Technology Advances Streamline Bioprocessing

Development
Solving ADC Challenges
Reformulation Strategies

Manufacturing
Microneedle Array Patches
Contamination Control Programs

Analytics
Toxicology Studies

Operations
Limits of Light Obscuration

Outsourcing
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Peer-Review Research
Calculating Passing Probabilities for Content Uniformity and Dissolution Tests
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**PEER-REVIEW RESEARCH**

**Determining the Probability of Passing USP Content Uniformity and Dissolution (Immediate and Extended) Tests with CuDAL-Excel**

The article reports on the CuDAL-Excel program, a set of MS Excel programs transformed and extended from Bergum’s CuDAL version 2 SAS program, designed for industry practitioners to calculate the United States Pharmacopoeia passing probability of content uniformity and dissolution tests for both sampling plan 1 and sampling plan 2 scenarios, and for both immediate release and extended release requirements.

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**OPERATIONS**

52 The Limits of Light Obscuration

Light obscuration testing is the preferred method of sub-visible particle quantification but is not suitable for every preparation.

**OUTSOURCING**

56 Ensuring Smooth Tech Transfer of Bioprocesses to Outsourcing Partners

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NEWS & ANALYSIS

FROM THE EDITOR

10 How Fast Is Too Fast?
Will moving at “warp speed” to develop a vaccine impact efficacy or safety?

REGULATION & COMPLIANCE

REGULATORY WATCH

14 Modern Drug Manufacturing Key to COVID-19 Response
Policy makers seek to ensure supplies of new therapies and to limit shortages.

ASK THE EXPERT

62 Starting a Career in the Bio/Pharmaceutical Industry
Having a better understanding about compliance will be of benefit when looking for a job or for furthering one’s career, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

DEPARTMENTS/PRODUCTS

12 Product Spotlight
59 Pharma Capsules
61 Marketplace
61 Ad Index

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How Fast Is Too Fast?

Rita Peters

Will moving at “warp speed” to develop a vaccine impact efficacy or safety?

The rapid spread of the coronavirus is a reminder of the interconnected nature of global populations and economies. A few other realities also should be obvious. First, no single individual, company, or country can solve the pandemic crisis alone. Second, while getting a vaccine to patients quickly is crucial, decisions about quality and efficacy should be based on science, not political or public pressure.

The competition for vital medical resources in the early days of the pandemic illustrated how uncontrolled or misguided competition and anxiety can quickly overwhelm response to an emergency. Fortunately, collaborative efforts are shaping the development of treatments and vaccines. For example, the World Health Organization (WHO) is coordinating global efforts for vaccine development and clinical trials for treatment options.

The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership is a public-private effort to develop a framework to prioritize vaccine and drug candidates, streamline clinical trials, coordinate regulatory processes, and leverage assets to respond to the COVID-19 and future pandemics. More than a dozen biopharmaceutical companies have joined the National Institutes of Health (NIH), Foundation for the NIH, Health and Human Services Office of the Assistant Secretary for Preparedness and Response, FDA, Centers for Disease Control and Prevention, and the European Medicines Agency in an effort to advance the most promising vaccine and therapeutic candidates (1).

The need for a coordinated manufacturing strategy cannot be overlooked.

While groups are collaborating on development and clinical trial phases; the need for a coordinated manufacturing strategy cannot be overlooked.

For an industry used to development timelines counted in years, the COVID-19 vaccine and therapy development process is moving very fast. Sponsors of the leading vaccine candidates now in early clinical trials are expressing confidence that the product can reach patients by the end of 2020, months or years earlier than predicted by experts just one week ago.

To achieve that goal, manufacturing capacity for unproven vaccines must be created now, a risky prospect for the companies developing the capacity and for patients. Drug companies and contract manufacturers are accepting the challenge; governments and taxpayers may bear the financial risk.

In April 2020, AstraZeneca and the University of Oxford announced a development and manufacturing partnership. Johnson & Johnson announced manufacturing agreements with Catalent and Emergent BioSolutions for its vaccine candidate, as did Lonza with Moderna for its mRNA vaccine. Both Johnson & Johnson and Moderna have received funding from the Biomedical Advanced Research and Development Authority.

In late April, a Trump Administration plan—dubbed “Operation Warp Speed”—committed to make 300 million doses of coronavirus vaccine available by the end of 2020 (2). Details for this program, including which vaccines were going to be manufactured—were not available at press time.

After weeks of stay-at-home orders, social distancing, closed restaurants, high unemployment numbers, and bad economic news, optimism about the early arrival of a vaccine, as well as treatments such as Gilead Sciences’ remdesivir, offers some good news and excitement.

With anxiety for a resolution to the pandemic driving vaccine development activity, it is crucial that science-based information—from the global bio/pharma experts—should drive development, approval, and manufacturing decisions.

References
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Modern Drug Manufacturing
Key to COVID-19 Response

Jill Wechsler

Concerns about access to medicines and diagnostics critical to containing the coronavirus pandemic (COVID-19) and treating infected patients have broadened support for advanced pharmaceutical manufacturing and test methods. FDA officials have long pressed industry to adopt continuous manufacturing and online testing methods able to scale up quality production quickly and efficiently. The current pandemic has boosted support for such initiatives, as global health organizations and US policy makers recognize the importance of being able to produce millions of doses of any promising new treatments.

While the lack of personal protective gear and respirators has dominated the headlines since the pandemic outbreak, potential difficulties in ensuring sufficient supplies of newly discovered therapies and anticipated vaccines have moved to center stage. China’s prominence in producing key APIs for antibiotics and many common medicines, plus a recent move by the Indian government to halt the export of multiple drugs and drug ingredients, heightened concerns about the United States’ dependence on global supply chains. Rumors that an existing malaria treatment might be effective against COVID-19, for example, created a run on the drug, leading to notable shortages at some manufacturers.

These concerns have spurred calls for greater US investment in high-tech biopharma production systems. In announcing the COVID-19 Therapeutics Accelerator in early March to advance treatments for the pandemic, the Bill and Melinda Gates Foundation cited the need to quickly build up manufacturing capacity to test a variety of drugs. Gates further emphasized that the federal government should provide support for building production facilities now, as making such investments before knowing that a product will be used is excessively risky for manufacturers.

Funds to advance efficient drug manufacturing systems to ensure access to vital therapies and prevent shortages due to supply disruptions from China and elsewhere were included in the initial $8.3-billion emergency coronavirus funding package enacted March 5, 2020. FDA gained $61 million to support the development of new medical countermeasures and vaccines, of advanced manufacturing for medical products, and for monitoring medical product supply chains (1). The subsequent $2-trillion coronavirus aid and relief package approved March 27, 2020 similarly provided an added $80 million to FDA to advance the development and approval of medical countermeasures and vaccines (2). The legislation also directed FDA to use some of the funds to further the adoption of advanced manufacturing systems for medical products and to monitor supply chains for potential threats to access to medicines and APIs imported from abroad. To help FDA anticipate looming supply problems, Congress instructed manufacturers to send FDA information on where interruptions in supply affect APIs as well as drugs and extended such requirements to medical device makers during this public health emergency. To further address these issues, Congress provided $1.5 million for the National Academies of Sciences, Medicine, and Engineering (NASEM) to prepare a study on ways to strengthen the manufacturing supply chain for drugs and devices to avoid shortages.

Millions for manufacturing
Added support for establishing advanced biopharma manufacturing facilities is found in sections of the pandemic relief legislation, which provides some $30 billion for federal health agencies to develop countermeasures and vaccines, plus platform technologies to advance US production of new therapeutics, diagnostics, vaccines, and medical supplies. Congress specified that a portion of $3.5 billion for the Biomedical Advanced Research and Development Authority (BARDA) should be used to construct or renovate US-based next-generation manufacturing facilities. Similar directions are included in providing added funds for the Defense Research Advanced Projects Agency (DARPA) in the Department of Defense, building on its research programs related to advancing biopharma manufacture. Among other things, these initiatives have supported the development of RNA and DNA vaccines to fight infectious diseases such as Chikungunya and Ebola and to overcome manufacturing challenges to faster scale-up.

The pandemic legislation also provides $27 billion for the Public Health & Social...
Regulatory Watch

Services Emergency Fund managed by the Secretary of Health and Human Services (HHS) to develop countermeasures and vaccines in response to the pandemic. This includes building the Rapid Aseptic Packaging of Injectable Drugs (RAPID) consortium with a network of up to eight domestic facilities to rapidly fill and finish millions of prefilled syringes for delivering vaccines and therapies for COVID-19 (3). An innovative syringe developed by Api-Ject Systems utilizes existing blow-fill-seal technology plus an interlocking needle hub to provide low-cost, easy-to-use injectables for the Strategic National Stockpile.

Similarly, additional funding for the National Institute of Standards and Technology (NIST) supports programs to accelerate production of critical materials, build additional production facilities, ensure supply chains for vital ingredients, develop and train manufacturing workers, and return to the US the manufacture of critical conventional drugs (4). NIST has worked with biotech firms for several years to address challenges in developing more efficient and reliable ways to produce high quality cell and gene therapies.

These and other projects stand to assist manufacturers on accelerated timelines for testing promising COVID-19 therapies and vaccines looking to establish systems for fast, reliable manufacturing scale-up capabilities. At a “virtual summit” in March sponsored by the Biotechnology Innovation Organization (BIO), industry leaders cited the challenge in needing to expand manufacturing capabilities before knowing they have a viable product, and the fast launch of clinical trials for candidate vaccines aggravates those difficulties.

On many fronts, industry is rising to the challenge, with pharma companies partnering with smaller biotechs and federal agencies that offer innovative drug and vaccine candidates for established firms to test and produce. In March, Johnson & Johnson announced that a $1-billion partnership of its Janssen unit with BARDA planned to rapidly scale up vaccine manufacturing capacity to be able to supply over one billion doses of vaccine globally (5). Such fast expansion of production capacity will be needed for clinical trials slated to begin this fall and then to provide emergency use access to any promising product.

References
Bioprocessing advances improve product yield, cut costs, and streamline integration between upstream and downstream processes.

Over the years, many advances have been made in bioprocessing as biomanufacturers strive to increase yield, improve product recovery, enhance product purity, and streamline manufacturing. Innovations in technology and equipment for both upstream and downstream processing have led to more integrated and efficient processes, but there still remain manufacturing challenges that drive the need for further innovation.

**Upstream advancements**

Successful upstream bioprocessing innovations have focused on key areas, including:

- Increasing volumetric productivity through process intensification (high seed fed-batch, perfusion, and continuous culture technologies)
- Increasing cell-specific productivity and control of critical product quality attributes (CPQAs) via novel cell expression and inducer technologies with greater molecular and cellular biology understanding through systems biology
- Accelerating the overall process development timeline.

“These improvements have resulted in the ability to quickly advance from cell-line generation to clinical current-good manufacturing practices (cGMP) manufacturing with bioprocesses that are more productive and reproducible,” observes Brian Follstad, director, upstream process development, Catalent Biologics.

“There have certainly been a number of revolutionizing, innovative approaches in bioprocessing in different product areas,” says Vasily Medvedev, process development manager at Uncercells. “If we consider monoclonal antibody (mAb) manufacture, one of the key bioprocessing advances seen over the years relates to the use of high cell density perfusion cell cultures. This technology reduces the size of the bioreactor needed, directly influencing the overall footprint of operations, capital expenditure (CAPEX), and, subsequently, cost of goods.”

Furthermore, Medvedev says the use of design of experiment (DoE) techniques is a promising trend in the industry, when these principles are correctly applied to process development and scale-up studies. “In order to fully benefit from the use of DoE studies, representative scale-down models are paramount to ensure identification of high-performing small-scale process design with seamless transfer to commercial manufacturing scale, reducing development timelines (time to market), and costs.”

Looking at the past five years in upstream bioprocessing, Thibaud Stoll, global head of operations, biologics, at Lonza Pharma & Biotech, notes three
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main innovations that have impacted bioprocessing operations:

- Continuous improvements in cell expression systems, leading to processes with increasing titers, reaching or even increasingly exceeding the 10 g/L-level
- Continuous development and improvement of disposable bioreactors and associated equipment
- Development of digital tools as part of the digital transformation of biomanufacturing.

“These innovations have contributed to improving process robustness in general, lowering cost of goods and services and enhancing flexibility to respond to fast-evolving demand,” Stoll states.

Other innovations, such as media development, cell line selection, improvements to host cell lines, optimized vectors, and the introduction of high-throughput screening technologies, have also revolutionized upstream bioprocessing, adds Atul Mohindra, senior director, research and development, Lonza Pharma & Biotech. Mohindra also counts improved process-modeling tools, which have enabled a better understanding of the cell culture process as well as the development of more advanced technical equipment (e.g., single-use technologies [SUT], inline testing technologies) as important upstream innovations. “This has enabled the industry to develop more complex molecules, to significantly shorten the time taken to manufacture a first-in-human batch as well as to reduce the costs of a development program,” Mohindra says.

“Besides the latest generation of single-use stirred tank and rocking motion (RM) bioreactors, one of the most significant recent introductions has been alternating tangential flow (ATF) filtration,” remarks Gerben Zijlstra, global technology consultant, continuous and intensified biomanufacturing, Sartorius Stedim Biotech, who notes that ATF provides for much more efficient and cost-effective perfusion culture than previous methods. “It is also gentler on cells, resulting in higher cell viability and lower levels of impurities to process downstream,” Zijlstra adds.

“This technology has enabled tremendous intensification of mammalian cell cultures by allowing 5–10-fold higher cell densities compared to traditional fed-batch processing,” Zijlstra explains. By applying different ATF filter pore sizes, continuous upstream manufacturing can be performed as either a dynamic or continuous perfusion, where the product passes the filter and is direct captured using continuous chromatography; or it can be performed as concentrated fed batch (CFB), where the product is retained in the bioreactor and is harvested batchwise, he says. “The productivity of these intensified cell culture processes greatly surpasses those of existing fed-batch platforms. For CFB, titers of around 30 g/L have been reported, while for dynamic perfusions, 60 g/L (equivalent) titers were reported,” Zijlstra says.

Another recent innovation is the introduction of several online process analytical technology (PAT) tools, such as cell density monitors that use capacitance sensors, adds Thomas Erdenberger, also a global technology consultant, continuous and intensified biomanufacturing, at Sartorius Stedim Biotech. “These sensors allow real-time cell density monitoring of viable cells without having to measure density using traditional methods by taking a sample, risking contaminating the culture. This new method allows the automation of bioreactor feeding as well as cell bleeding using the sensor coupled with a supervisory control system. At Sartorius, we can place these monitors in any of our single-use bioreactors and RM bioreactors to fully automate the entire seed train and main bioreactor,” Erdenberger says.

Another PAT tool gaining traction is Raman spectroscopy. Previously, the key difficulty of using this technology was the need to “train” the mathematical models, the correlation of individual metabolites with the complex Raman spectra. “To solve this challenge, Sartorius recently launched a scalable Raman probe interface so these models are already preset in the 15-mL ambr [Sartorius] high-throughput mini bioreactors. This allows deep process insight and improved process understanding from early development, onwards,” states Erdenberger.

Meanwhile, the latest generation of depth filters has also been a powerful innovation for upstream bioprocessing, emphasizes Peter Levison, executive director of business development at Pall Biotech. “As bioprocessing trends have continued to evolve, SUT have offered an alternative solution to drug manufacturers to accommodate shifting drug profiles. Yet, this presented a new challenge when looking at the clarification step,” according to Levison.

In traditional stainless-steel facilities, centrifugation has been a widely adopted solution for clarification, but when working in smaller facilities that deliver higher cell densities, such as the newer SUT installations, centrifugation is no longer as feasible, Levison explains. “Not only is it costly to implement, requiring large capital and process investments, it also has a larger footprint and does not scale down so easily. So, while centrifugation is well suited for 10,000-L stainless steel bioreactors and other large facilities, it is not an ideal solution for facilities based around 2000-L single-use bioreactors that many manufacturers use today,” Levison asserts.

Initially, depth filters offered an alternative to centrifugation with some performance limitations—traditionally handling cell densities of up to around 20 million cells/mL. “With advances in cell culture and titer increases, we are routinely pushing cell densities up towards the 30 million cells/mL mark, and this is where advanced depth filters deliver the next generation of clarification. The high-performance platform is flexible to support semi- to fully continuous bioprocessing, allowing users to process more product per unit of bioreactor volume. To achieve this performance improvement, two dual-layered depth filtration stages are combined into one clarification step
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with a flexible chassis to accommodate the capsule configuration needed to deliver consistent filtrate quality in a significantly decreased footprint,” Levison states.

For gene therapy products, the traditional technologies for cell culture and virus production are not suited for commercial-scale manufacture, notes Tania Pereira Chilima, deputy technology officer at Univercells Technologies. “This is not only due to capacity constraints, as these flasks are only compatible with a scale-out approach, increasing costs, and CAPEX, but also due to the laborious nature of operations associated with these technologies and the lack of control over critical process parameters (e.g., pH, dissolved oxygen). This poses some regulatory concerns related to process reliability and reproducibility. Moreover, there is an industry-wide shortage of skilled labor, which means that labor-intensive processes are not as feasible due to resource constraints,” Chilima states.

The use of bioreactors for viral vector manufacture poses several benefits, making cell culture and virus production possible in a highly controlled microenvironment. Moreover, these systems are highly scalable and can benefit from the incorporation of PAT to increase the level of process controlwhile simplifying operations. The most advanced bioreactors for cell culture and virus production incorporate principles of process intensification to enable high-titer and low-footprint virus production, Chilima says.

“Technology improvements in process intensification and connection of unit operations have enabled manufacturing updates to run more efficiently and produce higher yields in less time and space, reducing the amount of capital investment,” concurs Darren Verlenden, head of bioprocessing, MilliporeSigma.

“In upstream, we’ve seen that utilizing perfusion technology can increase cost efficiencies, decrease risk, and enhance manufacturing flexibility. Between 50–60% of companies are already exploring or have implemented perfusion technologies for seed train or production bioreactor steps,” he explains.

**Downstream improvements**

Innovations in technology and equipment have also benefited downstream bioprocessing. Recent innovations, which include acoustophoresis (ultrasonics) cell separation and high-precision microfluidics for label-free cell selection, in-line cell washing, and rapid gene delivery, have resulted in significant productivity gains, states Jenna Balestrini, head of precision medicine and cell bioprocessing at Draper, a Cambridge, MA-based not-for-profit engineering firm.

To accomplish cell separation on a clinical blood sample, for example, Draper developed a system that performs acoustophoresis in a high-performance microfluidic device compatible with a range of patient materials and input volumes. This system bypasses the need for centrifugation. “The module continuously and rapidly removes interfering cell contaminants without compromising cell health. With less handling than conventional approaches, acoustophoresis improves end-to-end yield of cells and accelerates delivery to downstream steps in the process,” according to Balestrini.

In the gene therapy space, Draper has developed a microfluidic transduction module that can co-localize viral vector around cells, increasing viral-cell interaction while using about half the viral vector typically needed to achieve high transduction efficiency. This allows for more controlled viral gene delivery. The system can transduce at standard efficiency levels in 90 minutes using a wide range of vector sources, Balestrini says.

And finally, to allow for a variety of payloads, such as ribonucleoprotein, mRNA, or DNA to be introduced into the cell without the need for viral vectors or even activation steps, Draper has engineered a practical continuous-flow electroporation module and in-line buffer exchanger that uses high-precision microfluidics to tightly control cells exposure to electrical signal, increase throughput, reduce manual-touch labor, and allow for in-line wash steps, Balestrini explains.

“Groundbreaking innovation is seen across different product classes in downstream processing,” adds Medvedev. “In mAb manufacture, the advent of continuous purification processes—namely, chromatography—has enabled significant improvements in process productivities, yields, and utilization of key materials (e.g., protein A resin).”

Chilima further adds that in the gene therapy field, the use of alternative media (e.g., monolithic or membrane chromatography, as opposed to traditional bead-based separation) has proven to increase the dynamic binding capacity (DBC) and reduce processing times as this alternative media can be operated at higher flowrates. “Moreover, the use of membrane and monolithic chromatography systems with advanced separation modalities has enabled a consistent increase of resolution in the separation of empty and full capsids to be achieved with this type of media, which is critical in gene therapy manufacture,” Chilima says.

The innovations in downstream processing have had similar impacts as in upstream processing innovations, namely the development of continuous manufacturing—in particular, continuous chromatography—that can increase facility throughput while reducing costs and the further development of disposable equipment and digital tools, Stoll says.

“Improved in-silico and in-vitro modeling tools, which, when combined with high-throughput screening technologies, can increase our capabilities and reduce time,” says Mohindra. Further downstream processing innovations he identifies are the introduction of end-to-end, single-use solutions for clinical manufacturing (e.g., prepacked columns, single-use flow paths) and the development of new, high-binding capacity resins.

Erdenberger further highlights the development of newer resins as a particularly beneficial innovation. “Firstly, for the capture step, improved (Protein A) resins with higher binding capacity and improved caustic compatibility have allowed for substantially improved down-
stream processing productivity, reduced cost of goods, and improved bioburden control,” Erdenberger observes. “Currently, even ‘closed, sterile’ chromatography seems to be within reach with gamma-irradiated pre-packed columns, enabling continuous, no/low bioburden chromatography operations. In parallel, continuous downstream technologies such as multi-column and simulated moving-bed chromatography have matured and are increasingly implemented to intensify downstream processing,” Erdenberger adds.

For the polishing steps, substantial improvements in mixed mode resins, membrane adsorbers, and associated equipment are now, and increasingly, allowing for flow-through polishing as a highly efficient mode of operation, Erdenberger states. He further explains that, for the virus removal steps, methods that allow for continuous virus inactivation and virus filtration are being introduced and that continuous methodologies are even available for crossflow filtration.

“These technologies result in continuous or semi-continuous product streams to the next unit operation in a process and in much more efficient chromatography at reduced media cost. Processing is also more rapid. When connected with certain upstream operations such as perfusion, the downstream process can be directly connected for a continuous transition from upstream to downstream,” Erdenberger notes.

**Integrated efficiencies**

These advancements in both upstream and downstream processing have had a mixed impact, but overall a beneficial one. While creating the requirement for more well-thought-out and nuanced processes, they have also allowed for closer integration between upstream and downstream. “Although these innovations have increased bioprocess complexity, they have contributed to substantially reduced overall costs, time, and risk in generating drug substance and product. In some bioprocesses, for example, initiating culture harvest while the production culture is still running over the course of a few days (or weeks in continuous) allows purification to begin earlier when compared to historical approaches. Furthermore, on-line analytics and product attribute control strategies permit the measurement and real-time adjustment of CPQAs during a batch, allowing for a more efficient method of reproducibly producing drug substance,” remarks Follstad.

“Continuous improvement and interplay between bioreactor productivity and advancements in downstream unit operations are increasing efficiency and streamlining manufacturing,” adds Verlenden. “An initial response to upstream intensification includes single-pass tangential flow filtration for downstream debottlenecking. In new facilities, implementation of continuous capture and flow-through polishing can remove process constraints while enhancing facility fit by reducing buffer requirements by up to 47%,” Verlenden states.

Continuous biomanufacturing will play an integral role in better integrating upstream and downstream operations over the next five years as manufacturers look to suppliers for integrated solutions because they are thinking holistically about their processes while visualizing future scale up, Verlenden explains. “Our customers expect that, in five years, 40–50% of their processes will incorporate continuous capture and flow through polishing technologies, though adoption of fully continuous processes from end-to-end is likely to be further out,” he estimates.

Hearkening back to traditional batch processes, Levison notes that traditional processes are inherently more disconnected step by step. In the upstream, more effective clarification with advanced depth filtration offers a flexible solution. “Users can work towards a semi- or fully continuous processing approach with continuous streams of feedstock, which also impacts the ability to integrate downstream processes.

With the ability to integrate the downstream, manufacturers can create more efficient processes, increasing product quality, saving time and money, and maximizing overall productivity and facility utilization,” Levison says.

Another development of note on the cell-therapy biomanufacturing front, meanwhile, is the integration of a complicated multistep process into a closed, modular, automated benchtop system that enables effective, safe biomanufacturing that can be used in a hospital (point of care) or in a central manufacturing facility, says Balestrini. Current instrumentation and methods for manufacturing cellular therapies are expensive, time consuming to use, difficult to scale, and limited in their ability to effectively deliver genetic material, Balestrini notes. “A modular system is emerging as an industry gold standard,” she states.

Yet, despite these advances in bioprocessing, additional work is still required to ensure that upstream and downstream processing are smoothly integrated, interjects Medvedev. He points to the struggle that current single-use downstream processing technologies for antibody purification are coping with—namely the increasing titers achieved in upstream processing. In gene therapy, on the other hand, the high performance of membrane, beads, and monolithic chromatography systems has caused a mismatch between what upstream processing is able to deliver and what downstream operations are able to purify.

“This is caused by the fact that current technologies for viral vector purification were adapted from the protein industry, which makes them extremely oversized for viral vector applications. The DBC achieved using the current resins available is high with respect to the product harvested in upstream processing. This may cause manufacturers to pull different batches together with intermediate freeze steps, which has disadvantages in terms of yield loss, cold storage space, batch-to-batch variability concerns, and overall process complexity,” Medvedev explains.
Finding the right targets and crafting an effective molecule has proven to be much more difficult than many researchers had expected at the outset of ADC research, adds Justin Sweeley, senior technology manager, biologics at Novasep. “It was initially understood that finding a good target antigen for an ADC-based compound would require a target with rapid internalization once it had reached the cell,” he notes. “The result,” he says, “was that in many cases targets that were ineffective for monoclonal antibody (mAb) therapies because of rapid internalization became perfect targets for ADC therapies.” This picture became much more complex upon the addition of payloads to these mAb candidates, however. This issue can be seen most clearly in the fact that the clinical trial landscape includes well over 50 different payload candidates, but only seven have successfully made it into commercial production, according to Sweeley. “As a result, there has been a recent shift in the industry to recognize that when trying to predict ADC effectiveness, researchers must take into account the target epitope, the physical attributes of the payload on the mAb once conjugated, and also the effect of the payload mechanism of action on the specific kind of cancer being targeted,” Sweeley observes.

AstraZeneca takes an empirical approach to target and payload selection, keeping the patient population top-of-mind, using data from clinical trial re-
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sults and non-clinical data to help validate target and payload selection. “With potency being driven by the strength of the warhead, we optimize the therapeutic index of our molecules by selecting the most favorable drug-to-antibody ratio (DAR) in designing our ADCs,” Coats says. “We believe,” he adds, “that establishing target rationale and strategy early on are key to determining the right payload.”

Is site-specific conjugation important?

Site-specific conjugation is looked at as the second generation of ADC conjugation techniques. “The homogeneity of these molecules allows for much tighter control at both the manufacturing and characterization levels,” Sweeley explains. Better definition for an ADC means that its therapeutic index can be further improved, adds Bertholjotti.

Additionally, the technology allowing for site-specific conjugation has evolved dramatically from the Thiomab concept piloted by Genentech to current techniques allowing site-specific conjugation with any native mAb, such as Synaffix’s glycogen modification techniques or Ajinomoto’s AJI-cap technology, Sweeley remarks. Many of the ADCs in preclinical and clinical stages are based on site-specific conjugation technology of one form or another, Bertholjotti adds.

On the other hand, Sweeley notes that even though more site-selective ADCs are expected in the future, ADCs with stochastic conjugation can still be successful. Coats agrees that site-selective conjugation does not seem to demonstrate significant differences in terms of clinical activity and safety when compared to classic non-site-selective conjugation. In fact, the seven commercially approved ADCs are not based on site-specific conjugation.

It is possible, according to Sweeley, that the lack of a commercially available site-specific conjugated molecule is just a result of the head start that stochastic conjugation has had, but it is also possible that simplicity in manufacturing and homogeneity in analytic testing methods doesn’t directly result in better outcomes for patients.

Linker technology matters

Finding an ADC that is better than standard therapy or that provides a solution to an unmet need definitely represents a challenge, just as with other drugs based on different approaches, according to Bertholjotti. The linker chemistry is an important component of ADC and has a significant impact on performance.

“Linker chemistry plays a critical role in in-vivo stability, but initially was assumed to have a passive role with the exception of either being stable or labile in the acidic cytosolic cellular environment,” observes Sweeley. More recently, however, he notes that there has been growing recognition that the linker plays an active role in conjugate hydrophobicity and therefore stability of the ADC as a whole.

Linker chemistry is an important component of ADC and has a significant impact on performance.

The technology, according to Coats, has advanced and matured during the past 20 years to a point where linker technology is stable and molecules in development demonstrate low levels of deconjugation in patients. Both protease cleavable and non-cleavable linkers are in development and on the market.

Classic conjugation chemistry approaches include maleimide and N-hydroxysuccinamide-ester moieties (Seattle Genetics, Roche, and Pfizer). There are also various newer technologies for linkers, with some, Bertholjotti comments, at the proof-of-concept stage and others already in preclinical evaluation.

An example pointed out by Sweeley is the use of non-natural amino acid-based click-chemistry (Ambrx and Sutro). “To my knowledge, these technologies have clearly simplified the conjugation process, but have not shown a clear improvement in product effectiveness in the clinic,” he states.

Undesired immune responses

ADCs are designed to be more selective than traditional chemotherapy agents. The mAb enables targeting of cancer (or other disease) cells where the payload is delivered with high selectivity, thus reducing the systemic toxicity in comparison with standard chemotherapeutic drugs.

Unfortunately, undesired immune responses have presented a problem that has been difficult to overcome. These responses are largely due to the massive number of variables being examined and the relatively small number of clinical trials going on, according to Sweeley. “Many of the warheads being investigated for ADCs induce immunogenic cell death, which may enhance anti-tumor immunity,” adds Coats. He also observes that there are recent examples demonstrating clinical activity with a combination of an ADC with PD-1 inhibition.

“In the process of taking any ADC through the approval process, it is necessary to look at the mAb, the linker, and the payload chemistries individually, the ADC as a whole, and the payload and linker residues after the ADC has been internalized and digested within the cell. The end result is that for each ADC trial, researchers must monitor all of the normal undesired immune responses that occur during any oncology trial, but then try to attribute the cause of any that are observed to one of the five different potential sources,” Sweeley explains.

“Factoring these additional considerations into the normal variables of any trial, such as the specific cancer type, patient population, and level of pre-treatments, etc., the picture becomes...
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incredibly complex. Even after 20 years of clinical testing, the issue is still not fully understood,” he concludes.

**Lower-than-expected therapeutic window**
The primary issue affecting ADC approvals today, according to Sweeley, is the lower-than-expected therapeutic window of these therapies. “If the therapeutic window of ADCs were as large as people expected when ADCs first came to light, then many more approvals would already be on the market,” he asserts. This window has proven to be much more complicated than originally hoped, however, and therefore the clinical impact less significant than originally imagined.

Here again, the complexity of ADCs themselves is the main problem. For instance, Sweeley notes that if an innovator company wants to test a new conjugation method, they might choose a mAb and payload pair that have already shown success in the clinic. Similarly, a mAb company with a new antigen target is likely to use an established conjugation approach (e.g., that for Adcetris) to lower their risk. “The best molecule, however,” Sweeley explains, “might be a combination of multiple new technologies that are too risky to investigate for a small company with a limited budget.”

**Complex supply chain**
The supply chain for ADCs is highly complex as well. ADCs are unique in that their manufacture is an amalgamation of classical small-molecule production and traditional mAb manufacturing with the added complexity of highly potent drug manufacturing. “All three characteristics are complex on their own, and combining them brings the complexity to a level where it is no surprise that the vast majority of ADCs are manufactured by outsourcing partners,” Sweeley says.

For the most part, he notes that innovator companies treat the manufacturing of an ADC as three separate processes:
- mAb manufacturing using traditional mAb techniques
- Payload synthesis using traditional highly potent synthesis techniques
- ADC conjugation using specialty contract manufacturing organizations capable of both working with both biologics and highly potent payloads.

“Taken individually, all three of these steps are actually defined quite well and have been orchestrated successfully for a long time. But because ADC manufacturing requires all three to happen together, any delays or issues in one process will necessarily affect the other two. The reality, therefore, is that ADC supply-chain management is one of the most complex processes in the pharmaceutical industry and must be managed by an experienced team who can mitigate risks whenever possible,” observes Sweeley.

Bertholjotti agrees. The supply chain for ADCs is complex and requires specialized companies to manage different steps in a safe way and with the necessary quality. “If the supply chain is not properly managed, delays and supply issues may arise. Therefore, compromises related to the supply chain can result in critical impacts on timelines and costs to bring a drug to market,” he asserts.

**Support from FDA**
FDA has shown willingness to work closely with sponsors to ensure that ADCs that truly benefit patients are brought to market expeditiously, says Coats. For example, he comments that AstraZeneca’s ADC Enhertu (developed in collaboration with Daiichi Sankyo) demonstrated significant benefit in a high unmet-need cancer population. FDA approved Enhertu four months prior to the FDA goal date for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. Enhertu is manufactured using site-selective conjugation and contains a cleavable linker technology that releases a warhead with bystander activity. It has also shown encouraging clinical activity in other HER2-driven cancers.

**Prudence and integration are warranted**
Over the past decade, awareness of these issues has increased dramatically, leading to the development of more optimized molecules. Even so, Sweeley emphasizes that the complexity of the space means that it is still prudent to go slowly and only tackle one challenge at a time. “Progress is therefore slow, but continually happening. Each success creates a new platform for companies to reach out a little bit farther. And as the industry matures, the rate of success will
increase, just as it has in every other area of pharmaceuticals,” he asserts.

Novasep has strong expertise in highly potent compound synthesis and for the past three years has brought this expertise into the realm of ADC conjugation, Sweeley notes. “Our focus has always been on producing the highest quality materials by developing the simplest possible procedures and coupling them with world-class analytics. The end result of these efforts is a simplification of the payload synthesis and conjugation steps along the supply chain, enabling rapid development of the two most complicated parts of the manufacturing of ADCs,” he states.

Since 2006, Lonza has been establishing a center of excellence for the development and manufacture of ADCs. Today the company offers an integrated solution, which helps to reduce the challenges presented by such a complex supply chain, according to Bertholjotti. “Integrating offers such as that offered by Lonza represent a competitive advantage. They afford ADC developers with better predictability of timelines and costs, along with substantially reduced complexity and supply risk,” he says.

AstraZeneca is developing novel ADCs and building a library of payloads using its antibody engineering expertise for site-specific conjugation and next-generation ADCs. “ADCs form one of AstraZeneca’s key oncology scientific platforms, along with immuno-oncology, DNA damage response, and tumor drivers and resistance mechanisms. Within these platforms, multiple technology and scientific options offer great potential to yield effective medicines for cancer patients,” Coats says.

**Growth expected despite the challenges**

As more ADCs are approved commercially, Sweeley believes a roadmap will be established for other companies to follow, leading to more success in the near future. “In the last 12 months alone, the number of approved ADCs on the market has more than doubled, and I would expect that this track record will be followed by a sizable increase in the amount of research being put into the molecule discovery and preclinical trial stage,” he observes. “With the healthy increase in candidates being brought into the preclinical stage, it is only a matter of time until some of those candidates make it through the rigorous demands of clinical testing and reach the market in the not-so-distant future,” Sweeley concludes.

The increased number of ADC candidates in the pipeline in combination with ever improving knowledge and the further development of new conjugation technologies will result in an increased rate of approvals, agrees Bertholjotti. Lonza expects that the number of ADC molecules will in fact rise at a 10% compound annual growth rate until 2029.

**Reference**

Reformulation strategies can provide drug developers with a head start to achieve promising options that benefit the patient.

A recent study has estimated the mean cost of developing a new drug and bringing it to market is $1.3 billion (1). Given this high investment value, the fact that drug development is fraught with potential failure and the increasing complexities of developing difficult-to-handle novel chemical entities, reformulation strategies can provide developers with promising options.

“Due to the high costs of drug development, as well as the high rate of clinical failures, it’s vital that pharmaceutical companies evaluate formulation opportunities for every approved or late-stage clinical product to determine how its commercial lifecycle can be optimized,” explains Paul Spencer, head of Pharmaceutical Polymers and Services, Evonik Health Care. “To minimize regulatory risk and accelerate speed to market, it is common for pharma companies to seek initial approval for products with a simple lead formulation followed by the introduction of superior formulations that can expand the patient population or enhance safety and efficacy.”

Getting a head start
“Reformulating an existing drug gives developers a head start, rather than developing a whole new drug from scratch,” says Jeremy Drummond, senior vice-president of Business Development, MedPharm. “This approach cuts product development times because studies can often bridge to those of previous regulatory submissions in particular with regard to non-clinical data.”

“One of the main benefits of reformulating drug products is increasing patient adherence to medicines,” adds Henny Zijlstra, director, Commercial Development, Lonza. Pointing to research from the National Institute for Health and Care Excellence (NICE), Zijlstra reveals that up to half of all patients prescribed medicine for long-term conditions do not take the medicines as intended (2). “Drug developers can help make it easier for patients to take medicines by, for example, changing the tablet or capsule size or geometry to make it easier to swallow or making it so a drug does not need to be taken strictly with or without food,” she says.

Additionally, beyond patient compliance, reformulation strategies have the potential to boost rates of brand preference, notes Spencer. “Reformulation may even help extend the product’s commercial lifecycle through the use of proprietary formulation technologies that can generate outcomes, which are difficult for prospective generic rivals to replicate,” he states.

Reformulation strategies
There are numerous reformulation strategies that are currently employed by the bio/pharma industry, with each offering a different way in which the patient experience can be improved from the original formulation. Examples of reformulation approaches include the following.

Modifying the original release profile. Most reformulation strategies that are pursued by developers of oral and parenteral dosage forms are based upon the modification of the original release profile, notes Spencer. “For oral solid dosage forms, functional excipients can be used to reformulate a product into dosage forms, such as multiparticulates and matrix tablets, to improve product performance,” he says.

Additionally, the drug release profile can be modified by using formulation technologies, which can help improve targetability and oral bioavailability. An example of a strategy to improve bioavailability is through the use of amorphous solid dispersions (ASDs), adds Deanna Mudie, principal scientist, Bend Research, Lonza.

“Enhancing the bioavailability can reduce the dose and remove the food label requirement that calls for patients to strictly take the product with or without food, which can improve patient safety,” explains Mudie. “Food labels may pres-
ent challenges to patients with trouble swallowing. Additionally, the food label sometimes creates further challenges for patients who have to take medication without food, causing them to skip meals or eat at inconvenient times.”

Other examples of reformulations of oral dosage forms that have been shown to improve patient adherence include minitablets or orally disintegrating tablets (ODTs) that offer improved taste sensation or swallowability for pediatric populations, confirms Spencer.

**Changing the route of administration.** Administering drug products via an alternative route is another reformulation approach that can overcome limitations of the original form. “For example, converting from oral to inhalation delivery may allow developers to mitigate side effects associated with the drug interacting with the gastrointestinal (GI) tract,” says Mudie.

“For some small molecules and peptides, it is possible to change the route of administration from oral tablets to injectable microparticles and implants,” adds Spencer. “There are a range of successful reformulation examples in this regard, such as a shift from orals to extended release, injectable dosage forms to enhance the treatment of schizophrenia, opioid, and alcohol addition, as well as contraception therapies.”

However, careful consideration is required when reformulating oral dose products as topicals, cautions Drummond. “In this circumstance, the route of delivery is significantly different, and formulation composition can have a major impact on efficacy as well as chemical and physical stability,” he says.

**In-vitro models** that are based on relevant human tissues to provide results that are directly relatable to clinical outcomes and can also provide answers to specific research questions can help to optimize reformulations, asserts Drummond. “Using these models often leads to novel discoveries that can extend existing patents, making reformulation an attractive option for drug companies,” he states.

**Reducing dose frequency.** Injectable microparticles that use the biocompatibility and resorption attributes of lactide/glycolide polymers can help to reduce administration frequency or enable localized delivery of drugs, reveals Spencer. “Lactide/glycolide polymers have attained decades of literature in precisely controlling the rate of drug release from microparticles over weeks, months, or a year or more following a single administration,” he says.

“Drug developers may also reformulate drug products as controlled-release versions,” adds Zijlstra. “This method can assist in reducing the dosing frequency, thus reducing the pill burden on patients.”

According to Spencer, ocular drug delivery is currently experiencing intense focus in terms of reformulation. “In ocular drug delivery, it is a therapeutic priority to minimize the number of required intravitreal injections per eye,” he explains. “Here, pharmaceutical companies are developing drug-loaded implants that can safely resorb via hydrolysis after months of drug delivery.”

**Combination products.** Comprised of two or more components in a single entity, combination products can enable develop-
operators to consistently maintain concentrations of API, minimize adverse effects, and reduce the number of dosing units required, confirms Mudie. However, there is the possibility that the single unit may be too large for the patient to swallow, she warns.

**Liposomes.** “Liposomes have also played a significant role in the successful reformulation of drug products,” says Spencer. “Decades-old cancer drugs re-formulated into liposomes and pegylated liposomes are therapeutically efficacious with improved toxicity profiles, better cardiac safety, and less side effects. Antifungal liposomes also show reduced toxicity along with extended-release performance, which results in longer retention times of the drug in tissues.”

Additionally, through reformulating pain drugs into long-acting liposome preparations, it is possible to reduce the frequency of epidural injections required, Spencer adds. “In all, several drugs re-formulated into liposomes have been strongly preferred to the original dosage forms,” he states.

**The target patient profile**

“When considering drug reformulation strategies, the target patient profile can play a role in developing the most effective product,” asserts Zijlstra. Giving an example, she explains that in the case of geriatric patients, who can have issues swallowing larger tablets, it may be beneficial to reformulate a drug product into a multi-particulate or sprinkle-capsule form, thereby enabling the patient the option to sprinkle the medicine onto food or in water.

“Reformulation strategies can be particularly beneficial to a range of chronic diseases and patient population sub-sets, such as pediatrics or geriatrics,” agrees Spencer. “Improving rates of brand acceptance amongst patient subpopulations, such as pediatrics, are also a key focus of reformulation strategies.”

For Drummond, the needs of the patient must be considered just as much as the chemical and physical properties of the drug in question, irrespective of whether it is a reformulation or a new chemical entity. “These factors all feed into the target product profile,” he adds. “In the case of topical reformulation, transforming an oral product to a topical formulation can often mean moving from systemic delivery to local delivery, which is important to consider when assessing the target patient group.”

In terms of specific disease area, prostate cancer patients have been shown to improve compliance after reformulation of daily injections to a single injection, extended-release, dosage form was done, Spencer continues. “Another example is the reformulation of a drug from a daily oral tablet to an extended-release parenteral dosage form that has improved compliance in schizophrenic and bipolar patients,” he says. “In addition to eliminating the need to remind patients to take their medication, it has also helped addiction patients from intentionally and prematurely stopping their therapy.”

Adding to Spencer’s comments, Zijlstra explains that some relief can be offered to oncology patients if the food label can be removed from the medicine through reformulation. “Many oncology patients have reduced appetites as a side effect of chemotherapy,” she notes. “However, the medicines they are required to take often have food labels on them, meaning that in some cases, the patients must take the dose with food. Therefore, a reformulation strategy that can remove this ‘food’ requirement can improve the patient experience.”

“Furthermore, formulations that combine local delivery with extended-release can dramatically improve rates of brand acceptability for patients who would otherwise face a series of uncomfortable intravitreal injections or injections into the knee or other joints,” Spencer iterates.

**Potential path forward**

According to Mudie, a potential future reformulation strategy could be a digital one. “For example, developers may insert a chip inside a dosage form to alert either the patient, healthcare provider, or both when the medication has successfully been administered,” she says. “This innovation could be useful for oncology patients, who may experience anxiety related to keeping track of their medications. It may also be beneficial for treating schizophrenia.”

Moving forward, Spencer anticipates there will be an increasing number of applications for local delivery. “In this application, drug concentrations in local tissues can be maximized for efficacy while minimizing systemic drug exposure resulting in reduced side effects via placement of the drug product directly into target sites, such as joints, the spine, the eye, infected areas, tumors, or the brain,” he notes.

“Furthermore, local delivery can minimize the total amount of dose required,” Spencer continues. “As specialized drugs continue to become more highly potent, the goal of reducing injection volumes and extending the period of drug release will become even more important.” As an example, Spencer highlights a recent approval of an ocular implant, which has the capability of releasing 10 micrograms of drug over a four-month period (3).

Another approach that may have promise for the future in Mudie’s opinion is the creation of a dosage form that has the ability to release in the GI tract non-traditionally. “For example, it may attach to the intestinal wall and release the drug contents for uptake into the bloodstream,” she says. “This approach could benefit patients who require frequent injections or have harsh GI environments.”

“Finding new molecules that have acceptable therapeutic profiles is not getting any easier,” summarizes Drummond. “Fundamentally, all reformulations, current and future, must benefit the patient, whether by providing a new solution to combating an indication or improving compliance and ease-of-use, to ensure there is no compromise to the patient.”

**References**

Manufacturing Microneedle Array Patches for Vaccine Delivery

Jennifer Markarian

Equipment and process optimization must be considered for scaling up these developmental technologies to commercial production.

Microneedle array patches (MAPs) have been in development as an alternative to injections for delivering vaccines and other drugs. Microneedle patches differ from transdermal patches that deliver medicine through the outermost layer of the skin (the stratum corneum), because the microneedles pierce the stratum corneum and deliver the drug into the epidermis or upper part of the dermis, but not deep enough to cause pain. Microneedle technologies include solid microneedles coated with the drug, hollow microneedles filled with a liquid drug, and dissolvable microneedles with the drug embedded in a soluble material.

Microneedle patches have been studied in a clinical trial for delivering a flu vaccine (1) and in preclinical trials for delivering inactivated rotavirus vaccine (IRV) and co-administration of IRV and inactivated poliovirus vaccine (2). Recently, MAPs are being investigated for a vaccine to fight COVID-19 (3). The University of Pittsburgh Medical Center (UPMC) announced in an April 2, 2020 press release that its scientists had developed a potential vaccine against SARS-CoV-2 that would be delivered through a MAP (3). The fingertip-sized patch uses 400 microneedles that deliver the spike protein pieces into the skin, where the needle pieces, which are made of sugar and the protein pieces, dissolve. Noting that scalability is crucial for vaccines intended for protection from pandemics, UPMC said that the process to make and purify the protein for the vaccine is scalable, and that mass-producing the microneedle array involves spinning the protein-sugar mixture into a mold using a centrifuge. Advantages of the vaccine, dubbed PittCoVac, are that (like other MAPs) it does not require a cold chain for storage and that it maintains its potency after being sterilized with gamma radiation. The researchers are in the processing of submitting an investigational new drug application to FDA.

PATH, a nonprofit, global health organization has been investigating transdermal drug delivery patches for more than 10 years and is in the middle of a four-year initiative, through its Microarray Patch (MAP) Center of Excellence, to accelerate development for global health needs, such as vaccines and essential medicines, in low- and middle-income countries. The group says that developing scalable, automated, good manufacturing practice (GMP) processes is crucial for success (4).

“Although microneedle arrays are being used commercially in some cosmetic applications in Asia, the technology is not yet commercial for vaccines. Optimization of equipment and manufacturing processes is crucial for producing these systems in the large quantities and reasonable costs needed for clinical studies and vaccination campaigns,” adds Stefan Bernsau, sales director for Needle Technology at Harro Höfliger (HH), which develops and manufactures various types of production and packaging equipment for pharmaceutical companies, medical device companies, and other industries. The company is working with organizations and partners to develop microneedle array patch (MAP) technology, and in January 2020, Harro Höfliger and PATH hosted a workshop on MAP manufacturing attended by MAP developers and representatives from the World Health Organization, UNICEF, the Bill & Melinda Gates Foundation, and the Gavi Vaccine Alliance. Pharmaceutical Technology spoke with Bernsau about some of the considerations for MAP manufacturing.

Advantages of MAPs

PharmTech: What are some of the advantages of using MAPs for vaccines?

Bornsau (HH): Vaccine delivery faces several challenges that can be addressed with MAP technology. A significant
Manufacturing

issue is that low- and middle-income countries often do not have a clear cold chain, which is necessary for transport and storage of liquid, injectable vaccines. MAPs do not require a cold chain. Another concern is that a significant number of people have a fear of regular injection needles and the associated pain. Microneedles in a patch form eliminate the pain. In addition, MAPs can be administered without skilled healthcare workers, by trained workers or potentially by self-administration. This advantage is beneficial for developing countries that lack skilled healthcare providers. Recently, it is also being thought of as a benefit for all countries for use in pandemics, where patients could potentially have the vaccine delivered for self-administration, thus avoiding the need for people to go to doctors’ offices or hospitals.

Microneedle array patches are being investigated for a vaccine to fight COVID-19.

Manufacturing considerations

PharmTech: What are the biggest challenges in microneedle patch manufacturing and what are some best practices for addressing these challenges?

Bernsau (HH): Companies developing products at the laboratory scale are looking at issues such as dosing (either by coating or filling) and drying. At the commercial scale, however, automation is crucial for obtaining output at an appropriate cost, with a reasonable total cost of ownership. As a machine manufacturer, we want to join in the development process as early as possible so that we can provide input to developers for how to optimize the process for commercial automation.

One of the constraints for vaccine manufacturing is that most cannot be terminally sterilized, therefore they must be produced in a sterile environment. One of the keys for sterile production is material flow through the processing line: raw materials must be brought into the machine; various automated steps are performed; then the product must be taken out of machine. Sterile environments can include isolators or various types of barrier technology, depending on the cleanroom setup.

Dosing of the API, either into the hollow mold or as a coating, must be done in a combination of high precision and with high output. These are very small doses, and different dosing technologies are used to obtain the specific tolerances needed for a particular process. There are some new developments in the market for dosing. VAXXAS, for example, has developed their own high-speed and high-precision dosing technology that is similar to ink-jet printing technology. As another example, scraper technology can be a solution for dissolvable microneedles, depending on the viscosity and the physical characteristics of the liquid or the vaccine.

For the automation of the lines, we use dedicated servo-driven units because the parts being handled are so small—the whole array may be about the size of a penny, for example. Robotic arms can cause turbulence in the airflow, which can be a problem regarding the aseptic requirements of such small, precise units. Another proven technology is a so-called ‘walking beam,’ which uses pick-and-place handling for small and delicate parts inside an isolator.

PharmTech: What are some best practices for inspection of MAPs after manufacturing?

Bernsau (HH): Several quality attributes need to be inspected, particularly that the required amount of drug is there (either coated or filled). Inspection of microneedles is more difficult than syringe inspection because of the size of the microneedles. Cameras are used to view the top and side. Other critical pieces are the light source, appropriate software, and hardware for fast computing speed. A best practice is 100% inspection of each part, but a challenge is the speed and an eventual reflectance of image acquisition to accomplish this.

Packaging requirements

PharmTech: What are the requirements for packaging of microneedle patches?

“To a large degree the microneedles are fragile.”

—Stefan Bernsau, Harro Höfliger

Bernsau (HH): To a large degree the microneedles are fragile; they are typically packaged in an applicator, with a rigid container to protect the needles. The patch must also be packaged in a sterile environment. After primary packaging, it must also be packaged for transportation. An advantage of MAPs is that temperature is not as much of an issue, compared to traditional liquid vaccines, because the MAPs vaccine is dry.

Outlook

PharmTech: Do you foresee in-country, for-country production with MAP technology?

Bernsau (HH): It is far too early to know whether production in developing countries is feasible, because the initial investment in these lines is high and a lot of technical knowledge and skill are needed to run these lines. However, some organizations are looking at this possibility, and the current pandemic may cause more governments globally to think about in-country production.

References

A robust contamination control program (CCP) does more than simply remove microbial contamination from cleanroom surfaces and equipment; a CCP ensures aseptic processes result in a sterile finished product. CCPs are critical to product and patient safety and must be multifaceted to consider all aspects of contamination to be effective. For pharmaceutical, biotechnology, and medical device manufacturing, CCPs are one of the foundational elements of a facility’s pharmaceutical quality system (PQS), as described in FDA Guidance for Industry, Q10 Pharmaceutical Quality System. The scope of International Council for Harmonization (ICH) Q10 includes the following systems, each of which is integrally related to CCP (1):

- Provision of facilities, utilities, and equipment
- Production, including packaging and labeling
- Quality control and assurance

Assembling a multidisciplinary team to evaluate microbiological risk to the product identifies key areas of focus in the CCP including elements of the science-based assessment, policy-based management, and risk communication (2). This exercise provides direction and prioritization within the elements of the CCP.

ICH Q9, Quality Risk Management provides a framework for the risk management process within a pharmaceutical organization. The goal is to proactively identify and manage product risk as a continuous process. The Risk Flowchart within ICH Q9 details the quality risk management process, using risk management tools and risk communication (3).

The Microbiological Risk Analysis and Risk Flowchart are proven industry accepted tools to supplement the CCP. These tools create the link between the CCP and sterile products, ensuring risk of microbial contamination to the products is minimized.

**The number one source of contamination in the cleanroom environment is people.**

**Elements of a contamination control program**

To meet the quality system requirement detailed in ICH Q10 for a CCP, the following elements must be considered:

- Environmental monitoring (EM)
- Gowning
- Cleaning and disinfection
- Materials and equipment airlocks
- Sterilization
- Parts and equipment use at filling line.

Best practices within these elements ensure the risk of a non-sterile product is minimized. Documentation within work instructions and/or standard operating procedures (SOPs) provides direction to trained staff, ensuring consistent execution of the best practices.

**Environmental monitoring.** Good EM practices demonstrate microbial control and identify adverse trends within the cleanroom environment. Data collected using an environmental particle counter over time validates the cleaning and disinfection process and gives evidence that the contamination control program is effective. Figure 1 shows an overview of points to consider when starting new or evaluating existing EM practices.
Gowning. The number one source of contamination in the cleanroom environment is people. Operators working in the cleanroom must adhere to strict gowning practices to ensure particulate and microorganism contamination stemming from the operator is kept to a minimum. Continued personnel training and monitoring is an essential part of the CCP. All operators should be included in a training program and undergo formal qualification (initial and periodic assessment of skill). Training should be conducted by subject matter expert(s) (SMEs), and employees should be restricted from cleanroom access until fully qualified.

Aseptic operators should be monitored at appropriate sites and frequencies (based on risk assessment). There should be an SOP-defined program for addressing poor

Table I. Cleanroom environmental contamination control program. EPA is US Environmental Protection Agency. DE is disinfectant efficacy. USP is United States Pharmacopeia. SOP is standard operation procedure. ISO is International Organization for Standardization. RTU is ready to use.

| Selection of agents                  | Formal program for qualification, use, and disposal of disinfectants. Disinfectants in the United States are Environmental Protection Agency (EPA) registered, with defined criteria for selection and suitability of agents (i.e., substrate compatibility, label claims, etc.) |
| Rotation                             | More than one type; use of a broad-spectrum disinfectant with periodic use of sporicidal (frequency driven by environmental monitoring data), use of sterile 70% isopropyl alcohol (IPA) for aseptically gowned operators in ISO 5/ISO 7 zones (e.g., frequently on gloves, surfaces after interventions). Disinfectants have detergent capacity, or formal program exists for cleaning of surfaces prior to disinfection. |
| Residue removal                      | Frequency and method for rinsing is based on usage of disinfectant(s). Procedure is defined in standard operating procedures (SOPs); use of high purity water (United States Pharmacopeia purified water or water for injection) or 70% IPA for surface rinsing and residue removal. Formulated detergents used as needed, based on residue type and build-up. |
| Application method(s)                | Well defined in SOP (e.g., specify two or three bucket systems, stipulate mop type(s), hands-on operator training, periodic audit of program by QA to verify application technique and contact time. |
| Recovery from loss of control (planned or unplanned) | Formulated cleaner used to help remove debris and soil. SOP-defined plan for shutdown recovery (e.g., 3X Clean & Disinfection with final round of sporicidal). In-situ study performed (1x) to demonstrate ability to recover from loss of aseptic control. EM program used to generate in-situ data to demonstrate effectiveness, i.e., area mapping via contact plates after worst-case event; mapping done pre- and post-recovery to document ability to reestablish cleanroom conditions. |
| Disinfectant efficacy (DE) studies   | Formal DE study performed using facility-specific substrates (surfaces) and microbial isolates. Substrates include all applicable facility surfaces: flooring, walls, equipment. |
| Wet contact time                     | Contact time is established in the DE study, and reflected in actual practice of disinfectant application in the facility. |
| Expiry dating                        | Stability of use-dilutions has been established via DE study. |
| Sterile vs. non-sterile              | Selection is based on risk. If used in ISO 5 zone, solutions must be sterile—either purchased as sterile or introduced into ISO 5 zone via validated process (e.g., sterile filtration). |
| Use-dilution                         | If not using RTU, then use-dilution is supported by DE study, with SOP preparation instructions including specified quality of water (e.g., USP Purified, WFI), method for accurate measurement, shelf-life. |
performance, remediation, or removal of access based on test results.

Cleaning and disinfection. A cleanroom environmental CCP includes frequent scheduled application of a phenolic or quaternary ammonium disinfectant, followed by periodic routine use of a sporicide, and periodic residue removal using water for injection or alcohol. Table I shows details on rotation, residue removal, etc.

Materials and equipment airlocks. The second highest risk of contamination to the cleanroom environment is from materials and equipment brought into the cleanroom from outside. Material-handling airlocks allow for contamination control, so decontamination practices should be used for these items prior to entry into the facility (see Table II).

Sterilization. For sterile parenteral products, product contact surfaces must be sterilized, and careful consideration must be taken to protect these critical surfaces before, during, and after processing. Sterilization wrapping materials must be of high quality, with regards to microbial barrier and low particle generation (see Figure 2).

Table II. Airlock contamination control. ISO is International Organization for Standardization. SOP is standard operating procedure. SME is subject matter expert. EM is environmental monitoring.

| Airlocks | Interlocking airlocks between entry points for classified areas of different grades (e.g., between ISO 8 and ISO 7). Restricted and controlled access to aseptic processing areas (e.g., card readers). |
| Preventing ingress of spore formers | Disinfection of pass-through materials includes effective procedure for spores (e.g., use of sporicidal, double- or triple-bagged sterilized items). |
| Pass-through procedures | Material pass-through process is well defined in SOP, with competency-based training program conducted by SMEs. Ability of management or appropriate SME to assess pass-through technique and compliance with written procedures (e.g., CCTV, periodic audit or documented spot-check observations). |
| EM and cleaning supplies | Supplies for maintenance and monitoring should be autoclave sterilized into the cleanroom or decontaminated through the airlock. Material decontamination procedure should include a sporicidal treatment and/or removal of a layer of wrapping to ensure contamination is not brought into the cleanroom. |

Figure 2. Product contact surfaces.

![Figure 2](https://example.com/fig2.png)

- Preparation for Autoclaved Parts
  - Minimum one layer of wrapping, critical surfaces (product contact) may have a second layer of protection.
  - Parts must be prepared and wrapped reproducibly and to not allow contamination (particles, microorganisms) after sterilization.

- Wrapping Material
  - Steam permeable, durable, microbial barrier, low particle shedding.

- Pre-sterilized Items
  - Consumable materials (i.e., supplies) can be purchased pre-sterilized using validated ethylene oxide or gamma irradiation cycles.

Case study
The following case study is an example of a failure in a contamination control program, as critical product contact surfaces were not protected from environmental contamination (4). A thorough multi-departmental investigation and root-cause analysis led to a simple solution. However, the root cause was identified, and preventive action was implemented after loss of product and significant production downtime due to the ongoing investigation.

Environmental contaminants (mold and Bacillus species) were repeatedly recovered from sterile bulk material and sterilized process equipment. Microbial analyses of the bulk material detected the presence of mold and Bacillus species. Investigational sampling via swabbing of the bulk tank’s interior surfaces also detected the same profile of contaminants. The specific species associated with the contamination events had no history of recovery by EM of the classified environments.

The root cause analysis followed a defined process with multiple disciplines involved. The CCP elements were reviewed within the team, using Figure 3 as a guide.

A review of the bulk tank preventative maintenance (PM) log showed that a rupture disc had burst prior to the onset of recovering mold and Bacillus species. Interviews with the technician revealed that the tank had been relocated to a non-classified area while a replacement rupture disc was ordered. No proactive measures were taken to protect the integrity of the tank...
while out of the controlled environment for several weeks. Upon re-introduction to the classified area, exterior surfaces of the tank were disinfected and treated with a sporicide. Clean-in-place (CIP) and steam-in-place (SIP) of the tank was performed; however, review of the tank’s SIP validation package showed that the interior area at the rupture disc connection proved to be a worst-case location for steam penetration. Investigational sampling in the unclassified area where the tank had been stored revealed the presence of genetically identical profile of mold and *Bacillus* species to that recovered from the bulk material and post-SIP tank interior. No proactive measures were taken to protect the integrity of the tank while it was held in an unclassified environment. Upon re-introduction to the classified area, exterior surfaces of the tank were disinfected and treated with a sporicide, and CIP and SIP cycles of the tank were completed. A concurrent review of the tank’s SIP validation package showed that although it passed validation criteria, the biological indicator (BI) located at the rupture disc connection was a worst-case location for steam penetration. The investigation logically concluded that the rupture disc zone of the tank had been exposed to the contaminating microorganisms while it was stored in the unclassified area, and that the ensuing CIP and SIP cycles were ineffective at removing surface contaminants from this specific area of the tank’s interior.

The resulting preventative action included a new policy to provide physical barrier protection of critical equipment and surfaces when moved to or stored in areas of lower classification. Figure 4 shows the location of the rupture disk on the tank. Figure 5 shows the good manufacturing practice (GMP) equipment cover being applied to protect the tank from potential environmental contamination.

GMP equipment covers manufactured using nonwoven spunbonded polyolefin material can protect equipment from particulate and microbial contamination during storage and when out of use. Regardless of how robust the CCP, environmental monitoring demonstrates that microorganisms are present at varying levels in any manned cleanroom environment. Additionally, aging facilities contribute to potential microbial risk to equipment in the cleanroom environment. It is important that barrier protection of critical surfaces be part of the CCP, especially during equipment staging and storage. Minimizing risk of microbial contamination, through prevention and protection of the product contact surfaces, should be the highest priority element in the CCP.

### Figure 3. Root cause analysis.

- **Define Problem**
- **Identify Problem**
- **Understand Problem**
- **Monitor System**
- **Identify Root Cause**
- **Corrective Action**

### Figure 4. Bulk tank.

Figure 3. Root cause analysis.

Figure 4. Bulk tank.
Summary
As part of a facility PQS, a robust contamination control program includes a diverse set of elements (e.g., EM, gowning, cleaning and disinfection, airlock and sterilization procedures, equipment use at the filling line) to minimize the microbial risk to the finished product, as well as to meet requirements in ICH Q10. Additional barrier protection increases sterility assurance of critical surfaces and further enhances the CCP.

The case study exemplifies how a simple solution like utilizing barrier protection over a bulk product tank would have prevented contamination of the bulk product. A proactive microbiological risk assessment in addition to the contamination control program will identify opportunities like this, where simple solutions minimize risk to the product. A holistic microbial risk assessment of all contamination control program elements ensures production of safe medicines and products.

References
1. ICH, Q10 Pharmaceutical Quality System (FDA, April 2009).
3. ICH, Q9 Quality Risk Management (FDA, November 2005).

Figure 5. GMP equipment cover.
A statistical sampling plan is not included within United States Pharmacopeia (USP) <905> Uniformity of Dosage Units and USP <711> Dissolution, which are only intended to determine conformance of a sample taken from routine batches or the pharmaceutical market. Passing USP <905> tests once does not provide statistical assurance that a batch will meet the target quality (1), thus testing against USP acceptance criteria is insufficient for batch release or process validation purposes. Statistical acceptance criteria with statistically valid sampling plans can better assess the quality of a process.

For in-process sampling of dosage units, FDA’s current recommendation is to use nested sampling plans—to test replicate samples (more than one, typically three, which should be sampled at closest positions) from each location of the stratified plan (2). In this way, the data can be subjected to variance component analysis, which divides the total variance into “between location” and “within-location” components (2), increasing the evaluation confidence for batch quality. The “between-location” component is the variability across the sampling locations in a blender, or during compression, encapsulation, or filling process, while the “within-location” component is the variability between samples within a given sampling location.

Bergum published a method to calculate a lower bound on the probability of meeting acceptance criteria of multiple stage tests (3), such as the USP content uniformity and dissolution tests, and gave examples in a book (4). Later, Bergum wrote a SAS program (CuDAL version 1), which implements his calculation method (5). In 2007, Bergum revised the calculation method (6), and a newer SAS program (CuDAL version 2) was developed and validated according to the revised USP 29 test for content uniformity (7). The CuDAL methodology finally became ASTM E2810 and ASTM E2709, which is referenced for establishing acceptance criteria for a stratified sampling plan. Bergum’s CuDAL tool is now the standard practice for demonstrating capability to pass USP content uniformity and dissolution tests.

However, the requirement of SAS software limits the wider use of CuDAL by industry practitioners. Alternative programs...
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based on readily accessible software would be more acceptable. R language programs, transformed from SAS programs, were written by www.pharmstat.com. Pramote Cholayudth, coauthor of this paper, first developed (8) and later revised (9) a Microsoft (MS) Excel program to compute the probability of passing a USP content uniformity test; however, it is no longer consistent with Bergum’s current CuDAL method. The International Society for Pharmaceutical Engineering (ISPE) has also published five common acceptance limit tables for sampling plans 1 and 2 based on ASTM E2709/E2810 and an Excel Workbook (10). However, due to the limited number of combinations of acceptable probability, number of samples and sample locations, and confidence levels, the tables are not capable of satisfying diverse company requirements.

The present work reports the CuDAL-Excel, a set of MS Excel programs transformed and extended from Bergum’s CuDAL version 2 SAS program. The CuDAL-Excel is used to evaluate data against the USP 29–43 <905> Content Uniformity and <711> Disintegration for both immediate-release and extended-release dosage forms (the test for extended-release dissolution is an additional function to CuDAL). It is designed for industry practitioners for batch release and process validation.

### CuDAL-Excel program

The CuDAL-Excel is an MS Excel file that contains eight MS Excel sheets with functions listed in Table I, and it calculates the passing probability of result data against USP multiple stage tests, <905> Uniformity of Dosage Units and <711> Disintegration. The CuDAL-Excel is based on Bergum’s methodology and is transformed and extended from CuDAL SAS programs as well as from R programs written by www.pharmstat.com. The calculation requires estimation of statistical lower and/or upper bounds for the mean and standard deviation (SD) of the samples of appropriate size. The calculation method assumes that the test results can be approximated by a normal distribution. For detailed calculation methodology, interested readers can unhide the hidden MS Excel columns and rows to understand the calculation algorithm. The open-source CuDAL-Excel file is available from the author.

### CuDAL-Excel inputs

#### Overall mean
The calculation of overall mean for both sampling plan (SP) 1 and SP2 are the same. Overall mean = AVERAGE(D2:D101) or = AVERAGE(F3:Y72), where D2:D101 or F3:Y72 are the individual results of all samples. All measurements of dosage units and criteria values are in percentage label claims (%LC).

#### Calculation of SD for SP1
SD = STDEV(D2:D101), where D2:D101 are the individual results of samples from all the locations.

#### Calculation of SD for SP2

- **Within-location SD (denoted as SE)** = SQRT(AVERAGE(D3:D72)), where D3 = VAR(F3:Y3), with F3:Y3 as the individual results of samples from the first location, and D72 = VAR(F72:Y72), with F72:Y72 as the individual results of samples from the last location.
- **Between-location SD (denoted as SM)** = STDEV(C3:C72), where C3 = AVERAGE(F3:Y3), with F3:Y3 as the individual results of samples from the first location, and C72 = AVERAGE(F72:Y72), with F72:Y72 as the individual results of samples from the last location.

#### Sample size
The sample sizes are different for SP1 and SP2.

- For SP1, one ($n=1$) dosage unit is sampled from each of the $L$ locations, with a total sample size of $L$. The locations should be equally spaced throughout the batch.

#### Table I. CuDAL-Excel program sheets.

<table>
<thead>
<tr>
<th>Spreadsheet name</th>
<th>Function</th>
<th>Dosage form</th>
<th>Sampling plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Calculate standard deviation (SD) for sampling plan (SP) 1</td>
<td>Calculate the mean, SD, maximum, and minimum</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>2 Calculate standard deviation (SD) for SP2</td>
<td>Calculates the mean, within-location SD (denoted as SE), between-location SD (denoted as SM), maximum and minimum</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>3 CUSP1</td>
<td>Calculate the passing probability against USP &lt;905&gt; Content Uniformity test</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>4 CUSP2</td>
<td>Calculate the passing probability against USP &lt;905&gt; Content Uniformity test</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>5 DissSP1</td>
<td>Calculate the passing probability against USP &lt;711&gt; Disintegration test</td>
<td>Immediate-release</td>
<td>1</td>
</tr>
<tr>
<td>6 DissSP2</td>
<td>Calculate the passing probability against USP &lt;711&gt; Disintegration test</td>
<td>Immediate-release</td>
<td>2</td>
</tr>
<tr>
<td>7 ExtDissSP1</td>
<td>Calculate the passing probability against USP &lt;711&gt; Disintegration test</td>
<td>Extended-release</td>
<td>1</td>
</tr>
<tr>
<td>8 ExtDissSP2</td>
<td>Calculate the passing probability against USP &lt;711&gt; Disintegration test</td>
<td>Extended-release</td>
<td>2</td>
</tr>
</tbody>
</table>

*SD, standard deviation; NA, not applicable; SP, sampling plan; SE, within-location SD; SM, between-location SD; USP, United States Pharmacopeia; CUSP1, content uniformity sampling plan 1; CUSP2, content uniformity sampling plan 2; DissSP1, dissolution sampling plan 1; DissSP2, dissolution sampling plan 2; ExtDissSP1, extended release dissolution sampling plan 1; ExtDissSP2, extended release dissolution sampling plan 2.
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For SP2, more than one (n=1) dosage units are sampled from each of the L locations, with a total sample size of n×L. The locations should be equally spaced throughout the batch, while the n samples within a location should be sampled as close as possible.

Confidence level. Confidence levels as well as probability values (P-values) are typically 50%, 90%, or 95%. A Parenteral Drug Association (PDA) Technical Report suggests the use of a 90% confidence level = 90%, and number of samples = 18, the minimum number of overall passing probabilities for LLU (B42) calculated in B30 and the passing probability of stage 2 is in B41. B28 and B36 are the probability integration results for stage 2. The integration calculation results, int2 (H304, sum of H4:H303), iint2 (T304, sum of T4:T303), iint3 (N304, sum of N4:N303), and the detailed calculation steps are demonstrated in the CuDAL-Excel file. The maximum one of the passing probabilities of stage 1 and stage 2 is in B41. B28 and B29 are the probability integration results for stage 1, while B35 and B36 are the probability integration results for stage 2.

The calculation formulas are demonstrated in the CuDAL-Excel file. With given inputs (cells B1:B5, the statistical lower bound, LLI (B23), and upper bound, ULI (B43), of the mean, can be calculated. For LLI, the passing probability of stage 1 is calculated in B30 and the passing probability of stage 2 is in B41. B28 and B29 are the probability integration results for stage 1, while B35 and B36 are the probability integration results for stage 2.

The integration calculation results, int2 (H304, sum of H4:H303), iint2 (T304, sum of T4:T303), iint3 (N304, sum of N4:N303), and the detailed calculation steps are demonstrated in the CuDAL-Excel file. The maximum one of the passing probabilities of stage 1 and stage 2 is in B41. B28 and B29 are the probability integration results for stage 1, while B35 and B36 are the probability integration results for stage 2. The minimum one of overall passing probabilities for LLI (B42) and ULI (B62) is the final passing probability and shown in B6.

For example, if target content = 100, confidence level = 95%, number of samples tested = 30, mean of tested results = 99.9%, SD of the tested results = 3.996, the calculated probability of passing USP Content Uniformity test for a future sample taken from the batch is approximately 97.78% (0.977799163). The obtained probability is larger than 95%, thus the batch is well within the release requirement, or the process is valid to produce products meeting USP Content Uniformity test requirements.

For another example (as shown in Figure 1), if the given target = 100, confidence level = 90%, and number of samples = 18, the passing probability is calculated by CuDAL-Excel with varying mean and SD. The obtained contour chart shows that passing probability increases with decreasing SD and with a mean closer to center target, and that a higher SD can be tolerated when the mean is close to the center target.

**Table II.** United States Pharmacopeia (USP) 29–43 <905> Uniformity of Dosage Units test procedure and acceptance criteria.

<table>
<thead>
<tr>
<th>Stage (S)</th>
<th>Number tested</th>
<th>Pass stage if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>10</td>
<td>AV = [M – X] + 2.4 s ≤ 15.0, where M is defined below.</td>
</tr>
<tr>
<td></td>
<td>S2</td>
<td>(1) AV = [M – X] + 2.0 a ≤ 15.0, using all 30 results (S1 + S2). (2) No dosage unit is outside the maximum allowed range of 0.75 × M to 1.25 × M.</td>
</tr>
</tbody>
</table>

M is defined as follows:

- If $T \leq 101.5\%LC$, then $M = X$ (AV = ks)
- If $X < 98.5$, then $M = 98.5\%$ (AV = $98.5 – X + ks$)
- If $X > 101.5$, then $M = 101.5\%$ (AV = $X – 101.5 + ks$)
- If $98.5 \leq X < 101.5$, then $M = X$ (AV = ks)
- If $98.5 \leq X < 101.5$, then $M = X$ (AV = ks)
and between-location SD. The contour chart shows that passing probability increases with decreasing within-location and between-location SD. To meet a passing probability, the allowable within-location SD is larger than between-location SD.

**Probability of passing USP 43 <711> Dissolution test**

The USP Dissolution test procedures and acceptance criteria are summarized in Table III and Table IV (12).

**Immediate-release dosage form.** For immediate-release dosage forms, examples for calculating passing probability of sampling plan 1 and sampling plan 2 are respectively demonstrated below.

**Immediate-release SP1 (sheet DissSP1).** For example, if the Q limit = 80, confidence level = 95%, number of samples tested = 30, mean of tested results = 84% label claim, SD of the tested results = 4.704%, the calculated probability of passing USP Content Uniformity test for a future sample taken from the batch is about 91.16% (0.911628045). The obtained probability 91.16% is acceptable (if there is a predefined acceptance limit of 90%), thus the batch is meeting the release requirement, or the process is valid to produce products meeting USP Dissolution test requirements.

**Immediate-release SP2 (sheet DissSP2).** For example, if the Q limit = 80, confidence level = 95%, number of samples tested per location = 3, number of locations = 20, mean of tested results = 88% label claim, within-location SD of the tested results = 7.5, between-location SD = 5, the calculated probability of passing USP Content Uniformity test for a future sample taken from the batch is about 94.31% (0.94309498). The obtained probability 94.31% is acceptable (if there is a predefined acceptance limit of 90%), thus the batch is meeting the release requirement, or the process is valid to produce products meeting USP Dissolution test requirements.

**Extended-release dosage form.** For extended-release dosage forms, examples for calculating passing probability of sampling plan 1 and sampling plan 2 are respectively demonstrated below.

**Extended-release SP1 (sheet ExtDissSP1).** For example, if the acceptable dissolution limit for this non-final time point is a range, dissolution lower limit = 48%, dissolution upper limit = 72%, confidence level = 95%, number of samples tested = 18, mean of tested results = 56%, SD of the tested results = 5, the calculated probability of passing USP dissolution test (extended-release) for a future sample taken from the batch is approximately 94.37% (0.943742397). The obtained probability 94.37% is acceptable (if there is a predefined acceptance limit of 90%), thus the batch is meeting the release requirement, or the process is valid to produce products meeting USP Dissolution test requirements.

**Extended-release SP2 (sheet ExtDissSP2).** For example, if the acceptable dissolution limit for this non-final time point is a range, dissolution lower limit = 48%, dissolution upper limit = 72%, confidence level = 95%, number of samples tested per location = 3, number of locations = 20, mean of tested results = 56%, within-location SD of the tested results = 5.2, between-location SD of the tested results = 4.5, the calculated probability of passing USP Dissolution test (extended-release) for a future sample taken from the batch is approximately 93.38% (0.933772184). The obtained probability 93.38% is not acceptable (if there is a predefined acceptance limit of 95%), thus the batch is not meeting the release requirement, or the process needs to be improved.

In another example where an extended-release tablet dissolution is tested at three time points, the dissolution specification is when the dissolution percentage at the first time-point is not more than 40%, the dissolution percentage at the second time-point is between 50% and 75%, and the dissolution percentage at the last time point is not less than 90%. When the given confidence level = 95%, number of samples tested per location = 3, and number of locations = 20, the passing probability of data obtained at the first time point is calculated by ExtDissSP2 to be 0.993062574 (inputs are the data from the final time point).
Validation of CuDAL-Excel

The CuDAL-Excel was validated by comparison of results obtained from the CuDAL-Excel with those from Bergum’s CuDAL SAS programs. The results, as listed in Table V, show that the above two programs generate the same passing probability values. The calculated intermediate parameters (not shown) are also the same for the two programs. The above results demonstrate that the two programs are equivalent.

As Bergum’s CuDAL programs do not cover probability determination for dissolution of extended-release dosage forms, it was not possible to viably compare against the original SAS programs. The authors have done their best to check the calculation steps/algorithm of sheets ExtDissSP1 and ExtDissSP2 under the principle of CuDAL statistical methodology. Users may decide to perform additional validation.

Conclusion

The developed CuDAL-Excel is used to calculate the passing probability of collected data against USP multi-stage Content Uniformity and Dissolution tests. The programs are based on Bergum’s methodology, and the functions have been validated.

Acknowledgement

This work fully respects and benefits from James Bergum’s great statistical methodology and original SAS programs. The authors’ intention is to make the great methodology performable on a software MS Excel which is widely accessible to industry practitioners. The authors are grateful to the reviewers of this paper for their valuable comments.
Table V. Comparison of results from CuDAL-Excel and Bergum’s CuDAL SAS programs. LC is label claim.

### Content uniformity—sampling plan 1

<table>
<thead>
<tr>
<th>Target (%LC)</th>
<th>Confidence level (%)</th>
<th>Number of samples</th>
<th>Mean (%LC)</th>
<th>SD</th>
<th>Passing probability</th>
</tr>
</thead>
<tbody>
<tr>
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Contamination Drives a More Concerted Approach to Genotoxins

Agnes Shanley

Discovery of nitrosamines in three of the world’s most widely prescribed drugs is driving efforts to better detect, control, and prevent their generation in APIs and finished drug products.

Since traces of the compounds were first found in batches of APIs used to make valsartan and other sartan angiotensin receptor blockers (ARBs) in 2018, drug manufacturers have been paying much closer attention to nitrosamines—in particular NDMA (N-Nitrosodimethylamine)—and how they enter the pharmaceutical supply chain. “Nitrosamines are extremely carcinogenic, as academic researchers have known for decades. The fact that NDMA is used to this day as a control to induce cancer in rats just underscores its immense carcinogenic potential,” says David Light, CEO of Valisure, an analytical pharmacy that filed the first citizen’s petition on nitrosamine contamination in ranitidine with FDA.

Some cases of contamination have been traced to solvents and to inadequate manufacturing and quality testing practices. In the case of the first contaminated API, for valsartan, one supplier had tweaked its synthesis process to improve yield and efficiency. Not only the manufacturer but the regulators who okayed that change failed to realize that it would result in contamination (1).

But ARBs were only the first sign of trouble, and, for one drug (so far), the problems go much deeper than manufacturing and quality control. In 2019, extensive testing found that ranitidine, one of the most widely prescribed treatment for ulcers and acid indigestion (whether as the trade-named Zantac or as one of many generic and over-the-counter brands), was also contaminated with NDMA. Valisure and Emery Pharma filed citizen’s petitions with FDA in 2019 and 2020 detailing the public health dangers posed by this contamination (2–4).

Although manufacturing and storage practices have led to contamination in some cases, the ranitidine molecule itself was found to be inherently unstable, breaking down and generating NDMA in the presence of high temperatures and humidity levels. After disputes about the best methods to use for analysis and testing (5), product recalls ensued, and on April 1, 2020, FDA followed other regulatory agencies in banning the sale of ranitidine and products that contain the compound (5). It had been on the market for almost 40 years and was widely prescribed to pregnant women and young children.

In December 2019, news came from regulators in Singapore, and later, from Canadian and Swiss health authorities that NDMA had also been found in metformin, the fourth most widely prescribed drug in the United States, and one of the most widely prescribed diabetes treatments in the world. In March 2020, after testing 38 lots of metformin from 22 suppliers, Valisure filed a citizen’s petition with FDA (6).

Far from being isolated instances, nitrosamine contamination is a systemic issue that manufacturers of all types and sizes need to take seriously. Although more is being learned about how it occurs, there are still gaps in that knowledge, says Ron Najafi, CEO of Emery Pharma. Emery is testing a number of pharmaceuticals in an attempt to clarify root causes of such contamination. The company has already developed and validated new analytical methods for such tests.

Later in 2020, The United States Pharmacopeial Convention (USP) will release new guidance to help manufacturers better face, address, and prevent nitrosamine contamination of pharmaceuticals and APIs. Included will be an informational chapter, as well as a series of six validated reference standards that can be used as controls and in method validation, says Jaap Venema, chief scientific officer with USP. Venema believes that decisive action is required now, since the contaminant has been found in three very different types of products from very different sources. Longer term, he says, more work is needed in assessing the risk, not only...
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of nitrosamines, but of other genotoxins. “We need to do more as a healthcare system and as a supply chain to control, test, and predict potential impurities,” he says.

Considering the first recent contamination case involving the valsartan API, initially there was a lot of finger-pointing and blaming of the manufacturer, a Japanese company doing business in China. Venema emphasizes that, though manufacturing facilities and processes were inspected, no one expected to find NDMA in that setting. “If there is one lesson to be learned by all, it is to expect the unexpected … It all comes down to the need for more control, more testing, and more predictive work,” says Venema.

Studying metformin
After other global regulatory agencies recalled metformin, FDA tested samples of the drug, examining material from 16 batches made by seven manufacturers. The agency released data in February 2020 that found contamination levels below the limit, Light recalls.

Valisure decided to investigate metformin after a person sent Valisure a sample of the compound and said that she was concerned about its purity, Light says. Valisure’s lab found a very high level of NDMA in that sample, he says. Valisure then bought more metformin from distributors, analyzing 38 batches of the material from 22 source companies. During testing, 16 of the batches failed. Half of the manufacturers had at least one batch that failed, while many had batches that contained more than 10 times the legal limit of NDMA, Light says (7,8).

Testing methods
There have been ongoing questions about the best analytical methods for detecting nitrosamines in pharmaceuticals. “I don’t think there will ever be a consensus among stakeholders as to a single set of ideal conditions or methods. Instead, I believe drugs should be tested by multiple complementary methods in an unbiased fashion, and the conditions/tests set on a case-by-case basis,” says Light.

As he notes, disagreements that ensued after NDMA detection in ranitidine using headspace gas chromatography-mass spectrometry (HS-GC-MS) have largely been resolved, and it is now well-established that HS-GC-MS should not be the method for analysis of ranitidine.

From a scientific perspective, Light says, it doesn’t really matter what method you use as long as you address primary issues. “We addressed the molecule’s instability by using lower temperatures with GC-MS; FDA did the same for liquid chromatography (LC)-MS. There is a need to think outside of the box. You cannot wait for there to be a very specific prescribed system for the exact drug you’re looking at,” he says.

Emery, which has also collaborated with Valisure on testing efforts and corroborated their test results, explored use of alternative methods, including LC with tandem mass spectrometry (MS/MS), which does not expose the samples to high temperatures. Using this method, together with stability studies, Najafi and his team found that ranitidine is an unstable compound, a time- and temperature-sensitive pharmaceutical product, that breaks down to form NDMA. “After nearly four decades in the market, we were the first to prove that ranitidine develops the carcinogen NDMA when exposed to heat during transportation and storage,” says Najafi, who notes that temperature excursions are quite common during commercial shipment.

Emery had a strong set of preliminary data (unpublished at this point) to support these claims, Najafi says, when, on December 4, 2019, FDA offered a directive for manufacturers regarding ranitidine product release. The agency said that distributors and manufacturers could release ranitidine drug products back into the market, so long as production batches showed NDMA levels lower than 96 ng/pill (the daily acceptable limit of NDMA).

“We were extremely concerned, because no formal root-cause analyses had been performed to determine why NDMA was observed in lots of Zantac and other ranitidine drug products,” says Najafi.

“Even if manufacturing lots were clean, NDMA could still be produced in ranitidine drugs products during downstream shipment and storage, or if stored by patients under less-than-ideal conditions (e.g., on a car dashboard),” says Najafi. “We felt an obligation to inform the agency of our findings, given the major implications they had for public health,” he says.

Existing regulations inadequate
The International Council for Harmonization’s ICH M-7 (9) is a comprehensive guidance for genotoxic compounds that has guided FDA’s approach to nitrosamine contaminants. Kristi Muldoon Jacobs, USP’s regulatory science director, likes the fact that it allows pharma to take advantage of advances in toxicology and collective knowledge. However, there are some places where it could be improved or added to, she says. For example, when discussing known and suspected mutagens, some chemicals, for which there isn’t enough information (and which include nitrosamines) are labeled “cohorts of concern.” The guidance doesn’t give much information on how those compounds should be addressed, so the pharma community should add to the guidance as more is learned from specific cases, she says. For example, there is a list of chemicals for which acceptable daily intake (ADI) levels have been published, and now that more information has been published on nitrosamines, it can be used to update the guidance, she says.

Current FDA and USP guidance is reasonable, albeit a bit dated at this point, says Najafi. One problem that he sees is the bureaucratic red tape that surrounds updating these documents. “We need quicker, more facile updates to guidance documents and monographs, and analytical methods from 36 years ago should be updated with newer instrumentations and methodologies,” he says. For example, manufacturers could be required to perform unbiased assessment of impurities in every production lot, using multiple analytical methodologies instead of being allowed to pick and choose their favorite method, says Najafi. Then, he says, they could pursue all new or unidentified peaks, identify the impurities/analytes responsible for these peaks, and ensure these are within established safety profiles before releasing a product lot. USP’s
Event Overview

Formulators must consider many variables in the formulation of oral solid dosage form (OSDF) drugs. Digitalization can help formulators of OSDF address certain challenges they typically face in their formulation journey. In this webcast, experts will review some of these challenges and the science behind ZoomLab™, an online formulation optimization and prediction tool available to all formulators, to help reduce significant amounts of trial and error during the formulation process. A demonstration of the tool’s ability to predict optimal formulation for direct compression, including aspects of processability, tabletability, and content uniformity—using excipients from a range of companies—will be featured.

Key Learning Objectives

- Learn about the variables that effect the optimization of an OSDF formulation
- Learn how a digital tool accounts for these variables to optimize an OSDF formulation
- Learn how a digital tool can make formulating an OSDF more efficient

Who Should Attend

- Pharmaceutical drug formulators at generic and innovator drug companies, particularly small- to mid-size companies

Register for this free webcast at: http://www.pharmtech.com/pt_p/digital_assistance
All attendees will receive a free executive summary of the webcast!

Presenters

Brett Burns
Global Strategic Marketing Manager
BASF Pharma Solutions

Dr. Ferdinand Brandl
Head of Laboratory
BASF SE, Nutrition and Health, Development Pharma Solutions

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions or concerns, email kmoore@mjlifesciences.com.
updated standards will help provide risk-based approaches and suitable, verified testing methods, says Muldoon Jacobs.

Greater familiarity of and compliance with FDA, European Medicines Agency, and ICH guidance is needed, Najafi says. “Regulators need to come down on non-compliance with an iron fist,” he adds. Generic-drug manufacturers, especially those offshore, should be required to stick with established procedures. During the new drug application (NDA) phase, chemistry, manufacturing, and control (CMC) review is very tough, but generic pharmaceuticals don’t undergo that same level of scrutiny. If a generic-drug manufacturer wants to make process changes, Najafi says, they should submit an application for re-approval to FDA, even if they’re only making a change as basic as switching solvents.

More rigorous testing
Manufacturers also need to do better on testing, particularly with residual solvent analysis, says Najafi, and manufacturers should be able to analyze, record, and report levels of each solvent. In reality, some manufacturers ignore these impurities, he says.

Scientists working in other industries have been studying nitrosamine contamination since the 1970s, says Light, but pharma and its regulators have often seemed disconnected from that research. In addition, he says, there is a very large body of research on the potential risks of nitrosatable drugs (e.g., those containing secondary and tertiary amines). Some have correlated use of the drugs with teratogenic effects, stillbirths, and tumors, says Light.

“The pharmaceutical world is getting better at keeping up with developments in other fields,” says Najafi. “Widespread cross-talk among scientists is the only way to bridge the existing knowledge gap, and government agencies and regulators should facilitate it,” says Najafi. Emery, for example, has started collaborating on studies of nitrosamines and other genotoxic impurities with professor Bill Mitch from Stanford University, a specialist in the field of environmental biomonitoring, and emerging carcinogens. In the meantime, the toxicological methods used to study nitrosamine impurities in pharma continue to evolve. “I believe this area is still a black box—long-term exposure risk is and will remain challenging to evaluate,” says Najafi. Valisure is working with Memorial Sloan Kettering Cancer Center on a study of ranitidine’s health effects, which underwent peer review and was scheduled to be published in January 2020, in the Journal of the American Medical Association, but which is being held for further review.

“Questions for the industry now are: how do we prevent more of these situations from occurring, how do we prepare for them, and how do we respond faster and more responsibly when they recur?”

—Jaap Venema, CSO, USP

The field of toxicology is advancing rapidly, adopting more predictive and in-vitro approaches, says Muldoon Jacobs. Some computer-based predictive models, she says, can be used to predict whether a contaminant’s given chemical structure might be mutagenic and whether or not it would test positive in the Ames assay (10), which has been used for over 25 years to identify mutagenic compounds. “These models are built on hundreds or thousands of individual data pieces based on actual studies, and some scientific papers have shown that these models are more accurate than the Ames test,” she says. Pharmaceutical industry regulatory agencies are applying these methods, for instance, at FDA’s Division of Applied Regulatory Science. Although MS and hyphenated gas and liquid chromatography methods are being used to detect nitrosamines, additional methods may be applied in the future. El-lutia, for instance, offers a Thermal Energy Analyzer detector technology, which uses chemiluminescence at the GC or LC interface, to measure levels of N-nitrosamines. The device is used in the rubber toy, brewing, water treatment, and food industries, and pharmaceutical companies are now exploring its potential.

The industry is taking the issue of nitrosamine contamination and its potential human health impacts more seriously. “As with the current COVID-19 pandemic, it’s not a matter of if, but when, situations like this will come up. The questions for the industry now are: How do we prevent more of these situations from occurring? How do we prepare for them, and how do we respond faster and more responsibly when they recur? The real lesson for our industry is to get better at predicting and preventing these problems,” says Venema.

REFERENCES
6. FDA, Statement from Janet Woodcock on Nitrosamine Impurities Found in Diabetes Drugs Outside the US, fda.gov, December 5, 2019.
Power can come in small packages especially when it comes to the Contec EasyReach™ Cleaning Tool with ultrasonically sealed pads! It’s small enough to clean mini environments yet strong enough to be used with a wide range of disinfectants and solutions. Featuring a stainless steel tool design and low particulate fabric – it is small AND mighty!
The Limits of Light Obscuration

Brent Denton, John Bak, and Jonathon Salsbury

Light obscuration testing is the preferred method of sub-visible particle quantification but is not suitable for every preparation.

Particulate matter by light obscuration (LO) testing quantifies particles in suspension by their projected shadow onto a photo sensor. This is the preferred method of sub-visible particle quantification (generally < 100 µm), as it has a high testing throughput and robustness compared to other means, such as membrane or flow imaging microscopy. However, not all preparations are suitable for testing by LO. In some cases, the issues may prevent usable results from being generated (such as an instrument being unable to maintain a flow rate due to viscosity issues or unable to measure particles in an opaque solution), and in other cases the results generated may be inaccurate (such as an instrument undercounting clear particles due to clarity issues or under-sizing aspherical particles due to shape issues). This article discusses both cases, with a focus on those where inaccurate results are generated because the added risk of the inaccuracy was not discovered.

Usable results unable to be generated
The most apparent symptom of a viscosity issue is the instrument’s inability to pull solution at the predefined flow rate. This almost always prevents results from being generated, though in borderline situations the solution may still flow through the instrument and simply generate errors at a higher-than-normal frequency. Errors should be reviewed carefully to determine if they are related to an increased load on the motor (or any other system responsible for pulling the solution through the instrument); such errors are a secondary symptom of flow rate difficulties. This and other viscosity issues can often be mitigated through dilution.

Coloration issues, a variation of clarity, can present symptoms similar to viscosity issues, such as being unable to generate results or generating results with a higher-than-normal frequency of errors in borderline situations. If the solution has significant coloration, well discernable to the naked eye, it may be the root cause. Coloration errors are distinguishable from viscosity errors as they stem from the bulk solution blocking too much light to resolve particle shadows, and generate errors relating to sensor contamination. This is because the instrument observation is the same as if there were a stuck particle in, or a film built up on, the sensor. This issue, similar to viscosity issues, can often be mitigated through dilution.

Any symptom-alleviating dilution should be carefully executed to perform its function without being unnecessarily extreme (1,2). High dilution factors decrease overall sensitivity to the test solution while increasing sensitivity to lab technique. Because of this, it is possible that symptoms are severe enough that they are not mitigated prior to generating new issues. In such cases, check to see if a different sensor type may be utilized (likely still in conjunction with dilution). Manufacturers typically have multiple types of sensors available, each with their own specialty, that may be of aid. However, if dilution cannot be made sufficient, particles may need to be quantified by another technique.

Inaccurate results generated—variability by instrument
Contrast limitations affect preparations exponentially as the refractive indices of particles and solution approach each other, which can lead to otherwise identical instruments generating noticeable differences in their results due to slight variation in their construction/assembly. Such an unexpected variation should be
Practical Considerations for Bringing Drug Candidates to Phase I Clinical Trial

LIVE WEBCAST
Wednesday, May 27, 2020
11am EDT | 8am PDT | 4pm BST | 5pm CEST

Presenters

Philip Jones, PhD
Vice President, Therapeutics Discovery
MD Anderson Cancer Center

Cliff Yin, PhD
Executive Director of CMC
Project Management, STA Pharmaceutical
WuXi AppTec Company (WuXi STA)

Xin Zhang, PhD
Vice President, Head of Integrated Services,
Laboratory Testing Division
WuXi AppTec

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Event Overview
New drug innovators face key challenges to advance their compound to clinical trials. An investigational new drug (IND) submission is a key milestone for every drug candidate. This webcast will discuss the best practices to advance small-molecule drug candidates quickly from discovery to IND filing, including safety assessment and chemistry, manufacturing, and controls (CMC) programs with real-world case studies.

Key Learning Objectives
- Key considerations for bringing a drug candidate to Phase I clinical trials
- Best practices for advancing small-molecule drug candidate CMC programs
- A comprehensive roadmap for successful global IND submissions

Who Should Attend
- Pharmaceutical and biotech companies developing innovator small-molecule compounds (NCE)
- Pharmaceutical and biotech companies aiming for IND submissions
- Program leaders of drug candidate pipelines
- Senior managers and executives from pharmaceutical and biotech companies
- Drug development and pharmaceutical consultants
- Pharmaceutical and biotech venture capitalists and investors

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evaluated to determine if it can be attributed to an instrument error, or if it may be a contrast issue. The contrast of a particle in suspension is defined by the absolute value of the difference in refractive indices (Δn) between the particle and surrounding fluid. Particle counts begin to be noticeably affected when Δn is less than approximately 0.10, with more significant effects when Δn is less than approximately 0.05 (3,4,5).

If the chemical composition of a particle population is known, the bulk refractive indices of each may be used as rough approximations to determine if contrast issues are likely. While the refractive index of a fluid often can be easily determined or well-approximated, a particle’s refractive index can be more challenging and laborious to obtain. Additionally, a single refractive index is rarely representative: even if a particle population is both isotropic and chemically homogeneous, the effective refractive index may be a function of particle size due to edge effects. Because of this, it is advised to reactively test for any suspected contrast issue rather than determining refractive index value(s) for particles in advance. Preliminary testing can be performed by slightly altering the solution refractive index, and thus particle contrast, between analyses and checking for an amplified difference in particle counts.

To illustrate how instrument variability can be attributed to contrast issues in even a relatively mild case, see Figure 1. Three instruments equipped with the same model of sensor that would typically be considered identical are compared, with one producing noticeably different results. A 30-µm standard preparation (Thermo 9030 glass standard: 29.5 µm diameter, 2.44 g/cm³ density, 1.52 refractive index) was suspended in a water–glycerol solution (Δn of approximately 0.11) and analyzed on each LO counter (HIAC Royco Model 9703 or 9703+ Liquid Particle Counting System with a United States Pharmacopeia [USP] <788> calibrated HRLD 400 sensor). Compared to counters B and C, the results obtained from counter A were subtly, though noticeably, different: both the mean and standard deviation of the particle distribution increased. Thus, counter A, though otherwise identical to counter B and counter C, must have a different sensitivity to contrast issues.

Inaccurate results generated—variability by flow rate
An aspherical particle can flow through an instrument sensor either in line with the surrounding laminar flow and appear smaller than actuality, or be rotating, or “tumbling,” and appear larger than actuality (6). If results are sensitive to flow rate, it may be a symptom of aspherical particles, as increased flow rate can increase the likelihood of tumbling. It is also likely that different instrument types affect the incidence of tumbling. Sensitivity to flow rate (as a symptom of aspherical particles) may appear subtly as a broadened size distribution, but may indicate that further evaluation is needed. While certain other types of particles, such as proteins, are also sensitive to flow rate, evaluation for aspherical particles should always be performed if they are at all a consideration. Depending on the level of accuracy required, an additional cal-

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**Figure 1.** Size distributions of a single standard preparation across three different light obscuration sensors of the same manufacturer and model. Each curve represents an (n=3) mean. All replicates were sampled in staggered order to reduce bias.
ibration curve or other means of correlation may be warranted. However, any LO result generated with an additional calibration curve should only be considered a worst-case scenario, as counts and sizes may be biased high for particles less aspherical than those represented by the additional calibration curve.

The simplest and easiest way to check for aspherical particles is microscopy, though any technique that incorporates visual analysis may be applicable. Observed particles do not need to be highly aspherical to indicate an impact on results, as symptoms may be noticeable for particles with an aspect ratio (the ratio of the minor to major axis) up to approximately 0.5, with more significant symptoms appearing if aspect ratios are approximately 0.25 or less. However, aspherical particles typically only noticeably impact results when they are a large portion of the particle population. Therefore, if they are not observed upon visual analysis it is highly unlikely they are a root cause of any symptom.

To illustrate how the apparent size of an aspherical particle is impacted by its orientation, see Figure 2. It is likely that only a portion of a particle is within the sensor’s field of view at any given time, as LO instruments are configured to reduce particle coincidence by only viewing a thin slice of solution (increasing the maximum analyzable particle concentration). As the field of view begins to approximate a cross-section for larger particle sizes, the apparent size of an aspherical particle will become orientation dependent. An aspherical particle that stays in line with the surrounding laminar flow will appear relatively small, while a tumbling aspherical particle may pass through the sensor sideways and appear much larger.

**Conclusion**

In summary, a variety of issues can arise while performing LO testing, causing symptoms that either make results unable to be generated, or generate inaccurate results. If results cannot be generated, dilution is typically an appropriate next step, though it must be done with care to ensure it does not cause any additional issues. If results generated appear inaccurate, further evaluation should be performed specific to the situation. When diagnosing any symptom, it is important to be aware of both the chemical and physical characteristics of any expected particles, as they can give critical insight. Symptoms that generate inaccurate results should be evaluated especially carefully due to the risk associated with their potential to be overlooked. In most cases, measures can be taken to ensure testing per LO is suitable, though in certain situations other techniques should be considered.

**References**

Ensuring Smooth Tech Transfer of Bioprocesses to Outsourcing Partners

Experience, communication, collaboration, transparency, planning, and prioritization contribute to success.

Technology transfer of bioprocesses, while common in the biopharmaceutical industry, can be complex and present numerous challenges. Projects with accelerated development timelines that also involve multiple contract service providers have the potential to magnify the difficulties. Both contract manufacturing organizations (CMOs)/contract development and manufacturing organizations (CDMOs) and sponsor companies can facilitate the process using pragmatic approaches that mitigate risks and ensure cooperation between all parties involved.

**Material, specification, and change-management issues**

When transferring a bioprocess to a CDMO, manufacturers often face multiple challenges that can include meeting the material demands of their clinical or commercial strategy and achieving aggressive timelines. These constraints must be met while accommodating the facility fit and scale-up needs determined by both the established process and the CDMO’s platform, equipment, and capabilities, according to Frank V. Ritacco, director of scientific and technical affairs for pharma services at Patheon, part of Thermo Fisher Scientific.

Abel Hastings, director of process sciences at Fujifilm Diosynth Biotechnologies, adds there are some themes that often slow the progression of sponsor projects, including materials challenges, specification ambiguity, and challenges with historical change management. “The implications of an ill-selected material can linger and hinder manufacturability. Once selected, materials dogma can be difficult to unpick because of the fear of the unknown,” he notes.

With respect to specifications, Fuji-film splits them into two general categories: safety/efficacy and manufacturability. It is important, according to Hastings, to convey the known safety/efficacy limits as early as possible and communicate what events might cause specifications to change. “As a CDMO, our primary goal is often to adjust the process design to reliably meet these specifications, and knowing the status of specifications up-front helps us guide our clients,” he explains.

Issues can arise, however, if sponsors establish specifications that are rooted in manufacturability too early, and then the process performance changes in the development stage or when moving a program from one site to another. Establishing expectations for process performance with limited data can, Hastings says, often over-constrain the development team, leading them to necessarily forego improvements in order to achieve a manufacturability specification.

Change management during process development, meanwhile, can challenge both sponsors and CDMOs as they work to expedite processes. “In this day and age of accelerated processes and ever-changing team members, capturing rationale for change becomes increasingly important to guard against knowledge loss as team members leave a company and to help guide development in an unemotional manner,” Hastings asserts.

While commercial processes typically have robust quality and change-control systems, earlier-phase projects can often change quickly and with limited traceability. “We recommend taking a balanced approach in order to capture pertinent information while not hindering development,” comments Hastings. Some sponsors use iterative risk assessments or failure mode and effects analysis tools to quickly capture changes and build catalogs of development and lifecycle changes. “This approach allows the user to both convey historical details and to project forward-looking risks in order to steer development in a planned way,” Hastings observes.
Phase-related challenges

The overall challenge in tech transfer is to ensure that the sponsor’s process will be reproduced in a similar, robust, and compliant way. Manufacturing product in the quality and quantity in the defined timeframe are indicators of a successful transfer of the manufacturing process to the CMO/CDMO, according to Andrew Bulpin, head of process solutions at MiliporeSigma. “This overall challenge,” he says, “is mainly linked to the process itself, but it also relates to the capacity to transfer the process knowledge built for several years to the CMO/CDMO that will be integrated to ensure a successful tech transfer.”

It often also varies depending on the development phase of the bioprocess being transferred. Sponsor companies’ early-phase programs are typically challenged by transferring processes that do not fit into their external partners’ platform operations, according to Emily Schirmer, senior director of process development at Catalent Biologics. “Those partners that can offer a high level of flexibility and unit operation expertise are more successful in accommodating unique or non-traditional processes,” she remarks.

In addition, as programs progress through clinical stages, process transfer becomes more difficult because there is less inherent flexibility allowed and process changes or adaptations become more challenging to justify, Schirmer adds. Bulpin agrees that the process parameters in Phase I or II can be slightly adapted or adjusted to ensure a successful tech transfer, while in Phase III the process is more locked with defined critical process parameters, critical raw materials, and designated critical quality attributes (CQAs). Thus, any changes in Phase III should be assessed, justified and, if necessary, validated.

Scale-up, equipment, and parameter adjustments

Adding in a scale-up element when transferring a process increases the overall risk for project success and comparability. “It is difficult to discern the differences observed from facility to facility and any disparities that can be observed on scale up independently,” Schirmer says. “These risks,” she notes, “can be minimized by having a good depth of knowledge of the facility’s specific equipment and well-established scaling models.”

Variations in equipment and material handling at facilities can complicate the tech transfer process, agrees Bulpin. “If the target facility uses different equipment, the raw materials must be compatible with that equipment,” he explains. In addition, to ensure a successful scale up, it is critical that raw materials are available at large scale and equipment capacity is evaluated. “The scale-up strategy of the CMO/CDMO, as well as its expertise in various process types, molecules, and innovative process methods—including perfusion, precipitation, and single-pass tangential flow filtration—is also key,” asserts Bulpin.

For cell-culture processes in particular, scale up can be challenging because scaling to larger volume is not linear, and multiple engineering parameters must be optimized to match process performance developed at the bench scale and confirmed at pilot to manufacturing scales of 2000 L and beyond, according to Ritacco. Harvest and downstream purification processes also need to be scaled up to match product quality and impurity profiles, and sometimes adapted to address differences in product titer and impurity profiles observed at larger scale.

Even if projects don’t involve scale-up, generally they still require a thorough investigation of which parameters need adjustment to fit best within the CMO/CDMO facility and equipment constraints without impacting specifications, Hastings observes. “In our view, scale changes and facility-fit adjustments are not complications but rather just part of what we do,” he says.

Accelerating complications

Many new biologic drug candidates are awarded some form of accelerated approval designation. While accelerated approval designations may allow a faster path to the clinic or to commercial approval for breakthrough therapies, the time it takes to develop a bioprocess that will be robust, scalable, and reproducibly deliver target product quality remains significant, according to Ritacco. “Fast-tracking the timeline and schedule without compromising product quality and patient safety is an additional challenge,” Bulpin says.

While some product development steps can be reduced, Bulpin insists that risk analysis and decision justifications should not be underestimated. “Sufficient understanding of the process is necessary to ensure control of operating parameters to consistently deliver safe and efficacious product to patients, and achieving this on an accelerated timeline requires a skilled team leveraging well-established processes and methods, as well as past experience to streamline development and avoid pitfalls,” adds Ritacco.

It is also extremely important for sponsor companies to work with a partner who has extensive experience with tech transfer and scale up into commercial launch, according to Schirmer. “A typical program with an external partner is designed to have a process-acquisition phase, which includes a paper transfer followed by establishing the process at a small scale. Then the scale up occurs within the facility infrastructure. These scale-up activities can, however, be minimized by performing the process acquisition at the manufacturing scale to meet accelerated timelines,” she says.

Fujifilm often observes three particular challenges with accelerated programs: prioritization, collaboration and communication, and planning. Most sponsors with accelerated designations greatly reduce timelines, Hastings says, by focusing on refining their processes to reliably achieve CQAs, often at a cost to the yield. “The most successful projects have a cross-functional team that is clear on their priorities and what success looks like. Ensuring all members of the team work together to settle on the right balance of yield and CQA reliability will ensure teams aren’t derailed by conflicting priorities,” observes Hastings.

One problem Hastings has observed, however, is that as teams turn attention to accelerating development timelines, they have a tendency to unintentionally reduce the circle of communication. “The most successful teams, however, enlarge their circle to engage all functional areas,
allowing everyone to be part of the process of building the best balance of speed, reliability, and risk," he asserts.

Planning for an accelerated designation project, meanwhile, requires a balance of creativity, dedication, and pragmatism, according to Hastings. "Teams need to be able to challenge their platform expectations to strike a balance to improve timelines. This planning cannot be done once, but rather needs to evolve as the scientific understanding of the process grows and teams need to be aware that any new data might require an adjustment to the project plan," he adds.

Engaging with multiple outsourcing partners
For many projects, it is necessary to transfer a bioprocess from one CMO/CDMO to another. Regardless of the reason, it is essential that everyone involved does not overlook the complexities associated with leveraging previous data and maintaining technical continuity, according to Hastings.

To proactively address this issue, Fujifilm identifies new, unique, or difficult (NUD) elements, such as process-specific factors that depend on equipment idiosyncrasies that may not be fully evident to a sponsor while the process is running at a CDMO. "When a process is moved from one CDMO to another, the receiving site rarely has access to complete equipment-specific details, which can make interpretation of previously generated data challenging and incur risk," Hastings says.

"At Fujifilm, we work hard to identify NUDs as early as possible and then categorize them as equipment-specific versus equipment-agnostic. This approach allows us to suggest studies that may improve facility fit," he adds.

Differences in equipment throughout the process, as well as differences in scale, require optimization of multiple engineering parameters to match process performance in cell culture, harvest, and downstream purification processes between facilities, Ritacco agrees. He also points out that analytical methods have to be transferred, established, qualified, and ultimately validated to assure consistency in analytical results between manufacturers.

Hastings also notes that some processes include historical elements that are difficult to translate into and out of batch records. "In some cases, sponsors deal with this issue by maintaining some of the same staff throughout transfers to minimize the chances that so-called tribal knowledge is lost," he observes.

Transparency between all team members, adds Schirmer, can actually be the catalyst to a successful development, scale up, and tech transfer of a drug with an accelerated approval designation. "Whether the process technology transfer occurs between the sponsor company and the external partner, or between two external partners, the importance of transparency is the same. Communication is also critical. If all parties are aligned and understand the path forward, it is much more likely that the transfer will be a success," she comments.

The general constraints are the same for any tech transfer process, including those between outsourcing providers, although the confidentiality becomes more marked and the training process can be slightly different. "The aim remains the same," Bulpin says. "In addition, any process, analytical, equipment, raw material, and/or regulatory gaps should be listed and mitigated to meet specifications and ensure a successful tech transfer."

Minimize risk for optimum success
Technology transfer introduces additional risk to the development and commercialization of biopharmaceuticals, so minimizing risk is fundamental to successful technology transfer of bioprocesses.

A clear project plan with milestones that are mutually agreed upon sets the stage for a successful program, Schirmer observes. "Risks should be identified at the onset of the project and continuously re-evaluated to determine effectiveness of mitigations and any additional risks," she says. In addition, risk assessments should be backed by scientific reasoning and process data.

The main strategy, according to Bulpin, is to consider tech transfer—with or without scale up—as an entire project with dedicated subject matter experts, communication flow, clear responsibilities, and planning. Dedicating one individual to the management of one CMO/CDMO group helps with this approach, except for quality assurance and regulatory topics, which Bulpin says should be managed globally to ensure process compliance.

The preparation and review of thorough process descriptions, facility fit, and tech transfer documentation, with appropriate quality review and oversight, go a long way toward achieving a successful tech transfer, adds Ritacco. The experience and expertise of the teams involved is also critical. "A highly skilled and experienced team will anticipate potential challenges and leverage their deep understanding of bioprocess development, tech transfer, and manufacturing to achieve the desired process performance and product quality in a new facility, even when the timeline may be challenging," he asserts.

It is also important, according to Hastings, for everyone involved in a tech transfer project to recognize upfront that priorities may change during the development cycle for biologics with accelerated approval designations. Risk-based tools can be used to segment process characterization into two or more phases and to design the process to prioritize CQAs over yield. "Using this approach, it is possible for sponsors to start their process performance qualification (PPQ) in parallel with some process characterization work, thereby shortening the timeline from clinical manufacturing to PPQ," Hastings observes.

On the other hand, it can result in post-approval yield fluctuation, which makes business-planning difficult. Fujifilm see this issue as an opportunity to move through a natural transition point. "Purposefully pivoting from biologic license application-enabling activities to business-enabling process improvements at the optimum time will allow programs to benefit from both accelerated PPQ and long-term commercial pay-back," he concludes. PT
Alnylam Pharmaceuticals and Blackstone Life Sciences Enter into Collaboration for up to $2 Billion

Alnylam Pharmaceuticals, an RNA interference (RNAi) therapeutics company located in Cambridge, MA, and Blackstone Life Sciences, a private investment platform, announced on April 13, 2020 that they are entering into a strategic collaboration under which Blackstone will provide up to $2 billion to fund Alnylam’s RNAi drugs to treat a range of diseases.

Through the agreement, Blackstone will offer $1 billion in committed payments for 50% of Alnylam’s royalties and commercial milestone payments for inclisiran, an investigational RNAi therapeutic for the treatment of hypercholesterolemia, according to a press release.

Blackstone will also offer up to $750 million in a first lien senior secured term loan, up to $150 million for the development of Alnylam’s cardiometabolic programs vutisiran and ALN-AGT, and $100 million for the purchase of Alnylam’s common stock.

“Alnylam is focused on building a top-tier biopharmaceutical company, advancing RNAi therapeutics as a whole new class of medicines with transformative potential for patients around the world. This exciting new relationship with Blackstone brings us much closer to that goal, securing our bridge towards a self-sustainable financial profile that we believe can now be achieved without any need for Alnylam to access the equity markets in the future,” said John Maraganore, PhD, CEO of Alnylam, in the press release. “A central component of this strategic relationship is a partial monetization of our royalty for inclisiran. If approved, we believe this therapy holds enormous promise as a potential game-changer in hypercholesterolemia management.”


Takeda and Evox Enter into a Rare Disease-Focused Partnership for $882 Million

Takeda and Evox Therapeutics, a United Kingdom-based exosome therapeutics company, announced on March 26, 2020 that they are entering into a rare disease-focused partnership for up to $882 million.

Through the agreement, Evox will receive $44 million in near-term milestone payments and research funding and is eligible to receive $882 million in upfront, development, and commercial milestone payments from Takeda, a press release said. Additionally, Evox will handle R&D activities for each program until investigational new drug-enabling studies as well as manufacturing up to and including Phase-I clinical trials. Takeda will reimburse Evox for manufacturing costs, according to the agreement.

The partnership will focus on the development of up to five novel protein replacement and messenger ribonucleic acids (mRNA) therapies, including Evox’s preclinical program for Niemann-Pick disease type C, a genetic disorder that inhibits the body from transporting lipids into cells, the press release said. Takeda will also have the option to select three separate rare disease targets.

“Evox Therapeutics has developed a novel approach toward treating devastating diseases, such as Niemann-Pick Type C. The targeted and non-targeted exosomes offer a highly differentiated platform with the potential to enhance tissue delivery for a variety of payloads like mRNA and proteins,” said Madhu Natarajan, head of the Rare Diseases Drug Discovery Unit at Takeda, in the press release. “Collaborating on the Evox exosome platform also complements our expanding capabilities in cell and gene therapies, particularly with the potential to develop new delivery approaches in addition to our cutting-edge adeno-associated virus platform, to provide transformative therapies or functional cures for people living with rare diseases.”


Thermo Fisher Scientific to Acquire Qiagen for $11.5 Billion

Thermo Fisher Scientific announced on March 3, 2020 that it is acquiring Qiagen, a Netherlands-based sample and assay technologies provider, for $11.5 billion.

Under the agreement, Thermo Fisher will acquire the company for €39 (US$43.69) per share in cash and the transaction is subject to the satisfaction of customary closing conditions, a press release said. The deal is expected to close during the first half of 2021.

This acquisition will give Thermo Fisher the opportunity to expand its portfolio with Qiagen’s molecular diagnostics capabilities and infectious disease testing, while broadening its commercial and geographical reach through Qiagen’s product portfolio, according to a press release.

“We are excited to bring together our complementary offerings to advance our customers’ important work, from discovery to diagnostics,” said Marc N. Casper, chairman, president, and CEO of Thermo Fisher Scientific, in the press release. “This acquisition provides us with the opportunity to leverage our industry-leading capabilities and R&D expertise to accelerate innovation and address emerging healthcare needs. For shareholders, we expect the transaction to be immediately accretive and to generate significant cost and revenue synergies.”

Catalent to Manufacture J&J’s Lead COVID-19 Vaccine Candidate

Catalent’s Biologics business unit announced the company’s Bloomington, IN facility will accelerate availability of manufacturing capacity and prepare for large-scale commercial manufacturing of Johnson & Johnson’s lead vaccine candidate for COVID-19.

In an April 29, 2020 press announcement, Catalent reported a joint investment with Johnson & Johnson to accelerate scale-up of segregated manufacturing capacity to support dedicated production of the drug company’s investigational vaccine candidate. Catalent said it will hire 300 additional employees for the Bloomington site starting in July 2020 “to meet operational readiness and 24x7 manufacturing schedules by January 2021.”

Catalent’s 875,000-sq.-ft. Bloomington facility has capacity for sterile formulation, with drug substance development and manufacturing and drug product fill/finish capacity for liquid and lyophilized vials, prefilled syringes, and cartridges, in addition to primary and secondary packaging.


MilliporeSigma Adds Viral Vector and Gene Therapy Capacity

MilliporeSigma announced in an April 21, 2020 press release that it is building a second commercial facility in Carlsbad, CA, for its viral and gene therapy contract development and manufacturing services. The new, $110-million commercial facility is expected to open next year.

MilliporeSigma’s existing Carlsbad facility manufactures gene therapies for its customers globally, and it was expanded in 2016 to 65,000 square feet, giving it 16 modular viral bulk manufacturing cleanroom suites with single-use equipment and two fill/finish suites for gene therapy, viral vaccine, and immunotherapy products.

The new, 140,000-square-foot manufacturing facility being built will support viral and gene therapy production at the 1000-L scale using MilliporeSigma’s Mobi-ius single-use equipment. It will add 11 suites used in various steps of manufacturing. The new site is located near the existing site in Carlsbad, and the company says it will leverage capabilities across both sites.


Room temperature crystal structure publication for Atazanavir, a potential drug for treating COVID-19, is available from International Centre for Diffraction Data, ICDD®
# Ad Index

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption Systems LLC</td>
<td>41</td>
</tr>
<tr>
<td>Adare Pharmaceuticals</td>
<td>47</td>
</tr>
<tr>
<td>BASF</td>
<td>49</td>
</tr>
<tr>
<td>BioSpectra</td>
<td>15</td>
</tr>
<tr>
<td>Catalent</td>
<td>64</td>
</tr>
<tr>
<td>Coating Place</td>
<td>3</td>
</tr>
<tr>
<td>Contec, Inc</td>
<td>51</td>
</tr>
<tr>
<td>CordenPharma International</td>
<td>13</td>
</tr>
<tr>
<td>Emergent Biosolutions</td>
<td>17</td>
</tr>
<tr>
<td>FG Clean Wipes</td>
<td>29</td>
</tr>
<tr>
<td>International Centre for Diffraction Data</td>
<td>60</td>
</tr>
<tr>
<td>LIGAND</td>
<td>7</td>
</tr>
<tr>
<td>PDA</td>
<td>11, 63</td>
</tr>
<tr>
<td>PYRAMID LABS</td>
<td>9</td>
</tr>
<tr>
<td>Renishaw</td>
<td>37</td>
</tr>
<tr>
<td>ROSS Mixers</td>
<td>19, 61</td>
</tr>
<tr>
<td>Samsung Biologics</td>
<td>2</td>
</tr>
<tr>
<td>STERIS Corp. Life Sciences Marketing</td>
<td>25, 26</td>
</tr>
<tr>
<td>Syntegon Pharma Technology, Inc.</td>
<td>27</td>
</tr>
<tr>
<td>Tergus Pharma</td>
<td>39</td>
</tr>
<tr>
<td>VELTEK ASSOCIATES, INC</td>
<td>5</td>
</tr>
<tr>
<td>Wacker Chemie AG</td>
<td>23</td>
</tr>
<tr>
<td>WuXi STA, a WuXi AppTec company</td>
<td>53</td>
</tr>
</tbody>
</table>
Starting a Career in the Bio/Pharmaceutical Industry

Having a better understanding about compliance will be of benefit when looking for a job or for furthering one’s career, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

Q.
While working on a variety of projects in three different continents, I had the opportunity to meet and work with young, enthusiastic newcomers to the industry. They were from a variety of different professional backgrounds, including pharmacists, engineers, and chemists. During our conversations, most of them asked the following types of questions:

- The college or university I graduated from did not provide courses on compliance or industrial operations—how can I fill this gap?
- Though I applied for many positions, I have been unable to find a permanent position yet—how can I improve my chances?
- On the Internet, I found several courses on good manufacturing practices (GMPs), for compliance experts, or similar. These are relatively expensive. Are they worth investing for someone like me (a beginner)?
- Should I work my way up within a particular department or would it be better if I gain experience in different departments?

A.

The following are not exhaustive or the only answers to these questions, but they will give some insight.

It is true that few graduates have seen industrial operations by the time they graduate, but that doesn’t mean that they don’t come equipped with many of the basic skills needed in the industry, such as team working, presentation skills, analytical thinking, and the ability to self-study. Companies will provide training, as a minimum on the applicable and relevant internal processes and procedures, which will cover both the operations and the compliance side of the business. A lot will be learning on the job, from peers and often also from mentors.

Finding your first permanent job can be a frustrating experience, but persistence usually pays off. Gaining experience through temporary voluntary engagements, placements, or positions is what helps improve the chances for long-term or permanent employment. And don’t forget to network through portals such as LinkedIn, Bing, or similar sites that have a good reputation with industry and job agencies. Also, it’s important to write a succinct and well-thought-out curriculum vitae, and there is a lot of great advice available for free online on how to do this. The Internet is the place to research jobs, but often also for potential employers to find the right candidate.

Having a better understanding about compliance will surely be of benefit, whether looking for a job or for furthering one’s career prospects. Whether you are lucky enough to have your employer pay for external courses, be subsidized (e.g., by a state job center), or have to pay yourself, in all cases you should scrutinize the courses offered:

- How relevant are they to your current or prospective work?
- Do they provide references? Is there feedback available?
- Are the certificates merely proof of attendance or are they widely recognized by the industry?
- Is it just classroom learning or is there also a practical element?
- Do they provide comprehensive documentation?

The answers to these questions will help you determine if the course is right for you. For example, if you want to become a certified auditor (be it for GMP or ISO 9001), you will have to pay for a course with an approved training company. If however, you want to get a basic understanding of the freeze-drying process, you will easily find free tutorials online. Should you need hands-on experience, then training courses offered by universities or industry associations with in-house training centers will be the right choice.

Switching careers

What if you have been in the industry for a while, but would like to change positions and/or area of expertise? Very often this is less of a question of opportunity, but more of a question of an individual’s preferences. There are equally excellent subject matter experts who never strayed from their vocation (say regulatory affairs, quality control, or manufacturing) and who are perfectly happy in their jobs, and there are those who worked in different departments to become more universal experts. Pharmaceutical companies probably look more for experts in a particular subject, whereas service providers, such as consultancies or contract research organizations, may have a need for experts with more varied backgrounds.

We may not always find the job we want, but we can always learn from what we do, and it will always be a beneficial personal and job experience.
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