Advancing Development & Manufacturing

Pharmaceutical Technology

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Establishing Acceptance Limits for Uniformity of Dosage Units: Part 3

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A skilled workforce is needed to deliver on technology’s promising medical advances.

Trade shows are a good opportunity to assess where an industry stands on new technologies, ongoing challenges, and future opportunities. It also is a good time to assess attitudes about prospects for the road ahead. As I write this, I am halfway through three consecutive weeks of industry events, each with a unique market focus, revealing the potential of biopharma to address patient needs and the work that must be done to achieve that goal.

Continuous manufacturing, which has gained momentum for small-molecule drugs with FDA approval of several therapies, was a popular discussion topic at INTERPHEX in New York, NY in mid-April. The strong interest is an indication that the pharma industry may be looking to consider advanced technologies that are common in other industries. In the biologics arena, the move to continuous manufacturing will be more difficult; experts on a panel hosted by Pharmaceutical Technology magazine noted that while some segments of a bioprocess may have continuous operations, an end-to-end continuous process will be difficult to achieve.

At CPhI North America in Philadelphia, PA, medical futurist Bertalan Mesko shared his vision of bringing science fiction to medical reality through the use of digital technologies and data management and identified actions that must be taken today to get the most out of future technologies. Smartphone-based monitoring, drone delivery of medications to remote regions, use of blockchain for data security of drug products, and Internet-based monitoring of patient medical conditions in their homes are a few advances he identified.

In another keynote address at CPhI North America, Nik Leist, senior director of ingestible sensor manufacturing and site leader at Proteus Digital Health, demonstrated how some digital technologies are currently available for monitoring patient adherence. In November 2017, Proteus and Otsuka Pharmaceutical Co. received FDA approval for the first digital medicine system, a drug-device combination product comprised of Otsuka’s oral aripiprazole tablets embedded with an ingestible event marker (IEM) sensor. Leist explained how the sensor, the size of a grain of sand, can be incorporated into a conventional drug tablet production system with some modifications. Regulatory approval could pave the way for other sensor-based applications.

The cost of new technologies may be high, creating a divide between those that can afford it and those that cannot, Mesko warned, and including the patient in the design of the medical advances—by asking them what they want—is crucial.

The human element
Mesko also noted that technology is only part of the solution; people are needed to implement this vision. The lack of a trained, qualified workforce to operate bioprocessing facilities spurred a partnership between Philadelphia-based Thomas Jefferson University and the National Institute for Bioprocessing Research and Training (NIBRT) of Dublin, Ireland to establish the Jefferson Institute for Bioprocessing, the first education and training institute for biopharmaceutical processing in North America. The partnership was announced in February 2018; further details were provided during the CPhI North America event by Mary Lynne Bercik, founder and CEO, GenZinnovation, and Ronald G. Kander, Dean, Kanbar College of Design, Engineering & Commerce Associate Provost for Applied Research at Jefferson.

When operational in 2019, the Jefferson Institute for Bioprocessing is expected to serve 2500 people annually, including an academic program for bioprocessing engineering from undergraduate through doctorate levels, industry training, workforce training through community college partnerships, and bioprocessing certifications through regional university partnerships.
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Robust ceramic bearings reduce the risk of breakage, are product-lubricated, and enhance mixer stability, reliability, and performance, as stated by the company. The bearings can be easily replaced on-site with no need for a spare impeller.

The unit is controlled by a variable frequency drive and covers a power range from 0.09 to 7.5 kW (0.12Hp to 10Hp) with operating speeds between 200–1000 rpm. According to SPX Flow, magnetic lifting of the impeller reduces the load on the surface of the bearings and enables the mixer to continue to run until the mixing vessel is completely empty, improving formulation mixing. Range options include a variety of bearings, O-rings, drive, and body materials.

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Gottlieb Tackles Tough Issues in First Year at FDA

Jill Wechsler

FDA’s commissioner addresses opioid abuse, drug costs, and manufacturing quality.

Scott Gottlieb has seen a whirlwind of activity since taking the helm of FDA in May 2017. He blasted brand manufacturer “shenanigans” for blocking generic-drug development and cited “pernicious” rebating schemes that expose consumers to high out-of-pocket costs for medicines. To help mitigate the nation’s deadly prescription drug epidemic, he has backed policies to reduce opioid prescribing and to develop less addictive pain treatments. And to continue last year’s notable gains in bringing important new drugs and gene therapies to market, Gottlieb has promoted innovative clinical research methods and other strategies to make drug testing more efficient.

The commissioner also told Pharmaceutical Technology that he is revving up FDA efforts to encourage industry conversion to advanced manufacturing systems able to scale up quickly to address public health issues. New policies to ensure quality manufacturing can facilitate the development of competitive biosimilars and prevent shortages of critical medicines to protect public health.

These and other initiatives have quieted critics on all sides. Democrats initially feared an industry bias but have been impressed by the commissioner’s criticism of drug pricing and his campaign to reduce nicotine in cigarettes. Republicans hoping for a free-market deregulator admire his efforts to combat opioid abuse and his support for innovation to speed new medicines, devices, and diagnostics to patients. Certainly, many of Gottlieb’s initiatives are not new and reflect years of hard work by FDA’s professional staff. But vocal support from the commissioner has accelerated action on many fronts.

A clear achievement is a proposed $400-million boost in FDA’s budget for 2019, as compared to the administration’s plan to cut agency appropriations by $700 million a year ago. The commissioner has gained support for FDA in Congress, which helped enact crucial user fee reauthorizations last year and blocked the Department of Defense from taking control of approving new treatments for the military. FDA also negotiated some modifications in “right-to-try” legislation to lessen its erosion of the FDA approval process and maintain patient protections.

Advancing quality

To convince the legislators to approve FDA’s new budget plan, Gottlieb outlined proposals for utilizing added resources (1, 2). Several initiatives advance the testing and production of new therapies, including greater use of real-world evidence and knowledge management systems to facilitate regulatory decisions, particularly for new treatments for rare diseases.

FDA also highlights the importance of modernizing drug manufacturing in proposing to spend $35 million to produce novel technologies, vaccines, and personalized medicines more reliably and at lower cost. Gottlieb now sees a convergence in regulatory resources, industry frustration with traditional production methods, and wider availability of new technology to advance more reliable and flexible advanced and continuous manufacturing systems.

“We’re now at a tipping point,” says Gottlieb. The agency will develop further guidance and standards to reduce uncertainty for industry in adopting high-technology platforms. And more highly trained field investigators will inspect for quality and those aspects of manufacturing that create risks, Gottlieb explains, and move away from a checklist system for uncovering viola-

Innovation may come from FDA funding of advanced manufacturing R&D projects to assess new quality manufacturing and analytical methods.

Jill Wechsler is Pharmaceutical Technology’s Washington editor, jillwechsler7@gmail.com.
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Another important focus is on bringing manufacturing home, as Gottlieb explains. He notes that high-quality, small-footprint manufacturing platforms have lower labor costs more suited to US operations. Advances in how FDA oversees medical device production similarly bolsters a “bring medtech manufacturing home” initiative that encourages firms to re-tool manufacturing processes in the United States. And streamlined oversight of software-based devices aims to lower the time and cost of market entry.

FDA also seeks to build the largely domestic pharmacy outsourcing industry through clearer manufacturing standards and policies. And more modern production methods for biologics are on the agenda to improve the agility, flexibility and reliability of manufacturing processes for vaccines and cell and gene-based therapies. In the wake of this year’s severe influenza outbreak Gottlieb has urged shifting from an egg-based to cellular system for seasonal flu vaccines, along with efforts to develop a universal influenza vaccine to provide multi-year protection, and ensure US access to vaccines to protect against a pandemic.

More advanced manufacturing methods also support more reliable production of biosimilars. Gottlieb plans to issue new guidance documents on reducing lot-to-lot variability over time for biologics by utilizing new tools better able to identify where lot variation raises potential risks to patients, along with more standard reference products that are easier to test and copy as biosimilars.

Challenges ahead

Despite a year of considerable success in broadening support for FDA initiatives and policies, the commissioner shows no sign of slowing down. He continues to tackle controversial issues, such as limits on flavored nicotine products, oversight of independent testing labs, and programs to limit food contamination outbreaks. The commissioner has emphasized the importance of promoting vaccination rates, despite continued opposition from vaccine deniers. And in another speech, he outlined plans to implement nutrition labeling standards and menu disclosures, which Gottlieb considers key to improving public health.

Gottlieb plans to remain a visible advocate for lower drug prices.

FDA also faces numerous deadlines for implementing key provisions of the 21st Century Cures legislation, including policies to support regenerative medicine and to speed the development of new cancer therapies, personalized medicines, and gene therapies. At the other end of the spectrum is a press for more efficient oversight and approval of over-the-counter medicines through a new user-fee program. And transparency remains a thorny issue, as FDA supports wider disclosure of data and analyses related to regulatory, safety, and enforcement decisions. Yet proposals for release of complete response letters remain on hold, as industry seeks to keep confidential certain regulatory decisions.

Combating the opioid epidemic is a prime challenge. While FDA supports the development of safer and more effective pain therapies and treatments for substance abuse and is re-examining the safety of abuse-resistant products, physicians are pushing back on proposals to limit opioid prescribing. FDA has gained added funds to expand its capacity to block imports of unlawful controlled substances at the border, and new legislation may strengthen its authority to require small-dose packaging of opioids and to remove from the market approved pain medicines found to raise safety issues.

Gottlieb plans to remain a visible advocate for lower drug prices, anticipating a continued roll-out of incremental changes to create a more competitive prescription drug market place. He has loudly criticized drug reimbursement and coverage policies for limiting consumer access to drugs, including a “rigged payment scheme” that blocks biosimilars, and suggested that FDA may be more flexible in setting standards for demonstrating product interchangeability.

The commissioner’s concerns about the high cost of medicines reflect his own experience as a physician and seeing ill patients “struggling very hard at the worst moments in their lives” to try to afford drugs that are “absolutely indicated for their disease.” He wants to be sure “that in my time here at FDA, I do something to address that.”

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Freeze-drying is widely used in the pharmaceutical industry to stabilize drug products. During freeze-drying, solvent is removed from a frozen product by sublimation to produce a dry product that can be readily reconstituted to its original liquid formulation by the addition of solvent. The process prolongs shelf life of the product by inhibiting chemical and physical degradation pathways that occur in the presence of moisture. The process, however, is one of the most expensive unit operations in a complete manufacturing line because of the slow drying rate arising from inefficient heat transfer, and the high investment and operating costs (1, 2). Cycle optimization is, therefore, crucial, especially for products produced on a large scale, where the cost factor increases significantly with time spent in the freeze dryer (1). A fully optimized cycle uses only the energy and time required, resulting in shorter process time and higher product throughput (3). Most importantly, it ensures optimum product quality and consistency between batches.

Freeze-drying involves three basic steps—freezing (solidification), primary drying (ice sublimation), and secondary drying (moisture desorption)—which can take several days to complete. A fundamental goal of freeze-drying is to produce a well-dried product with elegant cake appearance, short reconstitution time, long shelf life, and complete recovery of activity on rehydration (3, 4), among other requirements. Two major considerations for optimization of a freeze-drying process are the stability of the drug product, during the process itself and during the storage period after the cycle is terminated (5). Designing an optimized freeze-drying cycle requires identifying the critical properties of the formulation so that the processing conditions can be specifically tailored to the formulation’s freeze-drying characteristics, such as the collapse temperature ($T_c$), glass transition temperature ($T_g$), and eutectic temperature ($T_{eu}$) (3). As Arnab Ganguly, technology manager, IMA Life North America, underlines, thermal characterization of the product is essential to understand product limits.

The importance of proper freezing
The freezing step is of paramount importance in a freeze-drying cycle because it is a known equivalent dehydration step. Further, it determines the ice crystal morphology and pore size distribution of the product, which in turn affect downstream steps such as primary and secondary drying, observes Paritosh Pande, research scientist, IMA Life North America. Proper freezing creates the foundation for ef-
Angela Colarusso  
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HOW A FRAGILE BIOLOGIC TESTED A GLOBAL TEAM’S STRENGTH.  
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Cover Story: Process Optimization

Efficient and consistent freeze-drying cycles, according to T.N. Thompson, president of Millrock Technology (6).

“For freezing, we want to make sure that the product is thoroughly solidified,” says Steven Nail, principal scientist at Baxter Biopharma Solutions. He explains that freezing is often carried out at a shelf temperature of -40 °C to -60 °C for a period of time long enough to establish a steady state.

Critical parameters in primary drying

Once freezing is complete, primary drying begins. “The chamber pressure is reduced, and shelf temperature is raised to supply heat for the ice to sublime,” says Vaibhav Kshirsagar, associate scientist, IMA Life North America. “Normally, most of the water is removed at this stage.”

Primary drying is usually the longest step, taking up the largest fraction of the freeze-drying cycle time. Optimizing this process step has been shown to have significant economic impact (5). The temperature and pressure during primary drying will determine the rate of solvent removal and product temperature, according to Ganguly. “At or close to the edge of failure, increasing the temperature and pressure will speed up the primary drying process, but it may adversely affect product quality,” he says.

“Shelf temperature and chamber pressure are critical because of their influence on heat transfer, mass transfer, and ultimately product temperature—which is the most critical process variable, even though we can’t control it directly,” Nail explains. “Ideally, you want the product temperature to be a safe distance below the upper product temperature limit (usually the collapse temperature), without being so low that it unnecessarily slows down the process.”

Pande cautions that drastic increase of the shelf temperature in favor of more rapid ice sublimation during primary drying can lead to the collapse of an amorphous product or result in a eutectic melt for a formulation containing a crystalline product. “Both the collapse and eutectic melt can have significant consequences on product stability as well as for product appearance,” he says.

The optimal temperature and pressure during primary drying are determined based on the product collapse temperature and the freeze dryer’s capabilities.

Kshirsagar further adds that heat transfer to the product is not only dependent upon temperature and pressure, but also on the product containments such as whether they are contained in vials or syringes. He notes that increasing the pressure in the chamber will generally increase the heat transfer to the product, thus, increasing the mass transfer to the condenser.

Finding the optimum process conditions

The optimal temperature and pressure during primary drying are determined based on the product collapse temperature and the freeze dryer’s capabilities. “The optimum process conditions will prevent loss of pressure control in the chamber and maintain the product temperature below the collapse temperature,” says Kshirsagar. Pande highlights that there are also other variables that can influence the primary drying process such as fill volumes, vial size, freeze dryer geometry, nature of the solvent, and product concentration.

“To ensure successful primary drying, the product, process, and equipment characteristics must be factored in when deciding the appropriate conditions,” Ganguly explains. “The process of identifying appropriate conditions for primary drying typically begins with thermal characterization of the product of interest. During thermal characterization, the critical collapse temperature of a product is identified by factoring in its glass transition temperature (Tg’), as determined by differential scanning calorimetry, and identifying its collapse temperature through freeze-drying microscopy. The critical collapse temperature determines the maximum temperature that a product can withstand during primary drying without undergoing melt or collapse.”

From an equipment standpoint, Kshirsagar notes that aggressive cycles may be possible for products with high collapse temperature. “However, such aggressive cycles may sometimes lead to condenser overload or choked flow in the freeze dryer, if not well characterized,” he says. “In such situations, the equipment capability will be a limiting factor, and the temperature and pressure would be chosen accordingly.”

According to Pande, appropriate primary drying conditions can be determined with good accuracy using a combination of thermal characterization data and steady-state mathematical modeling performed using first principle methods. “This approach eliminates the need for trial and error,” he says.

Baxter’s approach involves constructing a graphical design space to determine primary drying conditions. “For us, that is a plot with sublimation rate on the y-axis, chamber pressure on the x-axis, and two sets of isotherms—one set for shelf temperature and the other for product temperature,” Nail explains. “We do this by measuring the vial heat transfer coefficient as a function of pressure and the resistance of the dried product layer to flow of water vapor. One of the boundaries design space is the upper product temperature limit, and the other is the equipment capability curve. The highest sublima-
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tion rate within the resulting ‘space’ gives the optimum shelf temperature and chamber pressure.”

The most widely used tools to monitor primary drying are pressure sensors, including the capacitance manometer and Pirani gauge. Temperature probes, which include thermocouples, resistance temperature detectors, or wireless sensors, are typically used during engineering runs, observes Ganguly. “Residual gas analysers and mass spectrometers can be used to determine the gas composition inside close environments and have proven to be extremely useful to monitor trace concentrations of contaminants such as silicone oils or even for process monitoring in primary and secondary drying (7). Tunable diode laser absorption spectroscopy is a well-established tool for monitoring the vapor flow rate between the chamber and condenser in real time. Heat flux sensors mounted on the freeze dryer shelves can be used to quantitatively obtain the vapor flow rate if prior heat transfer coefficient (Kv) measurements are performed,” he says. “These process-monitoring techniques gather enormous amount of data that can be used to determine the end point of a primary drying process.”

**Shelf temperature during secondary drying**

The purpose of secondary drying is to remove remaining unfrozen water that is either loosely associated with the crystal surfaces or buried within the glassy phase (1). The relatively small amount of water is removed by desorption, “typically to a final moisture content of 1–3%,” says Pande. “As the moisture content approaches 1%, the choice and concentration of excipients play an important role in preventing damage to the activity of any biological product,” he continues. “Excipients such as trehalose, for example, can better offset the effects of dehydration for a freeze-dried protein like immunoglobulin G by offering better H-bonding and a phase-homogeneous matrix with more suppressed β-relaxation, compared to large-sugar excipients such as dextran or inulin.”

Nail highlights that there is only one critical process variable during secondary drying, and that is the shelf temperature. “Both published literature and our own experience show that the chamber pressure doesn’t seem to have any effect on either the rate or the extent of secondary drying, probably because the rate-limiting step in secondary drying is diffusion of water through the glassy mixture of partly-dried solids,” he adds.

“We nearly always use a secondary drying temperature that is room temperature or above,” Nail says. “As a general rule, we like to keep the secondary drying shelf temperature as high as we can, because it results in a faster rate of secondary drying, and probably a greater extent of secondary drying.”

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In addition, Kshirsagar points out that the temperature of the product needs to be maintained well below the T_g during secondary drying. The rate of water desorption during secondary drying step is sensitive to the specific surface area of solid, he notes, which is impacted by the ice nucleation event occurring in freezing stage.

Kshirsagar explains that the rate of water desorption during secondary drying can also be influenced by the primary drying step. “Aggressive primary drying above the glass transition temperature can generate macro- or micro-collapse in the product cake,” he says. “To avoid product collapse during secondary drying, it is imperative that maximum water sublimation is achieved during the preceding primary drying step.” He reiterates the importance of maintaining shelf temperature during secondary drying several degrees below the T_g of the product. “Because the primary driver of water removal during secondary drying is the shelf temperature, as one example, it can be optimized by choosing a shelf temperature close to the T_g while maintaining a safety buffer,” he says. “In addition, a slow shelf temperature ramp rate is preferred to avoid exceeding the T_g and leading to viscous flow in the product.”

Nail explains that the appropriate combinations of shelf temperature and drying time are determined by taking “thief” samples during secondary drying and measuring the residual moisture content relative to a target residual moisture limit.

According to Kshirsagar, the Pirani and capacitance manometer pressure sensors alongside thermocouples can be used in the early stage of secondary drying. Pande adds that the use of mass spectrometers can greatly improve the secondary drying process monitoring, by which the exact gas composition in the chamber can be known and potentially related back to the batch average residual moisture (7).

**Conclusion**

Determining the right process conditions for a freeze-drying cycle requires an understanding of the effect of each step on the drug product. A confirmation run should be conducted at the end of cycle design to ensure that the process is robust and efficient and that it produces acceptable products.

**References**


The purpose of medicine is to make us feel better or even save our life. To keep it that way, Constantia has developed solutions to especially protect children from getting their hands on them.
Biologic drug substances are large, complex molecules prepared from living systems via complex cell-culture or fermentation processes. Given this complexity, it can be difficult to achieve consistent and predictable performance, with numerous factors from raw material variability to operator training to equipment selection influencing process outcomes. Biopharmaceutical manufacturers continuously seek new manufacturing technologies and approaches to improve process robustness and enhance product consistency and quality. Recent pursuits include continuous processing, the implementation of process analytical technology (PAT) and automation systems, the adoption of single-use equipment, development of enhanced modeling capabilities, and leveraging advances in data management and analysis. In the end, however, maximizing the benefits of these new approaches and technologies requires extensive collaboration within multifunctional teams.

**The people, process, and product matter**

Uniform production of biologic drug substances from batch to batch requires consideration of three key attributes, according to Elise Mous, director of sales and marketing and business development for Capua BioServices: the people involved, including their training, know-how, experience, and flexibility; the process itself, because each has its own unique challenges, characteristics, and requirements; and the desired product, for which the final specifications determine the end-game.

“The first step is to find the right approach needed to orchestrate all of the necessary requirements in the right manner to ensure a successful, scalable, and robust recipe,” she says. Those requirements include expression strain requirements/characteristics; raw material requirements; plant/equipment design needs; automation needs; training requirements; utilities requirements; key process parameters; regulatory constraints/requirements; and environmental, health, and safety constraints/requirements. For contract development and manufacturing organizations (CDMOs), much of this information can be learned either from past experience at the plant or from the client.

Attention to details can also make a significant difference in the robustness of a process, according to Mous. “It is important to analyze the potential risks and uncertainties upfront and define a custom onboarding trajectory for transfer, development, scale-up, and manufacturing campaigns, which includes definition and agreement of the joint objectives and journey required to achieve them,” she observes. Development of scalable, robust technologies as early as possible and establishment of a sampling plan and analytics are also important. Finally, attention should be paid to continuous improvement so that learning from the process and the data is ongoing. “Of course,” she adds, “safety and quality requirements can never be compromised.”

**So does the amount of data**

Because CDMOs work on both long-term commercial and short-term clinical and commercial projects, the amount of available process data can vary significantly. Fujifilm Diosynth Biotechnologies tailors its approach to uniformity- and consistency-control based on the amount of data that is gathered, according to Abel Hastings, director of process sciences at the company’s North Carolina facility.

“For processes with long histories and substantial data sets, we can leverage traditional statistical control. For processes with smaller datasets, we aim to improve early responsiveness to process control and consistency monitoring by applying a logic-based, piece-wise approach,” he explains. This methodology requires three main steps: process parameter to attribute linkage, development of an ideal distribution of expected data, and comparison of data against expectations.

Mapping out the expected process parameters to attribute linkage can form the basis for determining which
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data are most valuable to not only confirm that the process is running reliably, but also ultimately lead to tighter process control, even in circumstances where data are limited, according to Hastings. “This approach can also help teams focus on ways to capture the most informative information,” he adds.

Once parameter-attribute linkages are established, Fujifilm’s teams discuss and document the expected data results distribution. For example, they consider whether a normally distributed histogram or a sine-wave distribution should be expected, and whether the data might be skewed. “Developing expectations based on the factors and control elements can help teams establish a basic understanding of what ‘normal’ should look like,” Hastings explains. Once actual data are generated, they are compared to the expectations. “Even in the absence of statistical significance, this approach can allow processes to move toward increased process control and uniformity early in their lifecycles,” he observes.

And how it is acquired
Effective application of that actual data is essential to enabling meaningful interpretation, Hastings adds. “Most major equipment manufacturers have developed strong and deep data systems that gather information to help ensure reliable operation. In some instances, however, more data does not lead to more knowledge,” he asserts.

To ensure the right interpretation can be made, Fujifilm recommends assessing each data acquisition against the corresponding parameter-attribute pair. “Teams should aim to identify any points of ambiguity. Common points of concern can result from misalignment between parameters and attributes, limits of resolution in data, and data acquisition frequency,” Hastings explains.

An example of a parameter/attribute misalignment would be the difference between a temperature requirement for a shake flask operation and data recording of the temperature of an incubator. “While the temperatures may be the same, they are not the same element,” he says. Issues with data resolution can arise with many digital read-outs, which may clip or round data, potentially resulting in over-interpretation or under-appreciation of the degree to which the data may be skewed.

Hastings notes that it is important for users to recognize that automated data systems recorded at intervals may not give an accurate reflection of processes that change at higher frequency. “Teams should consider the rate of change of a process step before selecting a sampling frequency,” he says. To avoid these problems and similar risks, Fujifilm strongly recommends a cross-functional review of processes—from scientist to automation engineer—in order to ensure all data risks are considered.

Understand your equipment needs
In addition to types and amount of data and the way they are collected, the selection of biomanufacturing equipment can have a substantial impact on process robustness. Which aspects are most important can vary from one process to another, according to Gerald Hofmann, head of technology development at Capua BioServices. In addition, design attributes to be considered should not be limited to the performance during the actual cell-culture or fermentation process. “The hygienic design of the equipment, its maintenance needs, and what is required for an effective cleaning regime must also be well understood,” he says.

GMP Violations Spark Warning Letter and Import Alert

After observing birds and vermin near manufacturing equipment, as well as improperly cleaned equipment and out-of-specification test results during a 2017 inspection, FDA issued a warning letter on March 9, 2018 to Malladi Drugs & Pharmaceuticals Limited for deviations at the company’s Tamil Nadu, India facility (1). In addition, the agency placed the facility on Import Alert 66-40 on December 13, 2017 and stated, “Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.”

In the warning letter, FDA detailed observations during a Sept. 4–8, 2017 inspection that included inappropriately designed and cleaned equipment and vermin near equipment used for manufacturing. According to the warning letter, portions of the company’s facility are open to the outdoors, and inspectors observed birds and insects near open equipment that is used for drug manufacturing. FDA stated that the company failed to take adequate precautions to prevent contamination of product and must “provide a risk assessment for all drugs within their re-test date manufactured and distributed in the United States.”

The company also failed to use equipment suitable for production, and equipment was improperly cleaned. Vessels were partially filled with standing water, which may increase the risk of contamination, according to FDA. The agency stated the company should replace its equipment with equipment suitable for its intended use.

Proper process validation was also lacking at the facility. Processes lacked adequate control and out-of-specification test results were found in 24 batches over two years for an unspecified impurity. “Prior to the manufacture of process qualification batches, a manufacturer should identify all significant sources of variability and develop robust controls throughout the operation. Your process validation program failed to sufficiently address process parameters and other variables in the commercial manufacturing operation to support process reproducibility. It is essential that your process validation program provide substantial information and data to determine if the process can consistently produce acceptable quality products under commercial manufacturing conditions,” the agency stated.

FDA requested the company provide a data-driven and scientifically sound process validation plan, results from a stability study of validation batches, an evaluation of the company’s change management and correction action and prevention action systems, and an assessment of drug quality risk and toxicity of the impurity.

Reference

—The editors of Pharmaceutical Technology
Perhaps most importantly, selecting the equipment design that will provide the most robust process cannot be achieved without proper understanding of the full process requirements, according to Hofmann. “Making sure that these process requirements, and the needs of the user, are also well understood by equipment manufacturers can also have a measurable impact,” he comments. New equipment should therefore be selected to fit for a defined purpose in accordance with user requirements and critical process parameters.

When working with existing equipment, it is important to understand the opportunities and limits presented by the design and the potential for any modifications that can make the equipment more fit-for-purpose. Appropriate installation qualification, operational qualification, and process qualification protocols should also be prepared, reviewed, approved, and followed; and a proper maintenance plan should be developed and implemented, according to Hofmann.

**Develop an automation strategy**

Automation helps to ensure consistency by minimizing human errors and enabling repeatability and reliability of operations from one batch to another. Increasing adoption of automation and PAT in biopharmaceutical manufacturing is intended to reduce drug variability, increase yield, drive down costs, and maximize safety.

As CDMOs, both Fujifilm and Capua BioServices have a unique perspective because they work with a spectrum of processes, including products undergoing their first at-scale batches, decade-old processes being relocated to another facility, and commercial processes with a long history of continuous improvement. “The strategy necessary to ultimately implement automation ideals can often be challenging for processes striving to simply produce clinical batches,” says Hastings. “It is beneficial to find the right balance between manual versus automated operations; continuously evaluating investment versus added value,” adds Mous.

“When installing new processes into our facility, we aim to consider the full lifecycle of the process while also meeting the short-term goals of the project. To do so and overcome some of the challenges with implementation of automation, we design our process development work to simulate what can be both implemented as a manual operation and be transitioned into an automated step,” says Hastings.

**Cross-functional teams are essential**

Underlying all activities related to the development of robust processes for the production of biologic drug substances is the need for collaboration among scientists and engineers involved in all aspects of a project. “Selection, training, and coaching of the project team, from...”
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In many cases, finding the right solutions requires a bit of creative thought and collaborative work between the process development teams and manufacturing and/or quality-control operators, agrees Hastings. “We strongly recommend that cross-functional teams spend time in one-another’s area in order to build a solid understanding of flexibility needs, constraints, and long-term opportunities,” he comments.

Through this type of collaboration, it is possible for teams to find the right balance between speed, risk and reward, and cost, according to Mous. “In some cases, a project can be started quickly with a higher risk, while in others, investment in proper preparation upfront is the more appropriate approach,” she explains. Cross-functional teams are also better able to determine whether making facility or process modifications is more practical. “These teams know how to look for the best fit in terms of not only the best fit with the process, but the best fit with the budget,” Mous concludes.
The Role of Carriers in DPI Capsules

Choice of carrier can have a significant impact on the capsule filling process as well as the performance of the DPI formulation.

The use of capsules loaded into a dry powder inhaler (DPI) to deliver drugs to the lungs is a well-established method for the treatment of lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Developing a capsule formulation for inhalation, however, is not nearly the same as an orally administered capsule. For DPI capsules, powder properties not only affect the manufacturing process but also drug delivery to the lungs. Experts from DFE Pharma—Mohit Mehta, scientist; Gerald Hebbink, scientist; and Harry Peters, lactose inhalation specialist—spoke to Pharmaceutical Technology about the importance of carrier selection and how the capsule filling process can affect DPI performance.

Carriers in DPI formulations

PharmTech: Can you tell us about the role of carriers in DPI formulations?

DFE Pharma: DPI formulations contain micronized drugs. The aerodynamic particle size of these micronized drugs typically ranges between 1–5 μm. The majority of the drugs used for treatment of asthma and chronic obstructive pulmonary disease (COPD) are either beta agonist, anticholinergic, or corticosteroids, which can be formulated in combinations. These drugs have very low doses, usually in the microgram range. The carrier, therefore, provides the bulk, which enables ease of handling during dispensing, manufacturing, and delivery through the device (1). A carrier is an important component of the DPI formulation. Because micronized drugs have poor flow properties, mixing the drug with a suitable carrier enhances the flow behavior and thus improves dosing accuracy and consistency. Furthermore, the carrier facilitates the dispersion of the cohesive micronized drug during the inhalation event. Any change in the physiochemical properties of the carrier has potential to alter the product performance and drug deposition in the lungs; therefore, selecting and optimizing the right carrier is an important step in developing a suitable DPI formulation.

Excipients used as carriers

PharmTech: What excipients are commonly used as carriers?

DFE Pharma: Due to the lack of toxicological data concerning the potential hazard of carriers to lung tissue, the primary carrier currently approved or certified safe by FDA remains limited to lactose. Mannitol has been investigated as a carrier. However, mannitol can trigger issues related to bronchoconstriction, and using it as a carrier for treatment of asthma and COPD could be a regulatory challenge (2). Based on their functional role, there are other excipients, such as magnesium stearate, distearyl phosphatidylcholine (DSPC), and fumaryl diketopiperazine (FDKP), that have also been approved to be used for inhalations. The major commercially available formulations are, however, manufactured using lactose as the carrier (3). Lactose has been thoroughly investigated and described for this purpose. Mostly alpha-monohydrate lactose is used, although there are existing formulations that use beta-anhydrous lactose.

Selecting a carrier

PharmTech: What are the key considerations when selecting a carrier for a DPI formulation? What are the properties required in a carrier?

DFE Pharma: Selection of a carrier is typically based on:

- Functionality: powder flow and dispersion during inhalation
- Stability: physicochemical stability, biocompatibility, biodegradability, and compatibility with the drug substance
- Safety: it must be inert and non-toxic to lung tissues.

Consequently, it has been stated that the efficiency of a DPI formulation is extremely dependent on the carrier characteristics, and the selection of car-

Adeline Siew, PhD

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Carrier is a crucial determinant of the overall DPI performance (1). In case of DPI formulations, most of the micronized drug particles adhere to the surface of coarse carrier particles. During inhalation maneuvering, based on the velocity of inspired air flow, these drug particles are detached from the surface of the carrier particles. The larger carrier particles are deposited in the upper airways, while the small drug particles can reach the lower parts of the lungs (1). Detachment of drug from the carrier is based on the balance between inter-particulate adhesive forces and air flow velocity (4). The right cohesive and adhesive balance is, therefore, required between the drug and carrier to produce a stable formulation that at the same time allows easy separation during inhalation.

Often the question is raised to a lactose producer as to what grade of inhalation lactose should be used. There is, however, no single grade lactose that fits all purposes. One has to determine what kind of functionality needs to be addressed with the lactose. Is it the filling of the device, the mixing of the powder, the metering of the device, the deposition of the drug, or a combination of these?

**Lactose for inhaled formulations**

**PharmTech:** Can you discuss the differences between lactose for inhaled formulations versus lactose used in oral formulations?

**DFE Pharma:** Lactose for oral formulations is primarily selected based on the manufacturing process, the dosage form (whether tablets, capsules, or sachets), and the nature of the API (e.g., moisture sensitivity). In the case of lactose for inhalation, selection is based on filling of the device, device design, and deposition of drug into the lungs. In both solid oral and inhalation dosage forms, important characteristics to be considered when selecting a lactose are particle size and flow properties. However, in case of inhalation formulations, the particle size of the lactose plays a crucial role in determining drug deposition into the lungs and its pharmacokinetic behavior. For inhalation-grade lactose, health authorities require extra testing and controls, especially for some parameters, where tighter limits are required compared to pharmaceutical-grade lactose. Inhalation-grade lactose has to be manufactured specifically to meet the stringent specifications.

**Scaling up**

**PharmTech:** Can you elaborate on how capsule filling affects DPI performance, and what’s the best way to ensure reproducibility and consistency of DPI performance?

**DFE Pharma:** Capsules play an important role in delivery of drugs in the case of capsule-based DPIs. The capsule has a significant impact on powder deagglomeration and the detachment of the micronized drug from the carrier during inhalation. Capsule selection should,
therefore, be an integral part of DPI product development. In comparison to solid oral formulations, DPI capsules have low fill weights, and hence, it is often more challenging to fill the dry powders with accuracy and consistency. Filling of these powders often requires specialized filling equipment with built-in systems for in-process checks and the ability to reject under- or over-filled capsules based on the required quality specifications.

Temperature and humidity play a crucial role. It is important to avoid moisture uptake, as it may lead to powder aggregation and variability in the filling process (5). For accurate powder dosing, there are several mechanisms available, which include dosator filling, vacuum drum filler, and tamping pins. Generally, the filling mechanism is selected based on the amount and the characteristics of powder blend to be filled. Powder flow properties are one of the important parameters of the dry powder blends that can affect capsule filling and the DPI performance. It is important to have a thorough understanding of powder flow properties in combination with the mechanism of filling to optimize the filling parameters, which govern reproducibility and consistency of DPI performance.

PharmTech: What are the challenges of scaling up DPI capsule production and how do you address them?

DFE Pharma: There are several unit operations involved in DPI capsule manufacturing. However, the most important unit operations during scale up are blending and capsule filling. Blending is well established in the pharmaceutical industry, and manufacturing scale-up from bench to factory is generally well understood. However, blending is an important unit operation that plays a crucial role in determining the detachment of micronized drug from the carrier particles. In the case of a capsule filling operation, the major challenge is the unavailability of a defined scalability factor from laboratory scale to commercial scale. Hence, the whole process needs to be optimized based on the batch size, the filling equipment, and powder flow properties at commercial scale. To address these issues, the best approach is to have proper risk assessment done before optimizing the process. Risk assessment should take into consideration powder flow properties, filling process parameters, environmental conditions, storage after filling, and further packaging into blisters.

References

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Establishing Acceptance Limits for Uniformity of Dosage Units: Part 3

Pramote Cholayudth

The working acceptance limits for acceptance values (AV) are determined using the critical values at, for example, 95% coverage over the corresponding AV distributions. However, validity of such limits needs to be elaborated.

Part one of this article introduced the concept of sampling distribution of acceptance value (AV) in uniformity of dosage units (UDU) (1). With different sample sizes such as \( n = 10 \) and 30, their AV distributions will be different, resulting in different critical AV values (i.e., the values at the locations covering 95% of the distributions that are equal to, for example, 12.5 and 9.1 for \( n = 10 \) and 30, respectively). Such critical values will be employed as AV working limits rather than using the single compendial limit of not more than (NMT) 15 (2).

Part two of this article described how to establish the corresponding acceptance limits for AV data for process validation batches as well as the typical characteristics of AV distributions. Such validation AV limits are, for example, 9.1, 8.2, 8.0, and 7.4 for \( n = 30, 60, 70, \) and 140, respectively. Finally, it discussed derivation of relevant constants for AV control charts used in, for example, annual product review (APR) and continued process verification (CPV) reports (3). The applicability of such validation AV limits (Part two) will need to be elaborated because the author’s additional simulation study results reveal that there are some unforeseen relationships amongst those quality attributes, such as probability of meeting content uniformity test (4, 5, 6) and acceptance value (AV) at various content uniformity (CU) means.

One of the criteria for determining the more proper limits is to take into account the percentage lot coverage (7) in addition to such a 95% coverage. This is to guarantee that the high lot conforming rate is also achieved even at different CU means. In this part, those AV limits for routine batches (i.e., 12.5 and 9.1, \( n = 10 \) and 30, respectively) are demonstrated to be adequately justified at various CU means.

**CU mean vs. CU probability vs. AV limit relationship**

When analyzing the AV formula \( AV = M - \bar{x} + ks \), AV value is a function of sample mean (\( \bar{x} \)), sample standard deviation (s), and reference value (M). The most unpredictable out-

**contin. on page 38**
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Silicone tubing is widely used in biopharmaceutical manufacturing processes, especially in downstream processes after final sterile filtration and in fill finish operations where high purity is key. As a result, the quality, compendial and regulatory requirements for particulate, endotoxin, and bioburden content have become increasingly stringent for single-use components used for biopharma manufacturing.

“Biopharmaceutical players have increased requirements from suppliers for testing the purity of the single-use components to prove low contamination risk,” stated Dr. Pennadam Sivanand, MBA, Medical TS&D Manager, at Dow Medical Solutions, during a presentation delivered at CPhI Worldwide 2017 in Frankfurt, Germany. “And so, they expect us to provide testing data in support of their application’s final requirements.”

Sivanand explained how Dow Pharma Solutions has built strong experience in extractables testing on its Pharma tubing products. To ensure that its biopharmaceutical components meet and exceed customer and regulatory requirements, Dow expanded its validation testing documentation package to not only include extractables, but also cover all the required testing for particulates, endotoxins, and bioburden, per the industry standards.

“We are committed to help the biopharma industry in minimizing contamination risk from the supply chain,” said Sivanand, “So, we developed the most appropriate and stringent tubing-specific testing protocols to provide a supreme data package. We have tested the entire range of our Dow Corning Pharma Tubing product family.”

These tubing products were tested for endotoxins by Dow QC biolab in the United States and for particulates and bioburden by certified external laboratories in the United States and Europe, respectively. Studies were executed in multiple batches and in various sizes of tubing. “This provides a broad confidence in the data package we developed for our customers,” said Sivanand.

**Particle Testing**

The industry standard for testing subvisible particulates is the USP 《788》 Particulate Matter in Injections. Dow selected the Method 2; Microscopic Particle Count Test, which counts solid particulates alone that pose high risk to patients if present in the final drug product and does not enumerate gas bubbles and liquid particulates such as silicone oil extractables droplets.

Dow protocol involved the extraction of particulates from internal tubing surfaces using particulate-free water that was filtered through a membrane that was then microscopically examined and the particles, if any, were enumerated. The Membrane Microscopy counts results show that solid particulate counts obtained on the...
entire Dow Corning™ Pharma Tubing products were well below the USP <788> acceptance criteria (less than 12 particulates per mL for particulates ≥10 μm and less than 2 particulates per mL for particulates ≥25 μm).

“If you look to the results obtained on our range of pharma tubing that has gone through this testing, the average particulates count ≥10 μm is <0.3 particulate/mL, and <0.15 particulate/mL for particulates ≥25 μm. It is very evident that our tubing products pass with flying colors in terms of the subvisible particulates per USP criteria,” said Sivanand. “That gives our customers much confidence in the reliability of our tubing.”

More information on the USP <788> testing of Pharma tubing range is available. Please contact the Technical Service & Development, Dow Medical Solutions. Details of personal for EU & NA region respectively can be found at the end of this report.

Endotoxin Studies
Bacterial endotoxin content was tested using the limulus amebocyte lysate (LAL) gel clot method described in USP <85> Bacterial Endotoxins Test. Endotoxin was extracted from the tubing with pyrogen-free water and the extract was exposed to the quantity of LAL reagent sensitive to 0.125 EU/mL endotoxin. If the extract does not cause clotting, the test article contains less than 0.125 EU/mL of endotoxins and the test article passes the test.

All the Pharma tubing products passed the Dow acceptance criteria of less than 0.125 EU/mL. These results show that endotoxin content exceeds the very stringent limit of USP (as a comparison, the USP requirement for endotoxin in Water for Injection is less than 0.25 EU/mL and USP <161> Medical Devices—Bacterial Endotoxin and Pyrogen Tests have a limit of less than 20 EU per medical device or 2.15 EU/mL for medical devices that come in contact with the cerebrospinal fluid).

We are committed to help the biopharma industry in minimizing contamination risk from the supply chain.”

According to the USP method that we followed, we anticipate to have less than 0.25, but our products resulted with value well below the maximum limit. Hence again, this gives confidence to our customers and consumers that our tubing has got very high purity and high standards in the biopharmaceutical field,” stated Sivanand.

Bioburden Testing
The Pharma tubing products were tested for aerobic bacteria, yeast, molds and spores using ISO 11737-1 “Sterilization of Medical Devices—Microbiological Methods—Part 1: Determination of a Population of Microorganisms on Products.” The removal method for these organisms was validated with a very high recovery efficiency. After filtration of the extract and incubation of the filter, the retained micro-organisms were counted. The results show that none of the micro-organisms were detected from the Pharma Tubing samples.

Conclusion
The test results clearly demonstrate that the entire range of Pharma tubing products has a minimal potential for particulates, endotoxins and bioburden contamination, and thus a high level of purity that is particularly sought for bioprocess components usage in aseptic manufacture of drug products. Based on over 60 years’ experience in Healthcare Tubing Materials Science, Dow offers testing protocol development and data packages that support its leadership in high-purity solutions and that accelerate the validation process of Dow Pharma tubing products for biopharmaceutical manufacturing.

More detailed information on the clean tubing is available from Technical Service & Development, Dow Medical Solutions:

» For Europe: Lise Tan-Sien-Hee, lise.tan-sien-hee@dow.com

» For North America: Csilla Kollar, csilla.kollar@dow.com

“We are committed to help the biopharma industry in minimizing contamination risk from the supply chain.”
come of the formula is subject to the conditional determination of the reference value associated with the case whether or not the target is more than 101.5% label claim (LC) and the subcase that the sample mean is below 98.5, above 101.5% LC, or in between.

In the simulation study using MS Excel program (.xsm, not .xlsx) by the author, Figures 1–2 are two of the unforeseen examples that illustrate such an unpredictability where the CU probability results will sharply drop at means approximately 98.5 and 101.5% LC when the corresponding AV data are fixed at their working limits (e.g., 9.1, n = 30, and 8.2, n = 60).

For n = 60 or greater, it is fortunate that the minimum probability is much higher than 90% (98.27%). This implies that using such validation limits (introduced in Part two) needs to be careful because they are valid only when, for example n = 30, the means are between 99.5 and 100.5% LC, less than 97 and higher than 103% LC.

Such a validity is directly related to the probability results at not less than (NLT) 90%. The probability pitfalls at 98.5 and 101.5% LC locations in the two figures (and even in the others) will make the readers imagine how such a rigid formula (AV) affects the reliability of this particular parameter (i.e., AV). That is, the lower magnitude of AV data does not always correlate with the higher degree of meeting UDU as illustrated in Figures 3–6 where the CU mean is obviously the influencing factor.

Establishing validation AV limits with lot coverage taken into account
As discussed earlier, AV limits need to be adjusted for some ranges of CU means. One of the additional approaches to adjusting the AV limits is to take the lot coverage into account. The reason is to ensure that the high percentage of the conforming dosage units, say 99.999%, does fall within the specification limits.

Lot coverage may be defined as the proportion (p) or percentage (P) of the dosage units (in the lot) that falls between 85 and 115% LC (lot coverage 1) or 75 and 125% LC (lot coverage 2), as required by quality units, using the upper and lower bounds for mean and standard deviation (SD) as applicable. That is to say, the most acceptable lot coverage 2 (75–125% LC) must be practically close to 100% as much as possible.

From the simulation results, 99.999% coverage is determined to be the minimum because it is corresponding to the probability results readily above 90% (Figures 4 and 6). Justification of such a minimum is that those of the coverages below 99.999%, for example 99.99% in Figures 3 and 5, will have the probability totally less than 90%, which is not acceptable.

At the locations below 96.8 and above 103.2% LC (Figure 4, n = 30), the AV (limit) will increase up to 10.28 at 95 and 105% LC. So it needs to adjust those AV (limit) greater than 9.1 to, say, 9.1 as illustrated in Figure 7. In the figure, it looks justified because the relevant require-
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ments (for AV, lot coverage 2) are properly met. For larger sample sizes ($n = 60, 70$, and $140$), the AV limits seem to be practically and already acceptable.

Because AV data do not always correlate in magnitude with degree of meeting the UDU, the additional criteria (i.e., lot coverage) are essentially required as follows:

- AV limits introduced in Part two of this article can be used directly ($n = 30, 60, 70$, and $140$).
- All the following additional criteria are to be met:
  - The probability results are NTL 90%
Lot coverage 2 (75–125% LC) is NTL 99.999%. It is found that those parameters only for sample \( n = 30 \) need to be adjusted as illustrated in Figures 7–9. In the figures, those for \( n = 70 \) remain the same, i.e., no adjustment, 99.20% probability (green color), for example, is still existent. Figure 10 illustrates the distributions of the lot coverage 2 results where the minimum values (pitfalls) are still higher than 99.999% especially for \( n = 140 \).

Table I presents derivations of the working AV limits. In the table, all the AV results (reproduced from the figures) at mean locations throughout 95–105% LC need to meet the AV limits in the sky blue row, for example, 9.1 and 8.0 for \( n = 30 \) and 70, respectively. In the table, this particular set of acceptance criteria is intended for processes with target not more than 101.5% LC (mostly 100% LC). However, it may be applied to those processes with target greater than 101.5% LC as far as the additional acceptance criteria are met.

Figures 11–12 illustrate the the relationship between critical AVs and CU “lot” means (note: not “sample” means). The representative acceptance limits are those AVs at 100% LC such as 12.5 (\( n = 10 \)), 9.1 (\( n = 30 \)), and 8.0 (\( n = 70 \)) (assuming that sample mean results are about 100% LC most of the time if target is 100% LC) i.e., still confirming justification of those AV limits introduced in parts one [for routine batches] and two [for validation batches].

The most unexpected features are those illustrated in Figures 13–14 where the probability distributions will remarkably drop at means 98.5 and 101.5% LC for both \( n = 30 \) and 70, respectively. Note that all the distributions in the four figures (Figures 11-14) are based on lot CpK 1.33.

Application summary on validation acceptance criteria
Acceptance criteria 1 (expanded), 2, and 3 may be summarized as in Table II. The objectives of acceptance criteria 2 and 3 are to demonstrate that lot CpK on average is NTL 1.33 (criterion 2, i.e., qualitatively) and estimate the true value of lot CpK on average (criterion 3, i.e., quantitatively) (2, 3, 8, 9).
Figure 11: Critical AV (95% coverage) and CU lot means relationship (n = 10, 30, and 70). AV is acceptance value. CU is content uniformity.

Figure 12: Critical AV (95% coverage) and CU lot means relationship (n = 60 and 140). AV is acceptance value. CU is content uniformity.

Figure 13: Critical AV, probability and CU mean relationship (n = 30). AV is acceptance value. CU is content uniformity.

Figure 14: Critical AV, probability and CU mean relationship (n = 70). AV is acceptance value. CU is content uniformity.

Table II: Validation acceptance criteria 1 (expanded), 2, and 3.

<table>
<thead>
<tr>
<th>Sample sizes (n)</th>
<th>Acceptance criteria 1 (expanded)*</th>
<th>Acceptance criteria 2</th>
<th>Acceptance criteria 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AV limits (95% coverage)</td>
<td>Probability (%)</td>
<td>Lot coverage 2 (%)</td>
</tr>
<tr>
<td>30</td>
<td>9.1</td>
<td>NLT 90%</td>
<td>NLT 99.999%</td>
</tr>
<tr>
<td>70</td>
<td>8.0</td>
<td>NLT 90%</td>
<td>NLT 99.999%</td>
</tr>
<tr>
<td>60</td>
<td>8.2</td>
<td>NLT 90%</td>
<td>NLT 99.999%</td>
</tr>
<tr>
<td>140</td>
<td>7.4</td>
<td>NLT 90%</td>
<td>NLT 99.999%</td>
</tr>
</tbody>
</table>

**Additional acceptance criteria.**

**From 3 or more PV batches**

*For practical guidance, the sample mean ranges for n = 30, 70, 60, and 140 are expected to be 97–103, 98–102, 98–102 and 98.5–101.5% LC, respectively. More is described in the discussion section.

AV is acceptance value.

NLT is not less than.

PV is process validation.
Discussion
One characteristic of the statistics-based acceptance limits is that different numerical limits are established for different sample sizes.

The most obvious example is the relative standard deviation (RSD) limits for Uniformity of Dosage Units in the past (10), i.e., RSD ≤ 6.0 and 7.8% for \( n = 10 \) and 30, respectively (Figure 15), so that the AV acceptance limits are in the same manner (i.e., different AV limits for different sample sizes). The differences are due to the fact that different patterns apply to corresponding distributions for different sample sizes.

The definition of AV formula \( AV = M + x + ks \) is not natural. If the reference value \( M \) is replaced by the target \( T \), which is the single value, and equal to 100% LC in most cases, then the new (natural) AV formula is \( AV = T + x + ks \).

Figures 16–17 illustrate the simulated natural AV distributions with critical AV values (i.e., 13.5 and 9.8 for \( n = 10 \) and 30, respectively).

Such values are slightly increased (i.e., from 12.5 to 13.5, \( n = 10 \), and 9.1 to 9.8, \( n = 30 \)). The two figures, however, are intended for “For Information Only” as the detail is out of the scope of this part.

In the compendial AV formula, the value of CU sample means \( (x) \) is also important. One should need to know the natural ranges for mean data (i.e., know if the data are statistically acceptable). For \( n = 10 \), for example, the tolerance range should be 15∕√10 = 4.74 (i.e., the means should fall within 95.26–104.74% LC, assuming that the true mean is 100% LC).
The number 15 is commonly used as the tolerance range for individual data (i.e., derived from 115 - 100 or 100 - 85 [- - is minus]). If divided by the square root of sample size, the result of 15√n will become the corresponding range for the mean (average) data for sample size n. If n = 30, the range is 15√30 = 2.74 (i.e., the means should fall within 97.26–102.74% LC, under the same assumption).

For n = 60, 70, and 140, the tolerance ranges will be 1.94, 1.79, and 1.28, respectively. However, the justified working ranges covering, say, the unavoidable errors (e.g., lot mean error) are essentially required. Suppose the following justification criteria are given:

- Unit (individual) content range: ±15% of the lot mean
- Content mean (average) range: ±15√n% of the lot mean (this criterion is in the same manner as standard error of the mean σ/√n)
- Lot mean (average) range: ±10% error of unit content range (15), i.e., ±1.5% of the target (note: ±10% is just a guidance value. For practical implementation, the value needs to be determined on the basis of process by process).

For calculation example, if n = 10, the lower and upper CU mean limits are (100 ± 1.5) ± 15√10 (i.e., 93.76 and 106.24, or rounded to 94 and 106% LC).

Using the same criteria, the CU sample means for sample sizes n = 30, 60, 70, and 140 will have the working ranges as follows: 96–104%, 96.5–103.5%, 97–103%, and 97.5–102.5% LC, respectively.

**Conclusion**

From the simulation study, meeting the AV acceptance limits alone is not effective enough for product release. Additional acceptance criteria to form the expanded criteria are essentially required to provide complete confidence on uniformity of dosage units of the products.

In validation batches, meeting expanded acceptance criteria 1 (AV, probability, and lot coverage 2 introduced in Part three of this paper) will guarantee that NLT 99.999% of the dosage units in each batch will fall within 75–125% of label claim (LC) while the corresponding lot coverage 1 is 98.40% (n = 30) at minimum as illustrated in Figure 9. For larger samples, such coverage results will be greater, e.g., 99.32% (n = 70, Figure 9).

In routine batches, meeting the compendial acceptance limits will imply only that NLT 90% of the dosage units in each batch will fall within 85–115% of LC. By definition of the working acceptance limits introduced in this article, meeting the limits will also guarantee that batch release operation is successful at NLT 95% of the time (95% coverage).

AV data of the historical batches, or even continued process verification batches, may be evaluated using AV chart (trend analysis) and can also be used to determine if the true CpK on average at NLT 1.33 is achieved.

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10. Author’s personal communication with USP, Email dated Aug. 21, 2001. Regarding “USP Content Uniformity (CU)’s RSD Limit”. *PT*

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Streamlined Manufacture of Modified Release Matrix Tablets via Direct Compression

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Key Learning Objectives
- Understand the complexity and challenges of wet granulation process
- Gain insight to the benefits of direct compression as the most streamlined process for tablet manufacturing
- Discover how excipient innovation can streamline matrix tablet manufacturing

Who Should Attend
- Formulation and product development scientists, scale-up and production managers, and regulatory professionals

For questions contact Ethan Castillo at ethan.castillo@ubm.com
The data that pharmaceutical manufacturers rely on to make quality decisions come from electronic systems, hybrid practices that incorporate both paper and software, or paper records alone. But the pressure is on, from FDA and regulatory agencies worldwide, to ensure the integrity of data supporting the product lifecycle, from drug discovery to product manufacture and, ultimately, release.

The World Health Organization, FDA, and the UK Medicines and Healthcare products Regulatory Agency (MHRA) have each issued guidance in the past few years to improve data integrity in pharmaceutical manufacturing.

FDA, in its 2016 Data Integrity and Compliance with CGMP Guidance for Industry (1), noted it was seeing increasing violations of current good manufacturing practices (cGMP) stemming from data integrity infractions. Some of those violations were the result of an inability to audit temporary data that may have been entered, but not saved, into an electronic system. Within the industry, the expectation that data are attributable, legible, contemporaneous, original, and accurate (ALCOA) has been expanded to what is called ALCOA+. This new definition demands that the data also be complete, consistent, enduring, and available.

These “plus” concepts help give a datum context, especially during future reviews and audits. In other words, ALCOA+ takes into account not just the data, and associated metadata, that exist at the time of collection, it also shows a complete picture of the data throughout its life to ensure data integrity. It is no longer appropriate to just demonstrate that data were collected and verified; data must be shown to remain unadulterated, accurate, and attainable. This demonstration can only be done when there are controls around the data to prevent alteration, or measures in place to identify when data have been changed. It is noted that changing data is acceptable for appropriate reasons, such as the wrong entry (i.e., typing mistake) of a test result. It is not acceptable when data are changed just to meet a specification.

Integrated electronic solutions

Electronic data capture offers significant productivity and security enhancements over paper-based records, but also introduces new challenges for information technology departments, users, and regulators. Challenges include preservation of data, technical aspects of system integration and validation, and acceptance of electronic systems, which require a higher level of technical capability.

For confidence that data meet ALCOA+ standards, pharmaceutical companies and contract manufacturers are increasingly relying on integrated software solutions. Integrating the computerized systems that capture, collect, and archive data is one way to reduce the manual re-keying of data, thus reducing risk and improving integrity. Single data entry, coupled with the automatic transfer of that data across integrated systems, eliminates the possibility of human transcription errors and increases efficiency. Most significantly, it decreases lag time for manufacturing execution systems (MES) and production lines to receive data as they become available in a laboratory information management system (LIMS).

Without confidence in the integrity of data, such as quality and batch release data, there can be no confidence in the integrity of the drugs themselves.

Integrated computerized systems for data collection improve data security and offer a solution for handling temporary data.
In today’s manufacturing environment, paper-based and disconnected data systems don’t have any way to ensure that data are accurate and consistent—that they have integrity—other than by involving extra steps of human review, which is not ideal. Reliance on human intervention increases risk, which can lead to unusable product, product recalls, and lost revenue associated with recalls; warnings, fines, or consent decrees; negative publicity; and most important, possible harm to trial subjects and patients.

Therefore, various pharmaceutical companies are adopting strategies that reduce reliance on human/manual systems and deploying computerized systems instead. Although there is no single software solution for the entire pharmaceutical process, there are integrated systems and platforms that cover specific portions of pharmaceutical processes and that can be interconnected.

Integrated systems reduce risks and enhance product quality by using automated and systematic checks to verify data integrity. For example, solutions that integrate a LIMS, electronic laboratory notebook (ELN), and laboratory execution system (LES) into a single platform can effectively gather and share data on samples, methods of analysis, analytical results, environmental monitoring, and more, between the systems. These systems can also be integrated to enterprise resource planning, MES, and manufacturing control, which further enhances data integrity and efficiency.

New focus on temporary data
One aspect of data collection and integrity that is gaining attention is temporary data, which are data entered into a computerized system but not saved to the database, either accidentally or intentionally. As results are entered into a LIMS data entry page, it remains in a temporary state until the analyst commits it to the database. While in its temporary state, the results can be changed by the user, even multiple times. Such changes might be deliberate in order to make a sample meet certain specifications.

For example, if the amount of product to be filled in a bottle relies on potency, an incorrect potency could cost the company money by adding too much to a bottle (reduced yield), by not adding enough (reprocessing), or by missing stability specifications (product recall). To err is human, and while not rampant, there is evidence of data tampering to fit specifications. Hence the focus on temporary memory.

FDA’s latest guidance (1) recommends placing this temporary data under control so it may be audited. Tracking any changes in temporary memory, therefore, increases the integrity of data and helps pinpoint when data are being manipulated into passing. This control can be achieved using dynamic auditing. Dynamic auditing tracks changes to data once it is entered into a data entry field and prior to the data being saved/committed to the database. Traditional auditing involves auditing of data after being saved/committed to the database.

Benefits of integrated platforms
Integrated platforms can overcome the many potential ways in which data might be modified. Values entered into a connected system, via connected instruments, are not susceptible to transcription errors. It is much more difficult to modify data without authorization within a LIMS, particularly when data come directly from a connected instrument, compared to a paper-based system that relies upon observation and accurate, manual recording. Informatics systems, for example, can be designed to automatically save all entered data, to prompt a user to provide a reason for making a change, and to include all data in the audit review record. In addition, data entered into an informatics system can be checked for accuracy as it is typed; for example, an informatics solution can be configured to recognize that a pH cannot possibly have a value of 15 or a length cannot be negative.

Data from a connected system is still only as accurate and consistent as the interface that connects the component parts. Therefore, thorough verification and validation testing is crucial to demonstrating the reliability of the interface. An integrated LIMS/ELN platform, for example, offers a higher level of protection because no data are transferred between the two systems; instead, each datum is stored exactly once. Removing the double data entry and the duplication of values between systems over an interface between separate LIMS and ELN platforms reduces risk.

Integration with manufacturing systems ensures data integrity by eliminating re-keying of data. The data are automatically transferred between interfacing systems, reducing the time lag between result generation and reporting, which can reduce overall production timelines.

Integrated software solutions can make it much easier to achieve compliance with regulations, such as FDA’s 21 Code of Federal Regulations Part 11 for electronic records and signatures (2) and the European Union’s Annex 11 for computerized systems in pharmaceutical companies (3). These solutions enable human readable and printable audit trails and compliant electronic signatures. Pharma companies should also make sure the platform complies with new guidance on auditing data stored in temporary memory, that it does not allow users to change data that are marked as having come directly from an instrument, and that it features modern, secure, Internet-enabled system-interfacing capabilities.

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2. CFR Title 21, Part 11

Takashi Kaminagayoshi, Kosuke Takenaka, Tomohiro Doi, Shunsuke Omori, Makoto Sadamitsu, Shinji Tsuji, Yoshiaki Miko, Osamu Shirokizawa, and Andrew Walsh


The approach presented in this study uses process capability index results to establish sampling strategies for use with new product cleaning and to efficiently reduce the risk of insufficient cleaning.

Pharmaceutical development requires time and enormous cost, which can be an economic burden to pharmaceutical companies. Pharmaceutical companies, therefore, have been striving to make improvements, and since the 2000s, they have been focusing on activities such as operational excellence. Operational excellence is a concept proposed by M. Treacy and F. Wiersema in 1995, and it is one of the three competitive strategies for leading companies: operational excellence, product leadership, and customer intimacy (1). Many US and European firms, mainly major electronics manufacturers, employ operational excellence to reduce costs by optimizing processes. In firms where operational excellence is already implemented and the operation improvement process is well-established, a competitive edge can be assured. It is also considered that in such firms, the idea of constantly pursuing better operations is communicated to and understood by all personnel on site, and a mechanism that enables continuous improvement is already well established.

Operational excellence is just one of the concepts of task-improvement methods such as total quality management and Lean Six Sigma; the application to pharmaceutical products to minimize product risk has been limited and can be extremely difficult to implement. To strengthen the competitiveness of pharmaceuticals, it is necessary for the pharmaceutical industry to carry out discussions with a wide range of perspectives not only in research and development (R&D) but also in manufacturing. Despite the many challenges that must be addressed (e.g., pharmaceutical sensitivity to changes in the manufacturing process, complicated manufacturing methods, the need to meet high-quality requirements), few case studies discuss these manufacturing processes (2). In recent years, these issues have been discussed in the pharmaceutical industry, but in many cases, the manufacturing processes—including processes from API to finished pharmaceutical manufacturing from a holistic standpoint—have not been clearly identified. While biopharmaceuticals such as antibody drugs are greatly advanced in product development and technology, bioprocesses have variable factors that are distinctive to their processes. These factors attract the interest of regulatory authorities, and the highest priorities have been given to compliance with good manufacturing practice (GMP), safety, etc., which has caused a lag in research and manufacturing to provide pharmaceuticals more efficiently and economically without sacrificing the quality.

The demands for quality engineering methods are increasing globally, and the establishment of a system to carry out continuous process improvement is required to supply high-quality formu-
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The manufacturing process of antibody manufacturing activities for hygiene and quality control reasons, clean-in-place (CIP) and steam-in-place (SIP) are the major methods used. These methods clean the inside of the complex piping systems and tanks by running the cleaning agents through them followed by high-pressure steam without disassembly of the equipment. Parameters such as frequency and time of cleaning are optimized by measuring the actual residual amounts of product remaining on the equipment as found through swab, rinse, and other testing methods. For areas where cleaning may not be carried out effectively due to insufficient flow rate, a method to fill the system with a cleaning agent and holding it for a certain period time is applied.

After reviewing and organizing existing cleaning data obtained from the actual equipment used in the biopharmaceutical manufacturing, an evaluation of cleaning performance was conducted to confirm that the cleaning was effective in preventing cross-contamination, and to ensure consistent performance of the cleaning operation. For a process in control, the ability of the process to consistently achieve the desired level of quality (specifications) is called process capability (Cp). Cp is a simple, straightforward comparison of the spread of the process data (variability) to the spread of the specification limit for that process data. Basically, it is a measure of how well the data fit within the specifications. The calculation of Cp is shown in Equation 1:

\[ \text{Cp} = \frac{\text{Upper Specification Limit - Lower Specification Limit}}{6\sigma} \]

[Eq. 1]

Sometimes data are not centered within the specification range and are significantly closer to one specification limit than the other. In these cases, a modification of the Cp calculation is used that only looks at the distance of the mean to whichever specification is closest to the mean. This is called the process capability index (Cpk). Also, for data that have no lower specification limits (such as cleaning data), a variation of the Cpk can be used instead that calculates a Cp based on only one specification. This is the Cpu (upper) and is also a simple comparison of the spread of the data (its variability) to the distance from the data mean to the upper specification limit. In a cleaning process, the Cpu is determined using only an upper specification limit because cleaning processes are carried out so as to reduce the residual amount of pharmaceuticals, cleaning agents, etc., to the level below an acceptance limit. The calculation for the Cpu can be seen in Equation 2:

\[ \text{Cpu} = \frac{\text{Upper Specification Limit} - \text{Mean}}{3\sigma} \]

[Eq. 2]

When evaluating the cleaning process capability, therefore, the mean values and the standard deviations used in the formula should be those derived from the cleaning data, and the process capability index (Cpu) of the cleaning process will be defined by Equation 3:

\[ \text{Cpu} = \frac{\text{Cleaning Limit} - \text{Cleaning Data Mean}}{3\sigma (\text{of cleaning data})} \]

[Eq. 3]

In this study, the capabilities of the cleaning processes were statistically evaluated using the Cpu. The manufacturing equipment for antibody drug substance was classified into equipment groups based upon their manufacturing cleaning processes. First, the cleaning data of the products were converted into a percentage of their cleaning limits because these actual values are confidential and could not be used in this article. After that, the mean values, the standard deviations, and the Cpus were derived (see Table 1).

The bioreactor group, harvest group, and ultrafiltration/diafiltration (UF/DF) group had high Cpu values indicating that the capability of cleaning process was good. On the other hand, the Cpu values of the chromatography system
group and the purification tank group were lower compared to the other groups, although their data still fell below their cleaning limits.

The many horizontal and U-shaped piping pieces with smaller than 25.4 mm of diameter used in the chromatography system make these systems difficult to clean; this is considered to be the reason the Cpu value of the chromatography system group was not as high as the other groups. It is also presumed that the reason for relatively low Cpu value of the purification tank group was due to the relatively large variability in data, which was probably caused by various process tanks with capacity of over 2000 L and wide surface area that comprise this group.

A proposed Cpu-derived limit based on “overall cleaning performance”

Statistical evaluation of the capability of the cleaning process can be viewed from two directions. The first direction is whether the cleaning process is capable of removing the substance subject by cleaning to a level below a limit based on the acceptable daily exposure (ADE), which is synonymous with the permitted daily exposure (PDE), as used in the European Union. This viewpoint is suitable for evaluating if the target substances being cleaned can be removed to a level that ensures the safety of patient based on the cleaning limit of the substances subject to cleaning. This evaluation is particularly essential for commercial plants in which several items are manufactured.

Another viewpoint can be considered useful for evaluating the facility’s overall cleaning performance, regardless of the cleaning limits of the substances that are subject to cleaning; this approach is new to the pharmaceutical industry. The effectiveness of process evaluation based on “overall cleaning performance” will be examined in this section.

If Equation 3, which is used to derive the Cpu, is rearranged, a minimum desired Cpu could be substituted into the equation along with the known cleaning data parameters and a limit based on process capability calculated for use in all subsequent cleanings (Equation 4).

$$\text{Process Capability Limit} = \left(\frac{Cpu_{(Desired)}}{3\sigma}\right) \times \text{Mean} \quad \text{[Eq. 4]}$$

In other words, the desired Cpu becomes the starting point for calculating a limit for all residues on all product contact surfaces. For example, if the desired Cpu is 1.33, in Equation 4, it can then be used to define the analytical limits for swab sampling for all products. This approach would be particularly useful and easy to apply in a manufacturing facility where the analytical method is common (e.g., total organic carbon [TOC]), where all the manufactured products are similar (e.g., Immunoglobulin Gs that have a common molecular structure), and where the difference in cleanability between products is expected to be similar.

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Parenteral product quality is improving. Since 2014, when United States Pharmacopeia (USP) <790> “Visible Particulates in Injections” (1) became official, particle-related recalls of injectable products have dropped significantly. However, “I want to be cautious and not give all of the credit to USP <790>,” says John G. Shabushnig, PhD, owner and principal consultant at Insight Pharma Consulting and leader of the Parenteral Drug Association’s (PDA’s) Visual Inspection Interest Group. “There was a lot going on during this period including significant recalls from compounding pharmacies; however, I do think having clear guidance on inspection and acceptance criteria was a contributor to this drop.”

Publication of USP <1790> “Visual Inspection of Injections” (2) is another positive influence. Shabushnig says, “USP <1790> provides a more complete picture of good practices when implementing and operating a visual inspection program. It also clearly discusses a lifecycle approach to inspection, with an emphasis on continuous process improvement and using inspection data to drive that process. Defect prevention should always be the primary goal.”

In addition, there continues to be a shift toward lower acceptable quality limit (AQL) values for acceptance sampling after 100% inspection, according to a benchmarking survey (3) performed in 2014 by PDA. Shabushnig says, “This trend is especially true for critical defects, having moved from 0.10% to 0.065%.

More firms are classifying particles as critical defects despite an implied classification as a major defect, which would have a mean AQL of 0.65%, in USP <790>. The subsequent PDA benchmarking survey for difficult-to-inspect products also showed that many firms have not adopted the supplemental (destructive) testing specified for these products in USP <790>. Examples include reconstitution of lyophilized or powder products or dilution or filtration of opaque or strongly colored solutions.”

**Automated inspection**

Wider adoption of automated inspection ranks as another positive force on product quality. This effort begins with container production. “Aiming for zero defects in our pharmaceutical packaging production, we employ an automated inspection system (AIS),” reports Michael Feldhaus, director of Technology at Schott Pharmaceutical Systems. “This 100% visual inspection technology examines all key surfaces of our vials and cartridges and merges cutting-edge machine vision technology with our decades-long glass-forming expertise.”

Feldhaus explains, “Camera inspection allows for inline process control. The sensitivity and reliability of the system enable us to perform 100% cosmetic inspection for vials and pen cartridges, resulting in high-quality pharmaceutical containers. In addition, the data help us optimize process control.”

With quality control demands escalating continuously, both the software and hardware used for cosmetic inspection have improved significantly. “For example,” Feldhaus says, “we have further developed our AIS software, which creates a 3D image of the container based on visual material from multiple cameras with different light settings. This process allows the container surface to be analyzed in a more comprehensive way. Moreover, machine learning technology helps detect patterns and improve the process further. On the hardware side, higher processing power and improved illumination enable systems to provide more data and sharper images. In addition to using improved machinery, our employees regularly
take part in training to strengthen their overall quality awareness and ensure our products meet high quality demands.”

Makers of parenteral packaging components such as closures and stoppers also rely on automated inspection. Datwyler Pharma Packaging Division uses advanced 100% camera inspection technologies and improved lighting sources to ensure product quality throughout its manufacturing process. Increased processing power permits use of more powerful detection algorithms, which improve detection capabilities and minimize false rejects. As a result, “some of the most critical production defects have been brought to the lowest level ever recorded,” reports Dirk Vander Mierde, Datwyler’s site director in Alken, Belgium. Potential defects caught by the system include the presence of foreign matter, deformation, or damaged coating. In addition, any rejects undergo additional inspection to help identify ways to improve the process.

On parenteral packaging lines, automated inspection tends to be limited to high-volume operations due to capital and validation costs. As a result, manual inspection continues to dominate with approximately 50% of firms relying on it, according to the 2014 PDA benchmarking survey (3). Shabushnig reports, “Approximately 30% use automated inspection with the remaining 20% using semi-automated systems.” He notes, “This is actually a drop in the response rate for automated inspection since the 2008 survey (3). This does not, however, mean that fewer companies are using automated inspection; rather, there are differences in which companies respond to the survey each year. More importantly, the survey is structured so that each company/site has a single ‘vote.’ That vote counts the same if the company/site is making 10,000 or 100,000,000 units each year. If the results were normalized for units produced, I believe we would see more units inspected by automated systems. We should also note that manual inspection continues to be the reference visual inspection method in all of the pharmacopeias and that smaller-volume operations will continue to use manual inspection for the foreseeable future. Automated inspection does not ensure greater detection ability, and a well-run manual inspection process is very capable of delivering a high degree of security.”

**Improvements to inspection equipment**

Meanwhile, automated inspection continues to evolve and protect product quality with enhanced lighting, flexibility, container handling, and speed.

“LED lighting has provided a great improvement to our automatic inspection machine (AIM) in several ways,” reports Jose Zanardi, head of Vision Technology Engineering at Bosch Packaging Technology. LED lighting reduces downtime due to less frequent bulb changes and post-change verification. It also provides a consistent light level, eliminating the

[Image of automated inspection equipment]
need for the inspection machine to compensate for light degradation. Compared to the halogen lighting it replaces, LED illumination generates less heat, eliminating concerns about product exposure to potentially damaging temperatures and the need for time-out programming for lamps.

“LED lights offer both precision and flexibility,” says Christopher Nerreau, area sales manager at Laetus US, which introduced LED lighting for machine vision in 1994. Combining low cost and easy implementation, options address virtually any application with bicolored, ultraviolet, or standard LED illumination.

Higher resolution cameras and customizable software also enhance flexibility. For example, Bosch’s Halcon vision system in its flagship AIM 8 series provides a standard vision tool that can be customized to maximize identification of visual defects. Zanardi notes customized inspection algorithms are essential to protect the quality of parenteral products. He explains, “Most of the medicines produced today pose challenges for inspection due to product clarity, viscosity, and fill volume, as well as container challenges such as dual chamber design, increased use of plastic, and influence of siliconized components, which attract both product and foreign particles.”

Other new features on equipment from Bosch include a patented, dynamic puck material handling system. It eliminates glass-to-glass or glass-to-hard-surface contact and minimizes size changeover time via a semiautomatic puck exchange system. Finally, Bosch has developed a fourth-generation static division unit. The SD4 module inspects particles in motion and offers the highest reliability for solutions and light suspensions with easy-to-develop recipes and validation.

Despite advancements in software, off-line image storage and analysis, and inspection speed, automated inspection systems using machine vision still pose challenges related to tuning and validation complexity. “Machines also have difficulty in managing the ‘normal’ variation found in many container closure systems,” says Shabushnig. “This difficulty is especially true for molded vials, which results in a high false reject rate (i.e., acceptable units that the machine rejects to assure that true rejects are detected with sufficient sensitivity and certainty).”

In addition, challenges remain with line integration and interpreting inspection results. Shabushnig explains, “In most cases, a scratch and a crack look the same to a machine yet have differing risks to patients (critical vs. minor). This limitation makes analyzing reported inspection results difficult and often requires a reinspection of rejected units to assess the type of defects found in the batch.”

For optimum line performance, automated inspection must integrate with equipment before and after filling. Nerreau notes, “There is a wide variety of parenteral products requiring vision solutions. Some examples include: using color identification to recognize color-coded needles, pattern matching to identify missing products in the package, optical character recognition to identify expiration dates on vials, and serialization for security.” Each application poses challenges for machine integration.

Prior to filling, inspection equipment typically connects to exterior washing or capping machines. After filling, the typical connection is to container closure integrity testing equipment using high voltage or laser headspace or vacuum technology, or to a re-nester/re-trayer for syringe applications. “Ensuring proper container transfer with sensors to manage product flow is essential to the integration process,” says Zanardi. In projects where glass-to-glass contact must be eliminated, precise design engineering is necessary to assure that container handling and machine starts and stops do not damage the product or the machine.

“To perform complex image processing tasks in quality control environments, it is essential that the camera and lighting systems are tailored to the specific application,” says Nerreau, adding, “It is imperative for any machine integration to include extensive discussions and intensive consultations early on, along with a personal survey of the production environment.”

Next steps

With the industry focused on quality improvement, visual inspection continues to be a hot area, reports Shabushnig. A project at PDA is addressing visible particles in injectable products, with a current focus on improvements to the primary packaging materials. It seeks to better understand the risks as well as methods to detect and control particles in these components. This project is supported by both pharmaceutical manufacturers through the Pharmaceutical Manufacturers Forum and a number of primary packaging component manufacturers.

PDA’s Visual Inspection Interest Group was to meet in April 2018 in the United States and in Europe to discuss the draft revision of Annex 1 (4). “Changes included significant expansion of sections associated with visual inspection and container integrity,” says Shabushnig. In addition, PDA continues to provide hands-on training in the area of visual inspection in the US, Europe, and Brazil.

Meanwhile USP continues to review comments and suggestions for USP <790> and <1790>. “Current topics of interest include the selection and use of sampling plans for USP <790> and using risk-based methods to set alternative acceptance criteria for particles,” reports Shabushnig. “The Expert Panel responsible for these chapters is always interested in feedback to improve the understanding and use of these chapters,” he concludes.

References

Best Practices for Shipping Single-Use Systems

Shipping biopharmaceuticals in single-use containers requires a thorough understanding of the distribution cycle and potential transportation risks.

As single-use processing equipment becomes a more prominent part of biopharmaceutical development and manufacturing, a clear understanding of risk management and testing requirements are needed. Regulatory guidelines are not prescriptive, forcing manufacturers to develop clear strategies that will ensure that product safety and efficacy are maintained during shipment.

A thorough understanding of the distribution cycle and potential transportation risks is required. In this article, Elisabeth Vachette, senior product manager, and Jean-Marc Cappia, vice-president of marketing, both at Sartorius Stedim Biotech FMT, Aubagne, France, share with Pharmaceutical Technology some of the key issues and challenges involved, and how to meet them effectively.

**Regulatory issues**

**PharmTech:** Which regulations and standards govern long-distance shipping of liquids in single-use systems?

**Vachette:** Currently, there is no dedicated regulatory guidance on the subject. FDA, the European Medicines Agency (EMA), and other regulatory bodies require that companies have qualified processes and can prove that the process will meet the quality standards of the final drug product.

[Neither FDA nor EMA] provide very specific requirements. They want end users to be in control of their processes. What they say is that the process of drug making should be qualified, whether that involves filtration, bag or virus inactivation, transportation, or storage space during manufacturing.

It is up to end users to establish documented evidence providing assurance that processes are under control and meeting specs and defined quality attributes (i.e., that the process is stable, robust, and free of any leakage or contamination).

The Parenteral Drug Association’s (PDA) technical report TR66 recommends that shipping systems be qualified for intended use through “proper design and testing in consultation with a packaging engineer.”

Conditions for international shipment must be defined. They can be based on international standards such as the American Society for Testing and Materials’ (ASTM) D4169 or the International Safe Transit Association (ISTA) 3 series (Tables I and II). The level of severity for test conditions must be based on real-world shipping conditions. We recommend a holistic, four-step approach (Figure 1).

**Technical challenges**

**PharmTech:** What major technical challenges do pharma and biopharma companies face when shipping liquids in single-use systems over long distances by air or sea?

**Cappia:** The first and main challenge is preserving product integrity within the bag, and the robustness and integrity of the system. Any leaks or bacterial ingress must be prevented.

During shipping, bags can move, resulting in water hammer and stress. The challenge for the supplier is, first, to design systems that can pass these tests. Currently, single-use systems use better films and technologies than they did in the past, so the bags can more readily pass ASTM test requirements, which are very aggressive.

Once the integrity and robustness challenge is overcome, end users must monitor the shocks and temperature variations that the pharmaceutical
product can experience when it is shipped to its destination.

**Vachette:** For liquid shipping, there is a need first to understand the distribution cycle, what is really happening, and what kind of shipping transportation means you are using. By knowing the distribution cycle, process validation will integrate severe conditions over the normal distribution cycle in order to provide correct and meaningful qualification. This approach allows end users to validate processes in worst-case conditions.

ASTM’s testing involves worst-case conditions, and also requires monitoring that enables the complete traceability of product, which might include tracking temperature.

The responsibility is to define the distribution cycle. End users select a supplier of transport services and a means of transporting the product (i.e., dedicated shipment, during which product is passed in a controlled way).

For exceptions, they will use a dedicated truck with cold-chain management. The approach that is used depends on the transportation supplier, although our company offers contract supply chain management and testing services for this type of process validation.

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**Table I: International standards for shipping tests under worst-case conditions.**

<table>
<thead>
<tr>
<th>ASTM D4169 - Standard Practice for Performance Testing of Shipping Containers and Systems</th>
<th>ISTA 3 Series: General Simulation Performance Tests</th>
</tr>
</thead>
</table>
| **General Simulation tests covering a range of package types and distribution scenarios.** The user must choose from tests, alternatives, intensities, sequences, and specific procedures based on packaged-product and distribution characteristics. Applicable across broad sets of circumstances, such as a variety of vehicle types and routes, airplane, boat, rail, or a varying number of handling exposures. Tests are carried out sequentially on the same package. Distribution Cycles (DC): DC should be chosen close to the projected distribution, e.g.:
  - Preconditioning and conditioning
  - Handling: Manual and mechanical
  - Shock (Horizontal impact, Rotational flat drop and Edge drop)
  - Truck vibration
  - Low pressure (high altitude)
  - Compression and stacking
Three levels of severity (I, II, III) are described in the ASTM D 4169 | Designed to provide a laboratory simulation of the damage-producing motions, forces, conditions, and sequences of transport environments. Applicable across broad sets of circumstances, such as a variety of vehicle types and routes, or a varying number of handling exposures.

For example: 3E & 3H tests consist of seven to 15 individual tests that are carried out sequentially on the same package.

These tests simulate the handling and transit required in a road distribution network and cover truck transport only. They are composed of sequences, including, for example:
  - Preconditioning and conditioning
  - Shock (Horizontal impact, rotational flat drop and edge drop)
  - Truck vibration only
  - Compression (stacking) |

---

**Figure 1. Four-step testing approach.**
Table II: ASTM D4169's Distribution Cycle Number 12.

<table>
<thead>
<tr>
<th>Test name</th>
<th>Short description</th>
<th>Tests example for unitized load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule A: Handling</td>
<td>Manual &amp; mechanical handling determines the ability to withstand loading, unloading, stacking, sorting, palletizing operations</td>
<td>Example: Mechanical handling: - Fork lift handling – rotational flat drop test ASTM D6179 - Side impact test – horizontal shock on sides of the shipping unit ASTM D880 - Truck handling – ASTM D6055</td>
</tr>
<tr>
<td>Schedule D: Stacked vibration</td>
<td>Stacked vibration determines the ability to withstand the dynamic compression forces resulting from vehicle stacking</td>
<td>Example: - stacked load to be calculated and stacked system submitted to random vibration profile - ASTM D4728</td>
</tr>
<tr>
<td>Schedule I: Low pressure (High Altitude) Hazard</td>
<td>Estimates the potential impact of reduced pressure when the system is transported via aircraft.</td>
<td>Usual recommended test conditions: ASTM D6653 at a pressure equivalent to 4267 m (14,000 ft) for a period of 60 min.</td>
</tr>
<tr>
<td>Schedule E: Vehicle vibration</td>
<td>Subjects the load to a random vibratory profile</td>
<td>Truck vibratory profile ASTM D4728, Method A Air vibratory profile ASTM D4728, Method A</td>
</tr>
<tr>
<td>Schedule J: Concentrated Impact</td>
<td>Simulates anticipated low level concentrated impacts that are likely to be received by packages during sorting operations and in transit</td>
<td>Test method described in ASTM D6344</td>
</tr>
<tr>
<td>Schedule A: Handling</td>
<td>Determines the packaged product’s ability to withstand loading, unloading, stacking, sorting, and palletizing operations</td>
<td>Example: Mechanical handling: - Fork lift handling – rotational flat drop test ASTM D6179 - Side impact test – horizontal shock on sides of the shipping unit ASTM D880 - Truck handling – ASTM D6055</td>
</tr>
</tbody>
</table>

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Reportable Values: Where is the Variation Coming From?

Christopher Burgess

This article looks at a simple structured approach to assigning variance contributions and to assuring that the analytical procedure is fit for purpose.

The reportable value from an analytical procedure has three elements in its error structure: the error of the procedure itself, the error associated with the sampling of the batch, and the error associated with the manufacturing process itself. The first two errors need to be controlled and be sufficiently small as to ensure that any out-of-specification (OOS) result is unlikely to be from these causes. To do this, the developed procedure must enable the target measurement uncertainty (TMU), as defined in the analytical target profile, to be achieved on a routine basis via the analytical control strategy. The United States Pharmacopeial Convention (USP) Validation and Verification Expert Panel has been working on a new general chapter regarding analytical procedure lifecycle management (1–5).

For many existing procedures, however, the knowledge base regarding these three components is lacking. Therefore, one must resort to performing designed experiments to separate these variance components.

Consider the analysis of a drug product for an analyte, X, from an established manufacturing process and procedure that has a registered specification of 95–105% of claim. The USP analytical procedure uses a single sample from a batch and a singlet determination. This product has a history of frequent OOS results.

Examination of the last 10 batches, which are without adverse trend, reveals 100.0% is retained and 2.977 is replaced by 2.98. The process capability report based on these values is shown in Figure 1. Ten batches are used for illustrative purposes, and for reliable values of Cpk, Ppk, etc., many more batches would be needed.

Based on the available information, however, it would be expected that 9.3% of batches would be OOS. The issue now becomes one of identifying the size of the contributory sources of variance. In this instance, there are three: the analytical testing procedure itself, VT; the sampling process, VS; and the production process, VP. Because these sources of variation are independent, the total variance, V, is simply the sum of the individual variances.
One can design a simple experiment to estimate the various contributions by:

- Sampling and testing 10 batches once; \( V = \sigma^2_T + \sigma^2_S + \sigma^2_P \)
- From one batch, sampled 10 times, test each sample once; \( V = \sigma^2_T + \sigma^2_S \)
- From one sample, test it 10 times; \( V = \sigma^2_T \).

For this example process, the results are shown in Table I.

It is critical to estimate the size of variance contributions of the analytical testing procedure, the sampling process, and the production process.

Contributory variances can be estimated using simple arithmetic (Table II).

It is immediately apparent that the majority of the variation (59.4%) is coming from the process itself and about one-third from the analytical testing procedure. The sampling variance contributes only a little. One can calculate the individual standard deviations and, with the means draw, the overall picture of the variability (Figure 2).

From an analytical perspective, the ideal but unobtainable situation would be to a target measurement uncertainty of zero. Therefore, the question becomes one of how small a TMU for the procedure would be needed. In addition, would replication help to avoid OOS results due to the testing variance?

First, however, one should be confident that this simple approach is consistent by using a different approach.

Confirmation of the error structure using Monte Carlo Simulation

There are three components to the error structure coming from the test-
ing, the sampling, and the process itself. A value from each of the three distributions can be selected, at random, as shown in Figure 2 and for each of these values, the error associated with each value is calculated.

The analytical testing error, $e_T$, would be the mean (99.3) minus the value selected and similarly for sampling, $e_S$, and manufacturing, $e_P'$. These errors may be both positive and negative.

Then the observed reportable value would be $(100 + e_T + e_S + e_P')$. If the Monte Carlo Simulation is used (6), then the results from 1 million iterations should give data that closely match those found in Figure 1, which they do. The result is shown in Figure 3.

As the sampling and production variations are not controllable during testing, an attempt might be made to increase replication and/or to improve the target measurement uncertainty. However, Table III clearly demonstrates that increased replication does not give a major reduction in % OOS of the reportable values. Even if there were zero testing error, the predicted % OOS of the reportable values is still 4% (Figure 4).

**Conclusion**

It is critical to estimate the size of variance contributions of the analytical testing procedure, the sampling process, and the production process. In this simple approach, the analytical testing variance is estimated from the repeatability, which is smaller than the intermediate precision, which would be a better estimate. A more complex design can be made to estimate the intermediate precision.

In this example, the combined production and sampling variance is so large that the process will always produce more than 4% OOS reportable values in the long term, irrespective of the testing variance. The production standard deviation needs to be reduced to approximately 1% and the testing to the same; and the sampling standard deviation needs to be reduced to 0.6 before a Ppk of 1.1 is obtained, predicting about 0.1% of OOS reportable values. Control strategies need to be in place to achieve these values.

**References**

6. Companion by Minitab v5.1.1.0 PT
Outsourcing testing
PharmTech: Which aspects of testing and data collection can be outsourced for single-use shipping?
Cappia: We have qualified on ASTM standards and can supply technical data to provide a view of the regime and the constraints and stresses we have applied during testing, in terms of vibrations, shocks, and shakes.
In addition, when manufacturers are simulating shipping conditions, they can send us the bags to check for integrity. We can either make a pressure or ink tests on the bag, or perform bacterial ingress tests on the bags. We offer these services to support customer validation, since they must simulate shipping conditions and ensure that results are within the proper framework.

“The [Neither FDA nor EMA] provide very specific requirements. They want end users to be in control of their processes [and to provide evidence of this control].”
— Elisabeth Vachette.

The industry’s understanding of shipping requirements varies
PharmTech: Are most biopharmaceutical companies already aware of what they need to do to validate single-use shipping for liquid products, or are they leaving any vital steps out of the planning process?
Vachette: The level of understanding varies. Some companies, for example, the large biotech companies, are very well prepared and understand exactly what they need to include in their validation efforts. But that is not the case for all of the smaller and mid-sized manufacturers. As a vendor, we believe that we can play a role in educating manufacturers on what is required, and providing the testing services themselves if and when needed. PT

For more information on test methods, instrumentation, and approaches, please see the full-length article at www.PharmTech.com/pt/shippingsingleuse.
outsourcing outlook

CDMOs Driving Emerging Bio/Pharma Success

Jim Miller

CDMOs can claim credit for the robust growth of emerging bio/pharma financings.

Emerging bio/pharmaceutical companies are going through an unprecedented period of opportunity and growth and have contract development and manufacturing organizations (CDMOs) to thank for much of their good fortune.

Bio/pharma companies that are dependent on external funding have never enjoyed such a sustained period of funding support as they are now. Analysts who track the industry expect 2018 to be the sixth straight year of substantial new investment in emerging biopharma companies from venture capital, public markets, and partnering. Funding for emerging bio/pharma companies has traditionally been cyclical, with the positive portion of the cycle lasting three-to-four years at most. This continuous funding streak is nearly twice as long as is typical for emerging bio/pharma companies.

A number of factors have contributed to the explosion in funding for emerging bio/pharma companies, including:

- A plethora of new disease targets thanks to genomics and a better understanding of disease process
- An increased arsenal of weapons to aim at those targets with traditional small molecule and monoclonal antibodies being augmented by highly potent small molecules, antibody drug conjugates, and gene and cell therapies
- A favorable regulatory environment that offers faster routes to new drug approval
- A robust equity investment environment across the economy
- Aggressive partnering, in-licensing, and acquisition by global bio/pharmaceutical companies.
- A mature network of contract services providers that can get new drug candidates into clinical trials and end markets relatively quickly.

Individually and in combination, these factors have greatly changed the risk/reward equation for new drug development. Relative to what they could expect 10 or more years ago, investors in emerging bio/pharma companies today can put up less money and get proof of concept more quickly, for the following reasons:

- Most new drug candidates are highly targeted at narrow diseases, meaning that clinical trials can be smaller and faster, with less commercial infrastructure.
- Regulatory pathways such as the breakthrough therapy designation enable smaller clinical programs and faster approval times, while the 503(b)2 pathway for new formulations of older products may mean that only bioequivalence studies are needed.

CDMOs as enablers

While scientific research can discover targets and ways of attacking them, those discoveries are only valuable if they can be converted into physical products that can be safely and effectively administered to patients, and if that safety and efficacy can be demonstrated in clinical research. For that reason, CDMOs and contract research organizations (CROs) are the real enablers of success for emerging bio/pharma companies.

By relying on CDMOs, emerging bio/pharma companies can get a product into Phase I testing for $2–5 million and in one to two years from when they commence GMP-compliant development. Without the access to CDMOs, companies would need to invest at least $10 million in facilities and a similar amount on manufacturing, analytical, and quality professionals. It would take at least two years before that infrastructure could start making product, and much of that capacity would be underutilized.

In short, the presence of a robust CDMO industry probably reduces the cost of making the product by 50–75% and shortens the time to the clinic by half. Those time and cost savings accrue to the venture capitalists and public investors who back emerging bio/pharma companies. The amount of funding put at risk for any given company is much less, and the money and time expended on a product or company that is ultimately unsuccessful are much less. That means there is more funding available to back more companies with less risk.
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Symbiosis
The relationship between emerging bio/pharma companies and the CDMO industry is truly symbiotic: one could not exist without the other. Thanks to the economics cited previously, the emerging bio/pharma sector depends on CDMOs for at least 80% of its development and manufacturing requirements and is similarly dependent on CROs for their preclinical and clinical testing needs. CDMOs have enabled the formation of virtual companies with just a few staff overseeing a network of service providers.

On the other hand, the availability of funding for emerging bio/pharma drives the fortunes of the CDMO industry. Following the sharp decline in funding for emerging bio/pharma in the wake of the global financial crisis, many CDMOs hung on by their fingertips and some went out of business altogether. By contrast, in today’s environment, most are growing at double-digit rates and are sought after by private equity firms wanting to acquire them at valuations as high as 15 times earnings.

Emerging bio/pharma companies are much more important to CDMOs than they are to clinical CROs. The ability of CROs to reduce clinical research costs by absorbing large numbers of clinical staff from company payrolls and implementing advanced information technology made them valuable partners for global bio/pharma. By contrast, global bio/pharma have been much less willing to outsource their manufacturing operations.

Risks and opportunity
The two biggest risks to the emerging biopharma and CDMO industries would seem to be a downturn in macroeconomic conditions that would make investors more skittish about investing and a major change in the willingness and ability of the US healthcare industry to pay for expensive new drugs. Both of these risks are real. Many economists see the likelihood of a recession in the United States in 2019 or 2020; the Trump administration campaigned on the promise to bring down drug prices; and US corporations look to be getting more aggressive in managing healthcare costs, including the cost of drugs.

Nevertheless, CDMOs look well-positioned to ride the wave of emerging bio/pharma success into the foreseeable future. The year 2018 has started off well for new financings, and public companies have often been able to raise sufficient funding to last them for a number of years into the future. Further, while global bio/pharma companies have dominated new product approvals in recent years, thanks largely to their acquisitions and in-licensing, pipeline data suggest that more emerging bio/pharma companies are willing and able to remain independent entities.

Summary
At first, the capability of cleaning process was evaluated for an antibody drug manufacturing facility using the Cpu, which is one of the common methods to evaluate the process capability in quality engineering. Consequently, the authors succeeded in evaluating the capability of the cleaning processes for all equipment used in the actual production by classifying the equipment into groups. The study demonstrated that the cleaning process for bioreactor group, cell separation group, and UF/DF group had high process capabilities. It also indicated that the chromatography system group—which is a purification process with a combination of unit operations and having a structure that is difficult to clean—and the purification tank group had relatively low Cpu values compared to other groups, yet they still fell within their cleaning limits.

It is also generally known that in the purification processes of antibody drug substances the purified antibody proteins are likely to adhere onto the process equipment due to the process characteristics mentioned in this study and product properties, making it difficult to clean.

Acknowledgement
The authors would like to thank Prof. Shuichi Yamamoto of Yamaguchi University for his helpful suggestions and insightful comments.

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Q. Our company recently acquired several new production sites in Europe, Asia, and the Americas. As part of the integration process, we decided to harmonize our batch records. We appreciate that local regulations and differences regarding the type of production equipment we use may require some local adaptations and deviations from a standard template; however, we are faced with stiff opposition from many sites to change their batch record design. Can you advise on how best to convince everyone of the benefits of a harmonized template?

A. The integration you describe will without doubt require many changes to the documentation, and therefore, it is a sensible decision to think about harmonizing documents, such as batch records. You are correct that there will be differences in the equipment and the processes, even for the same product by the same synthetic method, but in different facilities. But, this in itself is not an impediment to creating a universal batch record template.

It is important to consider why batch record templates differ so widely. First, the workforce will be used to different styles of documentation. How much or how little detail do they require to perform a task? It is not unusual to find a 10-page document used for a process in one location to extend to 50 pages for the exact same process elsewhere.

Next, let us look at the style of the contents: Is it all text? Is there use of pictures or graphics? Is it all in a logical sequence? Is it in one language or in multiple languages? Does it require each page to be signed by five persons for each batch record, or is there just one signature page? All these styles exist, and they all are developed for specific reasons. It is thus important to understand these reasons in order to design a universally accepted template.

Having the opportunity to completely redesign the batch record template provides a unique chance to build in as many safeguards from a data integrity perspective as possible. This includes removing any ambiguity regarding what must be recorded, by who, when, and how. For example, the instruction ‘add 100 liters 10% NaOH over 1 hour’ should have fields for entering the actual values that should look like this:

<table>
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<th>Volume</th>
<th>liters 10% NaOH</th>
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<td></td>
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</table>

This technique makes it clear to the operators what fields to complete and how to enter the values correctly. The use of symbols and colors is encouraged (e.g., to highlight critical steps, warn of potentially dangerous substances, etc.).

This is also a superb opportunity to eliminate the ‘numeritis disease’ (i.e., the unnecessary and time-wasting use of highly complex numbering systems). Step 001 in the batch record should be followed by step 002, then step 003, etc. There is no need at all for having something like step 1.2.5.2.8a.

Depending on the level of automation in the plants, you may be able to move from paper batch records to electronic batch records. The latter will provide a higher degree of data integrity as much fewer manual entries of data will be required. Thus, the standardization of the batch record can indirectly also drive standardization of the computerized systems in your plants.

Now let us look at some indisputable benefits of having a standard batch record template rather than a free-for-all:

- Reviewing batch records for continued compliance with the regulations is facilitated across sites, countries, and continents.
- Extracting information for or verifying concurrence with the submitted dossiers (e.g., for new drug applications, marketing authorization applications, variations, post-approval changes, etc.) is straightforward and simplified.
- Batch record review by the qualified person (as regulated in the European Union) or the quality unit (e.g., for the purpose of batch release or audits) is streamlined.
- Extracting information from the batch records for preparing annual product reviews (or product quality reviews), or for the purpose of benchmarking is effectively repeatable and possible.

Every day a product can be released to the market earlier because of any of the above benefits can result in monetary benefits. And who is to dispute that advantage in your company?

In summary, if the regulatory compliance benefits of a standardized batch record template aren’t compelling enough, monetary benefits gained by earlier release of drug product will no doubt make it a straightforward decision.

Monetary benefits will outweigh the hassle of batch record harmonization, says Siegfried Schmitt, principal consultant at PAREXEL.

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