development.

**Shift in focus to next-generation therapies**

The future for nanomedicines certainly appears to be exciting. “Complex drug formulation will always have a place in modern drug development for the simple reason that new drugs and drug classes are getting ever more difficult to deliver as a result of poor stability, solubility, and permeability,” Stern observes. There will still be reformulation and repurposing of existing drugs as nanoformulations, but Song agrees that research will move toward a focus on developing new drugs in nanoformulations starting from the early drug discovery phase.

Research in nanomedicine has, according to Stern, already begun shifting toward the use of nanoformulation for immunomodulatory drugs and gene therapies. “Nanotech is well suited to overcoming the lack of selectivity and poor delivery, respectively, of immunotherapies and oligonucleotide-based drugs,” he says. One example is the use of gold nanoparticles rather than an inactivated virus to deliver clustered regularly interspaced short palindromic repeats (CRISPR) gene-editing tools to cells (2).

**References**

Several trends are driving change in oral solid-dosage forms and giving rise to the requirement of ‘fit-for-purpose’ excipients.

In Karry’s opinion, approaches to improve patient compliance and continuous manufacturing have been two further trends in the field of OSD formulation. “It is no secret that a large percent of the population has difficulty swallowing tablets and capsules. As a consequence, formulations such as oral dispersible tablets and mini-tablets have expanded the ability of patients to take lifesaving medications,” she notes.

“Finally, the adoption of continuous manufacturing platforms for solid oral dosage forms offers a cost-competitive advantage by reducing overall manufacturing footprint, accelerating drug product development, allowing for flexible batch sizes, being amenable for real-time release testing, and by enabling higher assurance of product quality through automated control strategies that react to process disturbances,” Karry continues.

Harald Stahl, head of application development at GEA, raises the point that the industry is moving away from the blockbuster and toward the development of specialized drugs that target rare and orphan diseases. “Consequentially, batch sizes decrease while at the same time prices per dose go up,” he adds. “As a result, companies are looking into technologies that allow for the necessary development and scale-up activities while using minimal amounts of API—one of the main drivers into continuous processing.”

“More than ever before, pharmaceutical companies are taking a holistic approach when formulating new drug products so that patients are at the center of everything they do,” says Jessica Mueller-Albers, strategic marketing director for oral drug delivery solutions at Evonik. “This has strengthened demand for solutions that can improve rates of patient compliance and brand preference, such as the development of pediatric or geriatric dosage forms, as well as coatings that enhance swallowability.”

Furthermore, Bruhalkumar Shah, senior formulation scientist at Cambrex highlights that outsourcing of
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pharmaceutical development and/or manufacturing to various contract organizations has also been rising. This is a result of an increase in merger and acquisition activity, pharmaceutical company downsizing, and the emergence of virtual companies, he explains.

“Each of the sector trends, however, require excipients that are ‘fit-for-purpose’ to overcome the various challenging tasks that face formulators of OSD drugs,” stresses Karry.

**Key considerations for excipient selection**

“Careful consideration must be taken in the selection of any functional or non-functional excipient as it greatly impacts the quality and efficacy of the finished product,” says Shah. “Special attention should be given to functional excipients, which can directly impact the stability of the product or can change pharmacokinetic performance, such as with controlled or modified-release products.”

Excipients are rarely now just bulk agents, asserts Savla. “Rather, such agents are increasingly used to serve an additional function, such as improving solubility. It is highly likely that multiple excipients, each serving a different function, are required,” he notes. “Polymers used in amorphous solid dispersions retard recrystallization of amorphous drug molecules. Understanding the functionality, stability, and API interactions of the excipients is paramount.”

Karry adds that of primary importance is an understanding of API properties and solubility in common solvents. “From there, formulation screening methods vary depending on whether the excipient helps solubilize the drug (e.g., by complexation or solid solution systems where the API is solubilized in a polymeric carrier) and pharmacokinetic considerations such as the rate of administration (instant or modified release), and preferred site of drug absorption (pH dependent solubility),” she says. Further considerations are then made on screening is to minimize risks, costs, and formulation development time,” he explains. “Some key areas of focus are keeping the drug in an amorphous state (for amorphous solid dispersions), change in polymorphism, and chemical degradation. Based on these results, formulation prototype development with other ingredients (binders, fillers, disintegrants etc.) is undertaken. For hot-melt extrusion, the miscibility of API and polymer is important, as is the melting temperature of the polymer.”

Then, it is vital to consider the amount of excipient in the formulation, as this should be kept under the maximum allowable potency per dose. “For pediatric patients, the number of allowable excipients is rather limited,” Savla continues. “An adult formulation may not be acceptable for pediatric use by regulatory authorities based on the components. Therefore, the formulator is challenged with designing a different formulation while maintaining safety and efficacy.”

If using large amounts of excipients in a dosage form, there may be a requirement to have a larger dosage unit or for the patient to take multiple doses to achieve the correct dosage of API, which can lead to swallowability and adherence issues. “The formulator must study the drug loading when choosing polymers for amorphous dispersions. Simply choosing the formulation with the highest drug load is not recommended, as high drug loading may lead to a higher propensity for recrystallization in an amorphous solid dispersion,” Savla stresses.

“The growing complexity of drug products has increased demand for specialized excipients and other delivery technologies that can facilitate the targeted release of the API at the right place over the right duration,” emphasizes Mueller-Albers. The crucial role these agents play in the properties and performance of the final drug product has meant that regulatory authorities have scrutinized the functionality and quality of excipients closely over the past decade.

“As a result of this scrutiny, pharmaceutical companies have been prompted to take a science- and risk-based approach towards the selection of excipients that are widely accepted across all key worldwide markets,” Mueller-Albers adds. Without the appropriate attention to excipient quality, companies may be taking significant risks to drug development and could end up with production downtime and supply shortages, she warns.

**Important advancements**

“As mentioned earlier, industry has been witnessing a shift away from the blockbuster style drug product and, as such, is seeing volumes of manufacturing decrease,” says Stahl. “Therefore, several companies have been focusing on a direct compression method, which negates the need for the wet granulation step, while also increasing the requirements on the physical characteristics of APIs as well as the excipients.”

Successful application of the direct compression method requires a critical selection of excipients, to ensure good flowability and compressibility.
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Formulation

“Powder flow is an extremely important property for processes such as tabletting and capsule filling, and therefore, excipients that can improve powder flow for ‘difficult’ powder blends are of interest to formulators,” emphasizes Savla. “These can be excipient grades with a particular particle-size and shape to provide good flow properties, or co-processed materials (e.g., siilified microcrystalline cellulose), which offer similar advantages.”

Co-processed materials are now more widely available and offer formulators a single, multi-functional excipient option, which helps to reduce development time and cost, particularly in early development phases, Savla explains. “Further, easy-to-prepare products, such as preformulated coating preparations for tablets are now freely available and can also cut down on processing time.”

As the drug development process itself becomes more complex, excipient suppliers are required to follow the various industry trends and innovate, confirms Shah. “Important advances have been seen specifically when developing novel drug delivery systems,” he says.

Giving some examples, Shah highlights that excipient advances have been seen as a result of industry trends towards immediate and controlled dosage forms, specialized delivery systems for poorly soluble molecules, and nanotechnology. “So, co-processed excipients and the development of new grades of existing excipients have helped with immediate and controlled-release dosage forms,” he adds. “Then for specialized delivery systems, cyclodextrins, mesoporous silica, new polymers to inhibit crystallization, and copolymer dispersions for taste-masking have been introduced. In terms of nanotechnology, the sector has seen the use of PEGylated derivatives and drug targeting moieties for stabilization and specificity, respectively.”

However, Karry states that innovation has remained relatively slow. “Naturally, it is a significant gamble for pharmaceutical companies to utilize novel or innovative excipients in formulations, largely due to the increased risk on the drug filing,” she says. “Nevertheless, innovation for excipients continues.”

As the drug development process itself becomes more complex, excipient suppliers are required to follow the various industry trends and innovate.

Still unmet market needs

“Even though there are a number of excipient options available today with a strong history of safety and performance, there are still unmet market needs when it comes to functionality,” notes Mueller-Albers. “As one example, despite several companies seeking to develop new permeation-enhancing solutions, there is still a clear need for additional excipient offerings or drug delivery technologies that can better address poor permeability. Likewise, despite the use of solid dispersions to help address poor solubility, we are still seeking specialized solutions that can tackle the bioavailability constraints of certain new drug entities.”

In Savla’s opinion, despite growth in the number of acceptable excipients available to help with solubility enhancement, it remains one of the main issues for formulators. “There continues to be a need for new excipients that can help overcome the challenges offered by chemically diverse compounds,” he explains. “The limited number of polymers used in amorphous solid dispersions is not adequate to cover the wide chemical diversity of drug molecules.”

Additionally, Savla believes that there is a great unmet need in the number of pediatric-appropriate excipients that are considered to be acceptable by regulatory authorities. “The development of pediatric medicines has become of key importance within the pharmaceutical industry as developers are increasingly required to conduct clinical studies in pediatric populations with appropriate formulations first, before going on to get regulatory approval for adult formulations,” he states.

Slow progress in oral delivery of biologics

It is generally known that oral administration of biopharmaceutical products has been limited and progress within the field slow. “Most macromolecules are still formulated into parenterals and applied subcutaneously or intravenously,” notes Karry. “While clearly, oral delivery of these would improve patient compliance and avoid injection-related injuries and illnesses, the stability of large therapeutic molecules in the gastrointestinal (GI) tract remains a significant challenge, mainly due to the inability to protect therapeutic proteins from the body.”

Although many attempts have been made to develop oral versions of biopharmaceuticals, such as insulin, the enzymatic and chemical degradation pathways in the GI tract are too problematic, confirms Shah. “However, delivering biopharmaceutical products orally remains the holy grail for this molecule class, and there are advances being made in nanoparticle drug delivery systems and advanced manufacturing technologies coming to the fore. So, more progress is expected in this area,” he says.

Mueller-Albers concurs there has been a strong demand within the industry for excipients that can reliably control transit of biologic drug products through the GI tract. “There are many promising examples in the
literature and in the start-up community to keep an eye on,” adds Karry.

**The foreseeable future**

“Oral solids are likely to remain the dominant dosage form within the pharmaceutical market for the foreseeable future,” confirms Mueller-Albers. “Above all, we expect tablets and capsules will continue to remain popular for use across the entire spectrum of drug candidates due to cost-effectiveness, stability, and strong rates of patient compliance. However, OSD forms will continue to become more complex and personalized.”

For Shah, the drug pipeline will continue to be healthy, with increasing numbers of small-molecule drugs being launched in the OSD sector, which is still considered to be the backbone of all medicines. “While OSD forms continue to remain an important part of the pharmaceutical industry, there is a continual drive to develop new drug delivery technologies, such as the use of nanotechnology for example,” he says. “On a manufacturing front, there seems to be a trend toward the application of continuous manufacturing technologies, improving processes for complex drug products, and introducing manufacturing technology for individualized and on-demand drug products.”

Spray-dried dispersions have been ‘on point’ for many drug developers in recent times, according to Savla, who believes this trend will likely continue. “There is a significant percentage of poorly soluble molecules whose sub-optimal solubility is not adequately addressed by current technologies or excipients,” he asserts. “This unmet need will require advancements in novel excipients or polymers, and novel technologies.”

Karry adds that cost-competitive manufacturing, increased use of functional coatings, dosage forms amenable for pediatric applications, and drug products with more than one API are all trends that have been identified and are anticipated in the future of global OSD forms. Adding to this list, Mueller-Albers and Shah raise the point that stronger collaboration between pharma and non-profit organizations or academia is benefiting drug development advancement and so should continue to be a promising trend.

**Reference**

Sterile Filtration

Considerations for Sterile Filtration of Biologic Drugs

Cynthia A. Challener

Equipment and processing can affect formulations.

Selection of a sterilization strategy for a drug product that requires aseptic manufacturing is generally determined by the stability of the drug substance. For stable products, terminal sterilization, including heat sterilization or exposure to radiation or chemicals such as ethylene oxide or vaporous hydrogen peroxide, is the preferred strategy. These methods are advantageous because the processes can be monitored and validated and they tend to be less prone to error.

Most biologic drug substances, however, are unstable when exposed to heat, radiation, or chemicals such as ethylene oxide or vaporous hydrogen peroxide, and generally require aseptic manufacturing using sterile filtration. Successful sterile filtration requires a drug product formulation with an appropriate viscosity and compatibility with the contact surfaces and shear stresses involved in pumping the fluid. Single-use technology is widely used in sterile fill/finish operations today, reducing the turnover time and cross-contamination risk.

Formulation factors

The main factors that must be considered from the outset when developing formulations for biologic drug substances that require sterile filtration include, according to Yunsong (Frank) Li, director of process development at Catalent Biologics, the product’s chemical and physical stability under various stress conditions (e.g., thermal, mechanical, photostability) during product manufacturing, storage, shipping, and administration; compatibility with the materials used during sterile fill/finish processing; and compatibility with the final container closure system and administration device.

Factors related specifically to sterile filtration that can impact the final formulation include the contact surfaces, shear forces involved, and the potential to induce aggregation or particle formation, notes Margaret Faul, vice-president of drug product for Amgen. The method used to sterilize the fill/finish equipment or primary packaging must also be considered because any residual chemicals may interact with the biologic. For instance, antibodies containing methionine residues in the related binding regions of an antibody can become ineffective (lose efficacy) if (accidentally) oxidized (e.g., by vaporous hydrogen peroxide during manufacture), according to Hanns-Christian Mahler, head of drug product services at Lonza Pharma & Biotech.

In addition, Faul observes that the concentrations of excipients or the biologic drug substance may be reduced by the filter. “The material of construction may affect material loss, while the filter system design may affect the flow properties, and the size may affect the overall process throughput,” she explains.

To address these issues, certain excipients may be added to minimize process loss to the filter, negative interactions between the biologic and the filter, or residual sterilization chemicals that might lead to particle formation, aggregation, or decreased rates of filtration, according to Faul.

To ensure that sterile filtration will be effective and that contaminants are excluded, it is therefore necessary to test the process for each batch, adds Andrew Bulpin, head of process solutions at MilliporeSigma. “The adsorption of components of the final formulations and the biologic drug substance to the sterile filter must be analyzed to ensure that the formulation and final concentrations remain within the desired values,” he says.

In addition, Bulpin notes that because biologic drug substances may be sensitive to shear stress, the mixing and pumping during formulation must...
be gentle to prevent aggregation and/or conformational changes of the biologic. Fill/finish processes must also be performed under controlled temperature conditions to avoid thermal degradation. Many biologics are in fact lyophilized during final fill due to their thermal instability.

“In general,” concludes Mahler, product development should carefully consider the intended method of manufacturing. Less obvious and less regulated, but equally important, is evaluation of whether each critical process unit operation (process step) of the manufacturing process within and beyond normal operating parameters would impact critical quality attributes.

As an example, Mahler points to the type of filling pump chosen, which is not only relevant from a good manufacturing practice and fill precision perspective but can also significantly and adversely impact product quality by causing aggregation and/or precipitation when operating within or beyond its parameters. He also observes that the choice of disposable tubing, filters, and primary packaging components, as well as the capping and 100% visual inspection processes, also play a significant role in impacting product quality and yield.

Single-use technologies

There are significant advantages with single-use technology in both drug substance and drug product manufacturing. “Its use eliminates the cleaning step, which saves time with batch turn-over, saves costs in facility construction, and improves the process flexibility,” states Li. Using sterile, disposable materials also mitigates the risk of microbial ingress during processing, according to Christy Eatmon, SME for sterile drug products at Thermo Fisher Scientific. “Using disposable technologies makes it possible to complete sterile connections in a non-sterile compounding area. The product can be almost completely processed using closed systems for product flow from a manufacturing area to the aseptic filling core,” she comments.

Li stresses, though, that with disposable systems, it is also necessary to understand and ensure compatibility between the single-use materials employed and the final drug product as part of the formulation development efforts. “It is necessary to ensure that there are no adverse impacts, such as aggregation, denaturation, or adsorption to the product by the materials used in the process. The extractable and leachable profile also needs to be fully understood to ensure that it is compatible with the product formulation,” he explains.

Other issues to consider with the application of single-use technologies during sterile fill/finish operations include particle shedding, permeation of water or oxygen out of or into the product (possibly leading to degradation), or loss of critical excipients such as polysorbate or preservatives, according to Mahler. “The latter components have been shown to possibly be adsorbed or be able to permeate across disposables, with the potential to lead to significant quality issues in the final product,” he remarks.

Therefore, while there are time savings during production, Faul observes that the advent of single-use technology for sterile fill/finish has impacted the formulation development process by increasing the need to assess and prevent degradations due to interactions with the contact surfaces of the disposable systems.

Concentration and viscosity challenges

Generally, many biologic drugs require high doses for injection via the subcutaneous route of administration, with the volume of injection typically less than two milliliters. “This delivery method requires the formulation to be at a very high concentration, and it becomes highly viscous, pos- sing difficulties in both manufacturing and administration,” notes Li. Due to the need of high protein concentrations in many biologic formulations, high viscosities still pose difficulties during sterile fill/finish, adds Bulpin.

Different approaches are under development to address this issue. Viscosity reduction in high-concentration solutions can be achieved through the modification of the formulation, Bulpin notes. One potential solution, according to Faul, is the use of excipients to reduce viscosity. The excipients can bind to certain regions of a protein to reduce viscosity and enable delivery of high-concentration formula-
While there are many new excipients investigated, according to Faul. This approach is, of course, only relevant for more thermally stable biologic drug products.

An alternative strategy, according to Bulpin, involves placement of lower protein concentrations using advanced biologic administration technologies that allow for higher volumes during administration.

Manufacturability issues
One of the biggest challenges faced when formulating biologic drug substances is trying to improve the stability of the molecules to achieve the target shelf-life of the product. “Formulation studies can only stabilize the target molecule to a limited extent. While there are many new excipients and approaches being attempted today, the molecule’s structure itself still plays a critical role in determining the molecular stability,” says Li.

The best way to address this issue is to conduct developability/manufacturability studies as early as the molecular screening step in the drug discovery stage, he notes. “By taking this approach, the most stable molecule will be selected from many molecules having the same bioactivities, and this selected molecule will have the best success rate in the subsequent development and manufacturing stages,” Li adds.

Compatibility difficulties
Compatibility of biologic drug substances with various surfaces is another challenge, according to Malgorzata Tracka, senior staff scientist at Thermo Fisher Scientific. “Compatibility studies should be conducted to ensure suitability of the formulation against product contact surfaces, including the primary packaging (IV bags, auto injectors, pre-filled syringes, etc.) and manufacturing design (tubing, connectors, filters, etc.),” she observes.

Formulations can be optimized with surfactants using a design-of-experiment approach, and contact surfaces can be selected carefully to minimize their negative impact. “Very often formulations advanced to the sterile fill/finish stage require optimization of surfactants to protect the biomolecules from effects that can lead to aggregation and subvisible particle or visible particle formation,” notes Tracka.

Controlling the fluid viscosity, product sensitivity to shear stress, and thermal stability are particularly important for biologics subjected to sterile fill/finish processing, says Bulpin. “Optimal formulation might reduce product viscosity with the addition of salts and other stabilizers or through pH adjustments, while temperature control during sterile fill/finish will prevent thermal degradation and adequate filter sizing, and process design will reduce pumping requirements and, therefore, shear stress,” he comments.

Formulation strategies
The key component of successful formulation strategy for biologics that will be subjected to sterile fill/finish processing is early identification of potential degradation factors. It is important to determine if the active will be damaged by the mechanical forces involved during processing or fill/finish activities, according to Eatmon. “The formulation development process involves identifying degradation pathways for the biologic, assessing which may be impacted by sterile fill/finish processing, identifying excipients that minimize potential degradation of the biologic and maintain potency, and empirical testing/verification of assumptions at appropriate milestones,” adds Faul. The potential for excipients to foam during processing or adhere to filter membrane during aseptic filtration must also be evaluated, Eatmon notes.

That is where process, flush, shear-stress, and compatibility studies come in, to ensure the correct mechanical parameters, determine the quantity of material required to saturate the product contact surfaces, identify the appropriate fill speed and pressure, and assure the suitability of the materials in contact with the drug substance.

The final filtration process is often developed on a small scale in parallel to formulation development to determine a chemically compatible filter membrane, according to Bulpin. Extractables in the final formulation, protein adsorption, and the adequate filter size are then factored in.

Other questions must also be addressed, Bulpin adds, such as whether the bulk drug substance will be frozen before final fill and whether the drug product will be lyophilized, because these processing steps require excipients such as sugars to stabilize protein conformation. In addition, based on the hydrophobicity of the biologic, an optimal solvent must be identified (mostly aqueous), the optimal pH conditions under final concentration must be determined, and the need for the addition of antioxidants evaluated. “In essence,” Bulpin remarks, “the entire formulation needs to be tweaked to ensure maximum stability of the product.”

Exploring new technologies
A new form of sterile fill/finish being explored through the development of several new technologies involves the production of sterile biologics in a powdered state, which are then used to produce sterile suspensions for injection. “All of these technologies are relatively new and in various stages of clinical studies,” Li observes.

The sterile filling of powders is also relatively new to the industry and poses additional challenges. Li adds, however, that these technologies are attractive because they can achieve an extremely high “concentration” of biologics even beyond the protein’s solubility.
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Regulatory agencies, including FDA, have switched from a management-based to a performance-based regulatory strategy. The stated reason for the change is “to give the industry enough flexibility to manage and improve quality on its own” in hopes of a several order-of-magnitude advance in performance using continuous improvement (1). The need for improving performance is caused by the industry’s ongoing failure to reliably supply patients with high-quality products resulting in many shortages and recalls due to industry-wide manufacturing quality levels around two to three-sigma (two-sigma is roughly a 30% failure rate) (1,2). In simple terms, a poorly performing industry is being told by regulatory agencies to “fix thyself.”

A case can be made that the shift has left the industry adrift in the rough seas of rapidly advancing medical technology without the necessary methods to keep up. The shift in regulatory strategy places a huge, but necessary burden on the industry to develop their own sophisticated, prospective, management-based methods required to achieve Six Sigma quality levels (roughly three failures/million attempts) typically found in many other industries while developing increasingly complex products and therapies.

Management-based approaches must be prospective if they are to be effective for developing and manufacturing future high-quality products. Performance-based approaches, particularly regulations, are retrospective measures of quality. Unless the management-based methods are effective, feedback from performance-based methods that depend on initial or past failures to improve performance will be slow to improve the industry’s performance. For pharmaceuticals, high performance must be achieved from the very beginning using prospectively developed control strategies. Further, these better methods must be developed and improved in collaboration with regulatory agencies to ensure the methods will have a perceived high likelihood of actually producing the initial results necessary to support regulatory actions for licensure and commercial manufacturing. The collaboration must also ensure that the methods’ results are consistent with existing regulations. A possible method for the industry collaborating with regulatory agencies is being developed around the voluntary consensus standards (VCS) draft guidance (3).
The best path for developing better industrial methods is likely to expand and supplement the existing management-based regulations developed before the shift in regulatory strategy. Old regulatory guidelines have been carefully written to avoid prescribing how approaches should be executed from a fear of establishing standardized methods that might prevent better approaches from being developed through continuous improvement. Only the industry, with the assistance of regulatory agencies, can prospectively develop and, most importantly, continue to evolve new and better methods and approaches to achieve excellence for ever-increasing product and manufacturing challenges.

This article reviews and suggests improvements to a few of the important management-based regulatory guidelines that currently drive pharmaceutical development and manufacturing.

**ICH Q8 (R2)—Pharmaceutical Development**

The ICH Q8 guidance contains important foundational concepts for prospectively managing the development of high-quality processes necessary for making high-quality products. However, these concepts are defined vaguely as “what” and “why” and must be expanded or industrialized, perhaps using the VCS route, to achieve their intended goal of guiding the industry. For example, quality-by-design (QbD) is defined in ICH Q8 as:

> A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (4).

This mechanistic-free definition has led to widely varying interpretations and implementations of QbD. A study commissioned by FDA concluded that the vague definition has led to many problems within the industry and regulatory agencies on how QbD can and should be used (5). Insights into the regulatory goals of QbD have been described, but again these goals focus mostly on a regulatory perspective of past performance (setting specifications, process capability, and change control) rather than methods for achieving excellence from the very beginning (6).

A more mechanistic description has been proposed as working-quality by design (wQbD) by the following definition:

> To achieve a well-defined goal during the design stage, iteratively apply science and engineering methods to anticipate, identify, understand, and resolve problems that will be encountered during testing, operating, and verifying the goal over its entire lifecycle (7).

This definition describes the use of thought experiments combined with testing mathematical and experimental models within a larger design algorithm, such as the design stage of the lifecycle process development and validation paradigm described in FDA’s 2011 process validation guideline (8). As will be discussed, wQbD drives the systematic use of prospective quality risk management (QRM), operations research (OR), and design of experiments (DoE) methods to build effective control strategies for controlling risks and improving process performance.

The results of the wQbD methods must be assembled and stored in a comprehensive process model for internal and regulatory communications. ICH Q8 defines the all-important process model as the design space described by the definition:

**Design space.** The multidimensional combination of interactions of input variable (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (4).

The first sentence is the functional definition while the remainder are three increasingly significant policy statements intended to provide emphasis and guidance. Again, no mechanism is provided. The three policy statements provide a tantalizing look into the possibilities of sophisticated management-based regulations. Implementation of these policies, however, remains unlikely given the regulatory shift and the recent draft of ICH Q12 that describes comprehensive change control (9).

The regulatory design space is defined primarily in terms of the following two ICH Q8 definitions:

**Critical quality attribute (CQA).** 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.

**Critical process parameter (CPP).** A process parameter whose variability has an impact on a CQA and therefore should be monitored and controlled to ensure the process produces the desired quality (4).

Defining the design space in terms of the CQAs and CPPs is sufficient for regulating the performance of a process, but when used to design and clearly define manufacturing processes, the limited definitions have led to a great deal of confusion and uncertainty. Much clearer definitions of process inputs and outputs are required to build control strategies (10).

To more completely describe the performance of a manufacturing process, both the product and the process’s behavior during product manufacturing are required. An alternative method of describing process outputs, previously proposed by the author (10,11), are:

- **CQA.** Use the ICH Q8 definition, except it refers to the product material produced by each unit operation in the manufacturing process. In the case of the final process, the output CQAs would describe the final product.
- **Critical process response (CPR).** A process output that measures or indicates the performance of the process (e.g., temperature, pressure, viability, yield, etc.) that results in
all the product’s CQAs. For complex biopharmaceutical products, measuring and controlling CPRs is required to control both unknown or unmeasurable CQAs as well as the known and measurable CQAs. If appropriate, a measurable CQA can be used as a CPR (10). A CPR is an output parameter using the above CPP regulatory definition. Clearly describing the performance of a process as a CPR focuses the development activities on the important aspects of controlling the process’s behavior to achieve maximum control over product quality.

With respect to defining input parameters, the regulatory definition of the various input CCPs should be divided into the proposed following three categories (10,11):

- **Critical operating parameters (COPs).** Input parameters used to define and manipulate the process during development and operation. Examples of COPs include media composition, buffer concentrations, mixing rates, gas addition rates, etc. COPs used to control the performance of the process in real-time based on measuring CPRs in a feedback control loop are called critical control parameters (CCPs).

- **Critical material parameters (CMPs).** Material attributes of the raw material input used by the process to make a product. CMPs are the same as a critical material attributes (CMAs). Thus, a series of processes are connected by the transfer of output material described by CQAs from one process that become the input material described by CMP/CMAs to the next process (6,11).

- **Critical equipment parameters (CEPs).** These parameters (sometimes called critical design parameters) define the equipment. Examples of CEPs include volumes, materials of construction, agitator type, heat transfer area, and so on. These parameters are part of the equipment’s user requirements specifications (URS) when the equipment is designed, selected, and acquired during engineering.

When designing process systems, separating the three types of input parameters is important because they play different roles in determining the performance of the process. These parameters also contribute different risk input threats to the performance of the process and are controlled using different control strategies (10). Using the expanded definitions results in a well-structured design space (11).

ICH Q9—Quality Risk Management (QRM)

ICH Q9—QRM is the regulatory guideline most urgently in need of rapid improvement and ongoing evolution (12). Too many times, regulatory guidance defaults to “do a risk analysis” to solve a problem or define a control strategy. Although ICH Q9 clearly states the “what and why,” the methods included in the document do not provide a viable foundation for the “how.” The methods described in ICH Q9 focus on process analysis (e.g., wishbone diagrams, failure mode and effect analysis, hazard analysis critical control point). Although an execution risk’s severity from a process can be described easily in a variety of ways (e.g., cost, supply impact), the highly subjective element of uncertainty, or likelihood of the risk’s realization, is not properly addressed by these methods. Improper handling of uncertainty frequently leads to confusion and misleading results (13,14).

The failure to deal quantitatively with uncertainty often leads to the risk analysis falling prey to the precautionary principle, which can be defined here as an overemphasis on the impact of the risk’s severity without properly considering the risk’s probability as a result of inadequate information or poor analysis methods of the likelihood of the risk’s realization (15). The industry desperately needs effective quality risk management methods that are prospective, theoretically consistent with using probabilities to describe uncertainty, mathematically sound, easy to use by all practitioners, and expandable to an appropriate level of detail for analysis and control based on the risk’s severity (16–18).

FDA’s 2011 process validation guidelines

Arguably the most important guidance for developing control systems using QRM is FDA’s 2011 process validation guidelines (8). The document provides an important paradigm for developing and manufacturing products. The paradigm can be used to develop virtually any process from procedures or facility designs to unit operations (10,16,18). The guidance is unusual because it is very close to a prescriptive “how” paradigm. The approach is aligned with the four basic questions for any undertaking: "Do what?", "How to do it?", "Will it work?", and "Did it work?" (10). Any analysis method that does not address all four questions is incomplete. If the four questions are correctly asked and answered, particularly in a systematic, documented fashion using wQbD to answer the second question, success is highly likely.

FDA’s 2011 process validation guidelines describe three stages (8):

- **Stage 1: Process design.** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

- **Stage 2: Process qualification.** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

- **Stage 3: Continued process verification.** Ongoing assurance is gained during routine production that the process remains in a state of control.

Although the above stages provide a good foundation, they do not adequately cover the four basic lifecycle questions necessary to provide a complete development paradigm for building excellence. They also lack mechanisms for their execution. A more complete lifecycle can be divided into planning stages for prospectively building the process along with its control strategies, followed by execution stages for retrospectively assuring initial and ongoing performance based on data. The execution stages provide the foundation for the performance-based regulations and are most effective when the process’s established conditions and quality metrics are intrinsically defined and incorporated during the planning stages.
Briefly, the expanded process validation lifecycle paradigm can be described as planning stages (Stage 0 and 1) for prospectively building and documenting the foundation for manufacturing and execution stages (Stage 2 and 3) for retrospectively proving and documenting initial and ongoing success based on predefined comprehensive performance criteria described in the well-structured design space. The stages are described as follows:

- **Stage 0: Define.** Establish clear product and process requirements, goals, and objectives to define success during the execution stages.
- **Stage 1: Design.** Using wQbD, DoE, and prospective QRM to systematically develop control strategies and performance criteria within a well-structured design space to test, qualify, operate, control, and verify all process inputs and outputs required to manufacturing high quality products.
- **Stage 2: Test and qualify.** Execute a documented prospective testing program that ensures the process will work during Stage 3.
- **Stage 3: Operate, control, and verify.** Operate and control the process using the control strategies defined and designed in the planning stages while assuring and documenting successful performance using prospectively defined performance criteria (10).

The key to achieving very high product quality is to prospectively build a foundation during the planning stages using wQbD and QRM for the retrospective assurance of performance during execution by building highly effective control strategies, including integral measures of performance.

**Summary**

If the industry and regulatory agencies are to achieve FDA’s 21st century goals, the focus must be on developing and continuously improving prospective methods for developing new products and their manufacturing control strategies (19). While the existing management-based regulatory guidelines (ICH Q8 and Q9 and FDA 2011 process validation, etc.) are a good start, they must be improved significantly into straightforward methods necessary to achieve Six Sigma levels of performance to reliably supply all patients with high-quality products. Building and working with such methods will require a great deal of courage on the part of the pharmaceutical industry. Regulatory agencies and the pharmaceutical industry will have to work together, possibly using voluntary consensus standards, to build the methods along with the collective trust to efficiently develop, launch, and manufacture the many challenging products of the future.

**References**


5. FDA, *Final Deliverable for FDA Understanding Challenges to QbD Project, Understanding Challenges to Quality by Design* (Dec. 18, 2009).
The potentially devastating effects of endotoxins to humans have been widely reported. At sufficient concentrations in the bloodstream it is possible for endotoxins to cause irreversible side effects and even death in severe cases.

Found on the outer cell membrane of Gram-negative organisms, bacterial endotoxins are one of the most potent toxins known and strongly pyrogenic (fever-causing) substances, explains Allen L. Burgenson, Testing Solutions, Lonza Pharma & Biotech. “These toxins are harmless outside of the body and in the alimentary canal. They are extremely potent, however, once introduced in the bloodstream or intrathecally,” he says.

“Bacterial endotoxins (also referred to as pyrogens) have the capacity to induce a high fever,” confirms John Dubczak, general manager, Microbial Solutions, Charles River Laboratories. “A large enough dose of endotoxin can lead to lung and kidney failure, intravascular coagulation, and a systemic inflammatory response that can lead to septic shock and death.”

As a result of the dangers of bacterial endotoxins, the importance of testing for them is plainly apparent, in the view of Victoria Watson, laboratory manager, Microbiology at Wickham Labs. “The importance of endotoxin testing is clear when looking at how susceptible and sensitive humans are to even minute amounts of endotoxin,” she says.

The importance of testing
“Bacterial endotoxins are ubiquitous in nature and a menace for the manufacturers of all parenteral drugs and medical devices,” asserts Dubczak. “Not only are they everywhere environmentally, they are very difficult to remove once they are introduced into a finished parenteral product.”

Introduction of these molecules can come from simple contact with contaminated parenteral devices or medications, notes Watson. “Ensuring that equipment and medication are free from endotoxins is particularly important when caring for vulnerable patients, including the elderly, patients in intensive care, and infants,” she says. “For example, sudden infant death syndrome has been linked to varying levels of bacterial endotoxin present in the bloodstream.”

“In the early days of injectable pharmaceutical products, there was no method for testing for pyrogenic contaminants,” reveals Burgenson. “If a patient received an injection, there was a high likelihood that they would spike a fever, which at the time was termed ‘injection fever’.”

It was the work of Florence Seibert and her team in the 1920s that brought forth the introduction of the Rabbit Pyrogen Test (RPT) (1), which was eventually incorporated into the United States Pharmacopeia (USP) in 1942 as an official test, Burgenson explains. “The clotting of Limulus blood was noted for many years in injured horseshoe crabs,” he says. “Frederick Bang and Jack Levin discovered the enzymatic pathway causing the clotting of Limulus blood (2,3), and developed the Limulus Amebocyte Lysate, or LAL test.”

During the 1970s, pharmaceutical companies experimented with the LAL test and compared it with the RPT, finding that the LAL test was a more reliable and sensitive assay (4), and offered cost-efficacy for companies as there was no need to maintain rabbit colonies for product testing. “FDA took notice, and decided that, since LAL was derived from blood, it was a biologic subject to regulation under Section 351(h) of the Public Health Service Act, and subject to
At Coating Place, every coating formulation is customized based on the unique characteristics of the project. Using our Oradel® oral delivery techniques, we can achieve a wide variety of release profiles. With over 40 years of experience in the CDMO industry, Coating Place offers technologically advanced Wurster fluid bed coating, high quality coating, linear scalability and superior customer service.

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The LAL assay works via the reaction (gel-clot, kinetic chromogenic, and turbidimetric) that may be used to test injectable pharmaceutical products and implantable medical devices for release into commerce, notes Burgenson. “There is also the endpoint version of the kinetic chromogenic assay.” (See Table I for a list of the advantages and disadvantages of endotoxin testing methods.)

Table I. Advantages and disadvantages of endotoxin testing methods.

<table>
<thead>
<tr>
<th>Assay type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Gel clot</td>
<td>• Fast: 60 minutes vs. 180 minutes</td>
<td>• Qualitative</td>
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<tr>
<td></td>
<td>• Greater sensitivity</td>
<td>• Semi-quantitative with many dilutions</td>
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<tr>
<td></td>
<td>• Less variability</td>
<td>• Subjective results</td>
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<td></td>
<td>• Many fewer false positives</td>
<td>• Product compatibility</td>
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<tr>
<td></td>
<td>• Much less expensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Alternative to animal model</td>
<td></td>
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<tr>
<td>Kinetic turbidimetric</td>
<td>• Quantitative over a large range</td>
<td>Colored products may show interference</td>
</tr>
<tr>
<td>Kinetic chromogenic</td>
<td>• Quantitative over a large range</td>
<td></td>
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<tr>
<td></td>
<td>• Better product compatibility</td>
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<td></td>
<td>• Software</td>
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</tr>
<tr>
<td></td>
<td>• Product trending database</td>
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<tr>
<td></td>
<td>• Assay choice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Data management</td>
<td></td>
</tr>
<tr>
<td>Recombinant factor C</td>
<td>• Quantitative using a standard curve</td>
<td>Currently not listed as an official test in any of the major compendia for use in testing pharmaceutical products. However, this status may change in the future.</td>
</tr>
<tr>
<td></td>
<td>• No animals used in production</td>
<td></td>
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</table>

Source: Lonza Pharma & Biotech

Main methods

The LAL assay works via the reaction of the LAL reagent—an aqueous extract of blood cells from the horseshoe crab—with bacterial endotoxins and lipopolysaccharides. “There are currently three compendial bacterial endotoxin tests (BET) found in the USP (gel-clot, kinetic chromogenic, and kinetic turbidimetric) that may be used to test injectable pharmaceutical products and implantable medical devices for release into commerce,” notes Burgenson. “There is also the endpoint chromogenic assay, which is a timed endpoint version of the kinetic chromogenic assay.”

By comparing the time it takes to reach a defined level of turbidity to the times obtained from a series of endotoxin standards (standard curve), Sensitivity can be higher with KTA over the gel-clot method, he asserts, and although it is possible for KTA to be performed in test tubes, it is more common to perform the assays on plastic, 96-well microtiter plates. “The spectrophotometers that are used to measure turbidity changes can be captured by the use of appropriate software, and the assimilated data are used to generate quantitative reports,” Dubczak continues. “Those same data can be uploaded to a LIMS database for tracking and trending.”

Watson adds that the most significant advantages of quantitative methods over the gel-clot method are the increase in sensitivity and ability to extrapolate results. “Being able to extrapolate quantitative results can be invaluable when testing raw materials because it can offer insights into potential sources of endotoxin contamination,” she states.

### Gel-clot LAL test

This method is the oldest of the three and the simplest, Dubczak explains. “The major advantage of the gel-clot LAL test is its simplicity,” he says. “It is easily learned and can be performed without expensive equipment.”

The gel-clot assay works through production of a clot in the presence of endotoxins by cleavage of a coagulogen to coagulin, notes Burgenson. “This method can be performed as either a limits test or a semi-quantitative assay, giving a positive or negative result at the sensitivity of the lysate used,” adds Watson. “Dilutions are tested with lyysate, and the endpoint is used to calculate approximate endotoxin level.”

Despite the method’s advantages, such as interacting with fewer materials, thereby giving rise to a lower likelihood of results being affected by sample inhibition or enhancement, certain disadvantages have hindered its popularity. “The amount of time that is required to prepare samples using this process has made it less popular for use in raw material testing in some laboratories,” Watson says. “Additionally, the lysate sensitivities used in the gel-clot method are less sensitive than the quantitative methods.”

“Furthermore, the test does not allow for automation and data assimilation by computers, making it difficult to track and trend results,” adds Dubczak.

### Kinetic turbidimetric LAL test (KTA)

The KTA is one of the quantitative assays in which the measurement of absorbance versus endotoxin concentration is used to create a standard curve, explains Watson.

“During the LAL-endotoxin reaction, the solution mixture becomes increasingly turbid as the gel begins to form,” adds Dubczak. “The time required for these turbidity changes to occur is inversely proportional to the amount of endotoxin present in the sample (i.e., more endotoxin requires less time). The endotoxin in a sample can be estimated by comparing the time it takes to reach a defined level of turbidity to the times obtained from a series of endotoxin standards (standard curve).”

Regulation and licensure by FDA,” confirms Burgenson.

“Since its introduction, the LAL test has become one of the most important tools used in the pharmaceutical industry,” adds Dubczak. “It has allowed for a level of bacteria and pyrogen monitoring that simply eluded manufacturers when the RPT was the only pyrogen test available. The LAL test has ensured the absence of pyrogens in raw materials, water for injection systems, in-process samples, and in the final products.”

### Main methods

The LAL assay works via the reaction of the LAL reagent—an aqueous extract of blood cells from the horseshoe crab—with bacterial endotoxins and lipopolysaccharides. “There are currently three compendial bacterial endotoxin tests (BET) found in the USP (gel-clot, kinetic chromogenic, and kinetic turbidimetric) that may be used to test injectable pharmaceutical products and implantable medical devices for release into commerce,” notes Burgenson. “There is also the endpoint chromogenic assay, which is a timed endpoint version of the kinetic chromogenic assay.” (See Table I for a list of the advantages and disadvantages of endotoxin testing methods.)
test, is a further evolution of the LAL test. “Instead of cleaving coagulogen to coagulin, the same enzymes cleave a substrate-releasing para-nitroaniline (pNA), and a yellow color develops,” reveals Burgenson. “Similar to the turbidimetric assay, the time of color development to exceed a threshold is measured. The more endotoxin, the faster the substrate is cleaved, resulting in a deeper yellow color.”

For Dubczak, these chromogenic tests have an elegant methodology and feature many of the advantages that are found with KTA, such as increased sensitivity and extrapolation of quantitative results. “Chromogenic tests are, however, more expensive,” he says. “The chromogenic substrate material requires months to synthesize and as such, is very expensive to manufacture.”

**Other options**

“The latest evolution of the LAL assay is the use of recombinant Factor C, derived from the DNA of a horseshoe crab,” says Burgenson. “The gene sequence for Factor C is inserted into cells and expressed in cell culture. This recombinant Factor C (rFC) is the same as the natural Factor C. The assay using rFC does not produce a gel, turbidity, or a yellow color; it produces fluorescence proportional to the amount of endotoxin in a sample. The more endotoxin in a sample, the more light is generated.”

Another *in-vitro* alternative is the monocyte activation test (MAT), which was developed on the principle of the human immune system response, reveals Watson. “When challenged by the pyrogens entering the body or coming into contact with the bloodstream, the host’s innate immune defense mechanisms cause the monocytes/macrophages to produce prostaglandins and pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α),” she says.

Additionally, the RPT is also an option, although this should only be considered as a final option once the LAL *in-vitro* methods have failed, Watson notes. “RPT is generally used for highly complex products that interfere with the *in-vitro* methods, and for release of products that require full pyrogen evaluation in markets that do not accept MAT as an alternative,” she explains.

There are some products, namely biological ones, that are exempt from the rabbit test as stated in US 21 *Code of Federal Regulations* (CFR) 610.13(b), clarifies Burgenson. Therefore, in his opinion it is prudent for the developer to look at every approach that may be able to help overcome any interferences with the LAL assay. Some formulations include a chelator (such as citrate), with a non-ionic surfactant (such as polysorbate) causing the endotoxin to be lost in the product formulation. “A magnesium chloride solution has
been successfully used to overcome interferences by chelating agents such as ethylenediaminetetraacetic acid or citrate buffers. There are other proprietary products, such as Pyrospere (Lonza) or a glucan blocker that have also been used.”

If difficulties persist, however, Burgenson recommends the best course of action is to contact the LAL reagent manufacturer, so that the work can be done in partnership. “These manufacturers have seen all types of interferences many times over, and, therefore, should be able to help,” he says.

Protecting the horseshoe crab
As LAL assays are performed using an extract of blood cells from the Atlantic horseshoe crab, the prehistoric marine arthropod plays an important role in patient safety. “This animal is under legal protection,” emphasizes Watson. “Without this protection, the horseshoe crab population would be threatened.”

Dubczak concurs, highlighting the fact that reduction of animal use for pharmaceutical testing has been a well-established influencer of the industry over the years, which has seen the LAL in-vitro test replace the traditional RPT to prevent the use of hundreds of thousands of rabbits per year to test for product safety and contamination. The LAL test is an animal-derived test, meaning the animal itself is not tested upon. “The horseshoe crab’s blood is collected only to a point where the crab stops bleeding as part of a natural mechanism to protect itself,” he notes.

Additionally, there has been much work and commitment by manufacturers of the LAL reagent to conserve the horseshoe crab. “Work has included sustainability partnerships to enhance the horseshoe crab population along the mid-Atlantic shores,” says Watson. “Such projects have focused on increasing the survival rate of the horseshoe crab in early stages of life. Eggs are collected, and the crabs are grown in predation-free, controlled environments then released into their natural environment when older and stronger.”

Other projects include the “Just Flip Em” program where volunteers scan the beaches to rescue horseshoe crabs stranded on the beach on their backs, adds Burgenson. Each year many thousands of stranded crabs are rescued.

“Without the protection of the biomedical industry, these prehistoric creatures would surely become endangered, if not extinct. For this reason, it is critical that we serve as advocates for the humane treatment of these animals and strive to achieve balance between our need for this valuable material and the life of the animal that provides it,” stresses Dubczak.

Raw material quality: Regulation required?
“There has been an increase in raw material manufacturers requiring their products be tested for endotoxins,” notes Sophie Bell, section head for Bacterial Endotoxin and Cell Culture at Wickham Labs. “These requests come in usually due to pharmaceutical manufacturers requiring materials that do not contain detectable levels of endotoxins. The responsibility of the manufacturer is to source adequate materials for their products, so regulation of raw materials seems unnecessary; especially as different endotoxin specifications in end-products can affect the level of endotoxin contamination allowed in raw materials.”

In agreement, Dubczak highlights that product regulations are designed to set forth the standardized expectations for finished drugs, biologics, and medical devices, and as such the responsibility of sourcing adequate raw material is that of the manufacturer. Using an example from FDA guidance on pharmaceutical good manufacturing practices (5), he states that it is clear that regulators expect the sound application of science and associated risk-based rationales to be the basis for a product’s development and manufacturing process.

“For instance, manufacturers should determine the level of risk for both active and inactive raw materials, and there should be a comprehensive assessment of critical raw material formulations, ingredients of in-process buffers, and final product formulations,” he adds. “However, to place strict regulations on this process would be counter to the intent of this approach.”

Furthermore, Bell emphasizes the point that raw materials are not the only source of endotoxin contamination in end products. “Manufacturing processes can equally be a source of contamination, so the requirement for endotoxin testing in the product is still necessary. Testing of products from the beginning, middle, and end of manufacture is still advised to ensure uniformity across the manufacturing process,” she says. “Products that can be terminally depyrogenated will not require as clean raw materials compared to those that cannot.”

Despite the fact that raw materials going into pharmaceutical products are not specifically regulated, drug manufacturers use the highest grade of raw materials obtainable, emphasizes Burgenson. “Many of these materials are USP grade,” he adds. “Manufacturers will test raw materials and purified waters for the presence of endotoxins, and determine if the raw material meets its specifications and is suitable for manufacturing use.”

“What is important is that the quality of the raw materials used in production meet the standards appropriate for their intended use,” clarifies Dubczak. “Raw materials or reagents do require science-based evaluation to establish the presence or absence of deleterious endogenous or adventitious agents.”

References
How do you differentiate suppliers?

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Automating Quality Checks

Hallie Forcinio

Today’s inspection systems catch tinier flaws, manage data, and increasingly rely on artificial intelligence to further boost performance.

For pharmaceutical manufacturers, product quality is a constant concern. Automating quality control offers several benefits, including reducing human error. Quality control systems help ensure consistent high quality, patient safety, regulatory compliance, and operational efficiency. Detection sensitivity is crucial. “Only if the system is able to detect even the smallest critical-to-safety quality defects will it be able to improve the production process,” says Michael Feldhaus, director of technology at SCHOTT Pharmaceutical Systems.

Quality control automation also simplifies regulatory compliance. “As increasingly complex serialization regulations take effect around the world, pharma product packaging must maintain the utmost quality while imparting critical information for all the trading partners in the pharma value chain—including the end consumer,” says Barb Brynstad, Pharma product marketing, Optel Group.

Oliver Stauffer, chief executive officer at PTI—Packaging Technologies & Inspection, agrees that regulatory requirements are driving many installations. He reports, “United States Pharmacopeia (USP) 1207 and Annex 1 have shifted the guidance for container closure integrity. Both documents highlight different needs and have varying angles of interpretation. Appeasing the EMA [European Medicines Agency] and FDA requirements harmoniously is a current challenge many sites are navigating. Shifting inspection requirements to more reliable technologies for new drug submissions raises concerns over implications of retroactive liability for legacy products in similar container formats.”

He believes the answer is the adoption of non-destructive deterministic test methods with higher throughput and data traceability. The resulting data empowers pharmaceutical manufacturers and allow them to improve product quality and operations.

Whatever the reason for installing or upgrading quality control equipment, flexibility is imperative to handle the myriad of labels, cartons, trays, devices, and cases while maximizing line accuracy, minimizing downtime, and reducing costs related to recalls or incorrect or misleading labeling. As a result, strong demand continues for automated seal integrity testing (leak detection), checkweighing, contaminant detection, and product/package inspection.

Seal integrity

Seal integrity is crucial. A good seal ensures “product efficacy, shelf-life stability, and microbial sterility,” says Jeff Morrow-Lucas, director of Engineering at Leak Detection Associates. Non-destructive leak detection technologies include vacuum decay, airborne ultrasound, helium trace, high voltage, and laser-based headspace analysis. Selecting the right technology depends on the product, package, and sensitivity requirements. Morrow-Lucas notes it’s important to understand what the equipment is protecting against and advises verifying that desired pass/fail limits can be delivered by the model chosen. He also recommends selecting flexible equipment that works across today’s and tomorrow’s packaging formats.

Recent equipment innovations in seal integrity testing include PTI’s updated VeriPac tester, a vacuum-based unit that combines the ability to locate smaller leaks and shorten test cycle time with several in-demand features, such as non-subjective results, qualitative data analytics, and data trending. FLEX test chambers accommodate multiple flexible package sizes (1).

Another recent introduction from PTI, the semi-automatic Seal-Scan airborne ultrasound tester, delivers an in-depth profile of seal quality and works with any material combination regardless of color, transparency, print, surface finish, or porosity (2).
For online applications, the Seal-Sensor airborne ultrasound tester identifies seal defects in less than one second and locates flaws that a human inspector cannot see. The unit passes or fails each pouch and also captures quantitative, traceable data (3).

Lighthouse Instruments supplies laser-based headspace analysis technology for the KHS Series inspection system from Bosch. It performs 100% container/closure integrity (CCI) inspection on vials, cartridges, and ampules and detects leaks by identifying changes in headspace gas composition or total headspace pressure. The company also offers FMS benchtop test systems as well as the Pulsar Headspace CCI Inspection Lease System for online applications (4).

CMP PHARM.MA combines high-voltage leak detection with visual inspection and labeling in its RS1-LAB/RS2-LAB machines, capable of handling 200 or 400 ampules, vials, or cartridges/min, respectively. Machines are equipped with four leak-test stations and a rotation system to support 360-degree surface inspection. Systems check for particles, correct fill level, leaks, and other flaws (5).

Although X-ray inspection typically checks for product contaminants, the Integrity-Check tools built into the Safe-line X34 system from Mettler Toledo can identify products trapped in the seal of a blister pack or other format (6). “Historically, vision systems were utilized to perform this inspection,” says Sarrina Crowley, marketing communications manager at Mettler Toledo, North America, Product Inspection. However opaque packaging can be challenging for vision technology. Because opacity doesn’t affect X-ray performance, it “can detect product in seals in most scenarios,” she reports.

For induction seals on containers, cooled thermal imaging technology can check seal quality through the closed cap. The Countec Coglix InspecSeal TI-200 machine, represented in North America by Key International, inspects for damaged, inverted, incomplete, or missing seals; over- or under-heating; and loose or crooked caps and generates real-time data and statistics. The system is compatible with glass or high-density polyethylene (HDPE) containers from 20–200 mm in diameter and 50–300 mm in height and HDPE, polypropylene, or child-resistant caps (7).

**Checkweighing**

Checkweighing equipment also offers higher sensitivity levels and data collection and management capabilities. New systems offer the accuracy needed for combination filling or specialized filling of capsules. Richard Stedman, CEO at ACG Engineering, explains: “Many customers are now requiring net weight technology where individual dosing weight can be checked in the capsule. In addition to improved quality control, this [technology] provides more accurate data for compliance with stringent market requirements and evolving FDA guidelines. In instances of multiple-product doses (two or more products in one capsule), individual formulation weighing is becoming more crucial. … Such systems are set up for pre-fill weighing rather than post-fill and exemplify the next-generation solutions that pharma companies are seeking when upgrading from legacy gross-weight technology.” Current models from ACG Engineering feature a format-free design to handle any product, regardless of capsule size; sensitive and accurate load cells; and seamless integration with the capsule filling machine to reduce downtime or waiting.

Mettler Toledo’s portfolio of quality control equipment includes the updated Starweigh rotary stepper checkweigher. It features an improved human-machine interface (HMI), load cells, motor, and reject bins and handles small bottles and vials at +/- 2-mg accuracy. A dual load cell configuration operates at 120 containers/min. A duplex unit with four load cells doubles output. An outflee with two rejects segregates over- and underweight containers.

The new Selekta checkweigher from MG America relies on capacitance technology from the company’s capsule fillers to check up to 160,000 tablets or capsules/hour. Models can be equipped to weigh and sort, weigh and count, or just count round tablets up to 10 mm in diameter, rectangular tablets up to 10 by 25 mm and capsules from size 000 to 5 (8).

**Contaminant detection**

For metal detection equipment, top-of-mind concerns include “stricter validation audits regarding metal detector testing, inspections, and calibrations as it relates to products and keeping electronic records,” reports Kris Tompkins, North America Pharmaceutical business and key accounts manager at Loma, which is celebrating its 50th anniversary this year. A comprehensive log book captures pertinent data from Loma metal detector, checkweighing, and X-ray inspection systems. Loma also pro-
vides TRACS remote data-management software to help companies meet record-keeping standards. Other pharma-friendly features found on Lomas’s IQ 4 metal detector include washdown compatibility; a larger, more user-friendly touch screen; and programmability so machine frequency can be matched to the product.

**Machine vision**

Machine vision inspection is more powerful than ever, as exemplified by camera-based systems from Acquire Automation, which simplify vial counting and check caps. The CountQ vision inspection system automates the counting of vials in trays, eliminating the need for counting manually or with a stencil as well as the duplicate counts generally required by standard operating procedures. The system consists of a linescan camera plus software, adjustable lights, and label printer. Advanced product counting tools enable it to adapt to targets with varying visual characteristics. Standard features include an easy-to-use HMI, report and audit logs, security levels that control access, two-touch changeover, and configurable run modes that increase the system’s flexibility (9).

The CapQ system from Acquire Automation performs a 360-degree inspection of caps up to 38 mm in diameter and 330 mm in height to check presence, color, height, and skew. It also confirms the integrity of the tamper-evident band and verifies fill level. The stainless steel, NEMA 4X/IP65 inspection unit fits over the conveyor, simplifying integration on existing packaging lines. Advanced software using artificial intelligence enables the system to ignore water droplets and plastic fragment shedding that can skew measurement results and cause false rejections. The system produces reports and audit data for production and inventory records and provides data for continuous improvement programs. Options include a height-adjustable main system enclosure, automatic camera and light adjustments during changeover, and a high-speed reject system (10).

For print inspection, Optel Group offers the HD PrintSafe digital inkjet with built-in 100% web inspection. The serialization-ready system checks artwork, alphanumericics, barcodes, and variable data and can grade print quality. Options include dual and multi-color printing, wide screen for large webs, and additional inspection capability for products inside blisters or trays (11).

Other serialization-ready equipment also integrates machine vision including the TQS Fast Track line from Wipotec OCS. The TQS-LI-Bottle machine, for example, prints, inspects, and labels bottles at a rate of 150/min. Changeover to a new size between 30 and 120 mm in diameter and 30 and 200 mm in height takes five minutes (12).

Machine vision also is used to ensure the quality of the package itself. “...Reducing packaging defects, such as cracks and bruises or even scratches in the glass, as well as particle generation is of high importance,” explains Christoph Döppes, project director New Production Concept Vials, Global Operations at SCHOTT Pharmaceutical Systems, which has partnered with SINCAD, a French engineering company and expert in modular vision control systems.

High-quality glass containers depend on high-quality glass tubing. Döppes reports, “As it is our aim to reach ‘zero defect’ in both tubing and pharma packaging, we moved from statistical quality control to 100% inspection of each FIO-LAX tube during the production process. The process known as perFeXion leads to a glass tube that has been completely evaluated.” The Automated Inspection System (AIS) inspects all key surfaces of vials and cartridges and can detect defects invisible to the human eye. Advanced software creates a 3D image of the container based on visual data gathered from multiple cameras with different light settings. “We can therefore analyze the container surface in a more comprehensive way,” explains Feldhaus. Next-generation camera systems, equipped with artificial intelligence, will be able to learn from images of defective products and use that knowledge to independently recognize containers with defects.

Another packaging supplier, family-owned Colbert Packaging, which is celebrating its 60th anniversary in 2019, also has upgraded its quality assurance (QA) capabilities and now provides 100% vision inspection capabilities at all three of its manufacturing facilities. Its Leary Array with LearyVIEW Print QA system, recently installed at its Elkhart, IN plant, detects and rejects folding cartons with quality defects including missing copy, blemishes, streaks, oil spots, or other imperfections. “The new Leary QA system has a camera that scans the entire carton against the approved customer-supplied proof for visual quality defects,” said Nick Stober, Colbert’s Elkhart production manager. Eye C inspection software supports 100% inline inspection at speeds of 400 m/min (1300 ft/min) (13).

**References**


Accelerate your Drug Development Process with Lonza Engine™

ON-DEMAND WEBCAST  Aired June 25, 2019

Register for this free webcast at www.pharmtech.com/pt_p/accelerate

All attendees will receive a free executive summary of the webcast!

EVENT OVERVIEW:
Speed and quality are key in pharmaceutical manufacturing. How can your equipment add value to your production process?

Join the Lonza team to discover how the new Lonza Engine™ equipment portfolio is designed to support bioavailability enhancement, encapsulation and early-phase clinical development technologies.

Lonza Engine™ offers state-of-the-art equipment including:

- CFS equipment: support for lipid-based formulations to improve the bioavailability of poorly soluble compounds
- Micronization equipment: flexible solution for micronization process, including different technologies and containment solutions for particles engineering
- Powder micro-dosing: precise filling of capsules without excipients or bulking agents

Key Learning Objectives

- Understand some common customer issues around micronization
- Understand what solutions Lonza has to offer for bioavailability enhancement and encapsulation
- More information about Lonza Engine™

Who Should Attend

- QA/QC
- Operations/Production Managers
- R&D / New Product Development
- Clinical Supply
- Pharmacists

Presenters

Mattia Wiedemeier
Sales Manager Engineering
Lonza Pharma & Biotech

Mary Ellen Johnson
Product Manager, Capsule Delivery Solutions
Lonza Pharma & Biotech

Paul Davis
Sr. Engineer Field Service
Lonza Pharma & Biotech

Moderator

Kristen Moore
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Sponsored by
Lonza Pharma & Biotech

Presented by
Pharmaceutical Technology Europe

For questions contact Martha Devia at MDevia@mmhgroup.com
FDA guidance may improve data integrity, but moving to true data quality will depend on addressing disparate standards.

Over the past few years, after some notable failures at a number of companies (1), global regulators have been paying much closer attention to how pharmaceutical manufacturers safeguard the integrity of their data, to prevent accidental manipulation as well as fraud. It is the foundation of current good manufacturing practices (cGMPs). According to FDA, between January 2015 and May 15, 2016, 21 out of the 28 warning letters issued to pharmaceutical manufacturers centered around problems with data integrity (2).

As Orlando López, senior site automation specialist for a Big Pharma company, has noted (3), connections between different data points (i.e., initial data capture, metadata, and records) cannot be weakened or broken because they provide the only objective evidence that operations meet regulatory requirements and are being managed responsibly. These intact connections are also needed for process validation and continuous process verification.

FDA’s 2016 draft guidance document on data integrity clarified a number of important best practices. FDA also introduced the ALCOA acronym that data must be “attributable, legible, contemporaneous, original (or a true copy), and accurate.” In December 2018, FDA updated this guidance (4). “The new guidance serves to clarify data integrity requirements that have consistently challenged organizations. It firms up expectations around data/metadata and the data lifecycle within a risk-based structure of systems and design controls,” says Kir Henrici, CEO of the Henrici Group, a consultant for the Parenteral Drug Association (PDA), which published best practices on laboratory data integrity in 2018 and plans to publish manufacturing data integrity guidance by the end of 2019.

FDA has emphasized the need for careful risk management, audit trails and access controls, and the importance of saving all records that could be relevant to cGMP compliance, she says. Its latest data integrity guidance also underscores the need for senior management support and involvement in data integrity efforts. Training and ongoing communication with senior management are crucial to establishing and maintaining this support, says López. Expressing potential losses or liabilities in dollars and cents can be especially effective, he says, noting a 2017 hacking incident at Merck & Co., which cost the company $105 million to fix (5) and might have been prevented if investment had been made in data security. He also recommends keeping senior management aware of regulatory citations in a way that allows them to connect data issues to lost batches, product recalls, incorrect labels, or formulation changes. “Senior management needs to hear about money. It gets their attention immediately,” he says.

Avoiding a fragmented approach

It is also important to take a systematic, risk-based approach to data integrity programs, says Henrici. Some organizations may roll out data integrity programs in fragments, or as a reaction to a specific event, but then allow efforts to trail off, she says. “Pharmaceutical companies need to structure a systematic, risk-based approach that integrates the quality management system (QMS), which assures the efficacy and sustainability of the entire data integrity initiative.” Process mapping is especially important in ensuring that the right documentation is easily accessible to staff, but also to regulators. “Companies should track their ‘quality
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decisions’ to identify where non-cGMP records (e.g., emails) will be required to demonstrate cGMP compliance,” says Henrici. “You need to understand each specific process. Then, if you do a good risk assessment, to record which systems and which data you will focus on, you will be in a much better position to demonstrate full cGMP controls to the authorities,” says López. “If you have done the risk assessment and the process mapping correctly, there should be no doubt that you are implementing controls to the correct records,” he says.

Getting to a deeper level

However, data integrity is only the first step in a continuum, says López. “Pharmaceutical industry guidelines often refer to data reliability, which is a step beyond data integrity,” he explains. “But, ultimately, the goal for our industry is data quality, which is a step beyond reliability. We cannot reach that point with the guidelines that we have now,” he says, and cGMP requirements alone will not suffice.

Another challenge is the fact that existing pharmaceutical industry data guidelines don’t go deep enough, to the engineers and IT professionals who are implementing the systems, says López. “ALCOA may give them the ‘why,’ but it doesn’t give them the ‘how,’” he says.

The European guidance document Annex 11, first published in 1986, addresses data integrity in a more explicit way than the US 21 Code of Federal Regulations (CFR) Part 11, he notes. López recalls working for one Big Pharma company that correlated Annex 11 with Part 11 requirements, which made things much easier for engineers and IT professionals. Currently, there are a number of different data integrity guidelines (6). In pharma, these include regional ones for the United Kingdom, US, and other regions, as well as those developed by professional societies such as PDA and the European Compliance Academy (ECA). In addition, the software industry has codes of its own, as does manufacturing industry in general. The focus of each of the relevant pharma guidelines is different, López says, and the definition of data integrity in software engineering standards (i.e., as mainly about data security and not changing the records), differs somewhat from its definition in the pharmaceutical industry. The result can be confusing to IT professionals initially, he says.

“I would love to see integration between pharma standards and the software engineering standards, because the industry is not speaking the same language as software development academics. For example, for the pharma industry, validation is a process associated with the system life cycle (SLC) that continues from the start of a project until decommissioning. For software development, validation is just the testing phase of the SLC, so when you hire a new graduate, he or she won’t understand the difference,” says López. Without understanding the pharma validation concept and the relationship between software engineering and software quality, people in pharma’s IT and engineering departments will have different understandings and the resulting programs will be incomplete, he says.

Common standards will be the key to moving from data integrity to data quality, López says, noting that the origin of the International Society for Pharmaceutical Engineers’ (ISPE’s) GAMP 5 guidance (7) is ISO 9000-3, which is also the foundation of the industry’s guidelines. “Why are we speaking different languages?” he asks. “We need to synchronize all the different standards (e.g., International Standards Organization [ISO], ISPE, the International Society for Electrical and Electronics Engineers [IEEE]), and pharma’s so that we are speaking one common language.”

The pharmaceutical industry’s approach to data integrity will need to evolve as the industry moves to a Pharma 4.0 model. At INTERPHEX 2019 in April, Henrici spoke of the need for a “Data Integrity 4.0” strategy (8). “Companies will need to create multifunctional data governance teams to bring different perspectives to this effort, and facilitate communication between industry and regulators,” she said. In the end, the required knowledge is already there for implementing new IT approaches, says López. “We need to understand the relationship between the system, process mapping, data wave sets, and intended use, and simply apply what we have learned during the past 30 years (9) to the new technologies,” says López.

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4. FDA, Data Integrity and Compliance with cGMP, Q&A–Guidance for Industry (FDA, 2018), https://www.fda.gov/media/97005/download.
Overcoming Challenges in Ophthalmic Drug Delivery Including Bioavailability and Sterility

ON-DEMAND WEBCAST  Aired June 19, 2019

Register for this free webcast at www.pharmtech.com/pt_p/opthalmic

EVENT OVERVIEW:
Delivery of therapeutics to the human eye is one of the most interesting — but challenging — endeavors a formulator can take on. The anatomy — and chemical composition of the eye make it highly resistant to pharmaceutical penetration. Successfully circumventing these protective barriers requires intimate knowledge of ocular delivery as well as specialized development and manufacturing expertise. This webcast will explore solutions to some of today’s most challenging issues in ophthalmic drug delivery including selection of dosage form, options for increasing bioavailability, improving drug stability, properly handling highly potent APIs, overcoming patient compliance issues, and meeting the sterility critical quality attribute.

Key Learning Objectives
- Review ocular drug delivery, including dosage forms, physiological challenges, and trends
- Uncover approaches to increase bioavailability of both topical formulations and/or poorly water-soluble APIs, as well as methods to improve the stability of injectable drug products
- Discover how formulators are mitigating patient compliance issues with controlled release formulations, such as implants, long-acting injectables, and bioadhesive formulations
- Consider the various approaches to meet one of the key ophthalmic drug product critical quality attributes: sterility
- Understand the special handling requirements across a variety of ophthalmic drug products, particularly biologics and highly potent compounds such as steroids

Who Should Attend
- Formulators, researchers, scientists, biotechnology experts, innovators, drug/device engineers, and product development managers from:
  - Branded and generic pharmaceutical companies
  - Start-ups
  - Medical combination-product companies
  - Academia

For questions contact Kristen Moore at KMoore@mmhgroup.com
Gene Therapies Propel Outsourcing Investments

Susan Haigney

The increasing growth in the cell- and gene-therapy markets is inspiring CDMOs to expand their services in this emerging biologic drug arena.

Gene therapies are becoming a fast-growing area in the biopharmaceutical industry, creating a crowded pipeline of products in need of manufacturing. FDA expects the agency will receive more than 200 investigational new drug applications for cell and gene therapies by 2020, with the agency predicting that it will be approving 10–20 cell- and gene-therapy products each year by 2025 (1).

Because gene therapies use the patient’s own body to manufacture the active ingredient, the treatment is specific to that patient. This tailoring can often be a more effective and longer-lasting treatment, according to Chris Murphy, general manager for viral vector services at Thermo Fisher Scientific. “Because of these developments, novel, life-changing therapies are being realized that may transform the lives of patients in need.”

This growth is causing contract development and manufacturing organizations (CDMOs) to take a look at their portfolios as their clients require more and more biologics-related services. Catalent has been focused on the clinical pipeline of gene therapies and anticipating the need for commercial manufacturing. “There is an abundance of gene therapy product candidates in the pipeline, and on the heels of market approvals of gene therapy products each year by 2025 (1).”

According to Clark, outsourcing the manufacture of gene therapies requires relatively low volumes to fulfill demand, making it an attractive option. To better service its clients’ outsourcing needs in this area, Catalent acquired Paragon Bioservices, Inc., a viral vector development and manufacturing company for gene therapies with expertise in adeno-associated virus vectors, in May 2019 (2).

Clark believes the acquisition will help Catalent accelerate its growth. “Paragon offers its partners GMP-compliant manufacturing capacity, scale-up expertise, and customized downstream processing without the added time, costs, and risks of building a new viral facility,” says Clark. “The acquisition also brings complementary capabilities that will fundamentally enhance our biologics business and our end-to-end integrated biopharmaceutical solutions for customers. We have also gained the experienced leadership and dedicated team at Paragon, who will continue to run the business going forward, bringing their expertise and capabilities to the Catalent family.”

Thermo Fisher Scientific Inc. took a major step into the viral-vector manufacturing arena with the announced purchase of Brammer Bio, a leading viral vector CDMO, with 600 employees and locations in Massachusetts and Florida. The purchase agreement, announced in a March 24, 2019 press statement, is for approximately $1.7 billion in cash. Brammer Bio joins Patheon, acquired in 2017, and Fisher Clinical Services, which have been combined to form the Thermo Fisher’s Pharma Services business (3).

The acquisition enhances the company’s pharmaceutical and biotechnology customer value proposition by combining cell-culture media, single-use bioprocessing capabilities, analytical instruments, and related consumables. “Brammer Bio is an exciting addition to our Pharma Services business. By sharing our combined capabilities, expanding commercial scale and broadening deep customer relationships, we will strengthen our position as a trusted partner to our pharma and biotech customers. We will accelerate advancements in gene and cell therapy, meet the increasing demand of the customers we serve and bring life-changing medicines to patients in need,” says Murphy.

Viral vector challenges

Viral vectors are crucial to gene therapy because they deliver the therapy into the patient. “Viruses are evolutionarily designed to enter mammalian cells and reproduce themselves. Gene therapy harnesses this feature to transport the genetic material—or ‘active ingredient’—to target tissue or cells. Viral vectors are engineered to be safe for humans and can target specific cells or tissues in our bodies to maximize the effect of the treatment,” says Murphy. Thermo Fisher Scientific’s acquisition of Brammer Bio’s viral vector process development and manufacturing leverages capabilities in the company’s biologics business. Clark also emphasizes the importance of viral vectors. “During gene therapy
biomanufacturing, cells package the therapeutic genetic material into viral vesicles and secrete the vesicles into the media to be purified, then undergo formulation development to be ultimately filled into a vial or syringe,” says Clark. According to Clark, however, few innovators have the capacity, expertise, or resources to manufacture viral vectors. Catalent’s acquisition of Paragon helps the company manufacture viral vectors for their clients. “There are several types of viral vectors that can be utilized for gene therapy. Adeno-associated virus (AAV) is the vector most commonly used today in clinical trials and approved gene therapies, due to its safety and tissue-specific targeting abilities, and Paragon is one of the leading development and manufacturing providers for AAV vectors,” says Clark.

Expanding other services

In May 2019, Thermo Fisher Scientific announced that it is investing more than $50 million into its global bioproduction capabilities. The expansion will provide additional capacity for manufacturing single-use bioprocess container (BPC) systems. In Cramlington, United Kingdom, the company will expand assembly capacity and add BPC systems manufacturing. The proximity of these capabilities to customers in Europe will shorten lead times and improve overall global efficiency, according to the company (4).

In the United States, the company will expand cleanroom space for BPC chamber and related assembly production processes at its site in Logan, UT, and further expand capacity at its site in Millersburg, PA. Construction is expected to be completed by the end of 2020.

“The demand for our bioproduction products and services continues to outpace the market,” said Cory Stevenson, president of Thermo Fisher Scientific’s bioproduction business, in a company press release. “These investments will expand capabilities across our existing bioproduction network while we look to extend our footprint into new regions to meet increasing customer demand for our industry-leading single-use technologies.”

To further develop its biologics offerings, Catalent is launching OneBio Suite, a new offering for the integrated development, manufacturing, and clinical supply of biologic drugs. The Suite is designed to address challenges that arise when accelerating programs to clinic or market, while also reducing complexity and risks from projects. The OneBio Suite is built on Catalent’s track record in biologic drugs development, which includes more than 115 global clinical trials and 11 commercially marketed monoclonal antibodies using the company’s GPEx cell line development technology, and 20 approved products through fill/finish and commercial supply to global markets, the company reports. According to Clark, the company has multiple initiatives in the works to shorten timelines and increase efficiency (5).

“Time is often lost for sponsors on the path to clinic from contract negotiation, site inspections, handoffs, and poor communication between multiple vendors,” commented Clark in a press statement announcing the service. “Through our new OneBio Suite, Catalent is uniquely positioned to provide an integrated offering that can accelerate biologic development potentially shaving weeks to months off standard timelines and allowing our customers to get to clinic and market faster.”

References

Playbooks are Not Just Child’s Play

Q. We are preparing for our first inspection by an overseas regulatory agency. This will be a challenge from several perspectives: language, culture, and presentation style. We believe we have covered the first two issues through highly experienced translators and cultural training sessions with coaches. Our concern is about how to present and respond in an appropriate manner. Can you give any advice?

A. Hosting a foreign agency for the first time is always challenging, but as with all inspections, nothing beats preparation, practice, practice, and more practice. Even seasoned personnel can become flustered, nervous, or even unsure how to respond to unfamiliar questions or requests, especially when asked in a foreign tongue. One tool proven to be particularly useful in such situations is a playbook. Playbooks may be known by other terms, but essentially these are aide-memoires that function as references for company representatives who need to present or answer questions from inspectors or auditors. The playbook may include prepared answers to anticipated questions the auditor may ask and/or detailed information about process steps.

How detailed should these playbooks be and in what format? Here is what has stood the test of time:

- Always start with a succinct, logical, and convincing few lines of text and/or graphics.
- If necessary, have a second playbook with more detailed, supporting information.
- Have a third party (i.e., someone unfamiliar) review your playbook and/or provide feedback.

The first point is the most important. As we all are experts in what we do, we can talk in great detail about it. But inspectors do not have unlimited time. They want to receive answers that provide them with clear and easy-to-comprehend information. This is best illustrated with an example. The inspector may ask: ‘What is your bioburden control strategy for this product?’ Without a playbook, the answer may go like this: ‘In step 5 after vessel 234 on the second floor, remember you saw this reactor on the tour of the facility. We have installed a 0.2-micron filter. . .’

With a playbook, the answer would be more similar to this: ‘We have a bioburden control strategy that takes into account environment, process equipment, material handling, product properties, and regulatory expectations. For the five steps produced in our facility, we have prepared a strategy paper, which has subsequently been verified during the validation studies and ongoing monitoring.’

Of course, should the inspector then want to know more details, this is when all the evidence can be presented. Again, it may be useful to have a playbook ready for this, especially if many activities should be organized in a logical sequence and timeline.

Playbooks have several benefits, as they help those responding in an inspection to give clear answers. They also help prepare the site personnel to find answers to difficult questions (e.g., why certain deviation investigations are overdue, or why a particular change hasn’t been documented as per requirements). They also help summarize convoluted event histories or complex situations. Often, one has to overcome obstacles to reach a successful outcome, and playbooks help to focus on the positives, rather than to overemphasize the difficulties experienced.

Then why should one have these playbooks reviewed by someone from the outside? Well, the inspector will be exactly such a person (i.e., an outsider who isn’t necessarily familiar with the terminology, the facility, or the processes used at the site). Therefore, by having an outside third party review the playbook, you essentially perform a dry run of the inspection.

In summary, these playbooks are a useful tool in any inspection or audit, whether foreign or local, but writing these in a clear and concise manner is anything but child’s play.
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