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September—the traditional back-to-school time—has arrived, and the annual holiday shopping season is sure to follow quickly. Personally, I don’t like rushing the holidays and shop at the last minute. The publishing profession, however, forces me to plan and work well ahead of the calendar.

While we have yet to enter the last quarter of 2019, the editorial team is looking ahead to 2020, planning topics, special issues, and features that Pharmaceutical Technology will cover next year. It is also prime time to remind readers of the opportunities to share knowledge about bioprocessing by contributing a technical article or peer-review paper to the publication.

Through peer-reviewed papers, technical articles, technology reports, regulatory and business columns, and expert commentary, Pharmaceutical Technology publishes objective information related to process development, formulation, manufacturing, analytics, drug delivery, packaging, and distribution topics in print magazines, digital publications, ebooks, and online at www.PharmTech.com.

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Peer-review papers are a vital part of Pharmaceutical Technology’s coverage of scientific and technical advances in biopharmaceutical development and manufacturing. Four types of peer-review papers are considered: standard data-driven, novel research; topical literature or patent review; technical case studies/technical application notes; and science-based opinion papers. Manuscripts for peer-review papers are accepted and reviewed on an ongoing basis; papers are published in the order in which they are accepted by the editorial advisory board. The review, revision, and acceptance process takes 6–8 weeks.

Pharmaceutical Technology editors also welcome technical articles that are not peer-reviewed from experts at bio/pharmaceutical companies, regulatory authorities, industry suppliers, and consultants. The magazine’s editorial calendar lists the topics scheduled for the monthly print issues, supplements, ebooks, or online at www.PharmTech.com. All submissions are reviewed and edited by the editorial team; final publication is determined by the editors.

Ideas for contributions should be discussed with the editors in advance, preferably four months prior to the publication date. The editors will review an abstract (250 words) describing the article focus and other details. If the topic is suitable, a word count—typically 1800–2000 words—and deadline are assigned. Final articles, figures, and signed license agreements are due approximately two months prior to publication.

The article/paper must be objective and cannot promote a company or its products; it must be original and submitted to Pharmaceutical Technology on an exclusive basis. The article/paper cannot have been published previously in any format, including a company website or marketing literature. Manuscripts should not be under consideration for publication elsewhere, including on the Internet. All authors must sign a license agreement that provides Pharmaceutical Technology permission to publish the original article and its associated figures/tables in print and online.

Share your knowledge

The editors also interview industry experts from biopharma companies, contract service providers, industry suppliers, regulatory authorities, and consulting groups for technical articles on drug development and manufacturing topics. And, similar to contributed articles, responses to questions must be objective and non-promotional. To be considered for an interview, consult the editorial calendar for scheduled topics and contact the editors approximately four months prior to the publication date.

Learn more

Pharmaceutical Technology’s 2020 editorial calendar, which lists topics scheduled for publication next year, is available on the Submission Guidelines page on www.PharmTech.com. In addition, prospective contributors can find more information about the submission process, link to sample articles, and use an online form to submit an article idea to the editors. PT
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The SLA5800 Series Biotech and the SLAMf Series Biotech are two new mass flow controller (MFC) models from Brooks Instrument designed specifically for improved gas flow control in biotechnology applications. The new models allow biotech equipment manufacturers to reduce the number of MFCs they need for their equipment, which allows them to simplify their designs along with reducing system costs, purchasing complexity, and spare parts inventory requirements.

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Improved Mixer Lift and Seal Designs
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More Predictable Post-Approval Change Policy on Horizon

Jill Wechsler

Industry and regulators seek global system that reduces regional differences.

Regulatory officials in the United States, Europe, and other regions are collaborating with manufacturers to advance a new framework for managing chemistry, manufacturing, and controls (CMC) changes more efficiently across the product lifecycle. The process is outlined in the Q12 guideline developed by an expert working group formed under the International Council for Harmonization (ICH) (1). ICH is expected to approve a revised core Q12 guideline at the November 2019 ICH meeting in Singapore, along with more detailed annexes and a global training plan for industry and regulators.

Support for a harmonized approach to authorizing new manufacturing and testing methods on approved drugs and biologics reflects general agreement on a risk-based system for categorizing and managing changes, despite continuing differences among authorities over specifics for reduced oversight of certain variations. In the works formally since 2014, the Q12 guideline is expected to provide flexible oversight of post-approval changes with reduced regulatory reporting for manufacturers able to demonstrate enhanced knowledge about product, manufacturing process, and analytical procedures, as provided by a company’s product quality system (PQS).

A key feature of Q12 outlines how manufacturers should define those established conditions (ECs) that are considered necessary to assure product quality. Thus, a change to an EC would require a regulatory submission, explained Chikako Torigoe, biologist in the office of the director of FDA’s Center for Biologics Evaluation and Research (CBER). At the same time, those parameters that have less risk of impacting product quality or process consistency would not be considered ECs and could be managed by a manufacturer’s internal PQS and implemented without prior approval, Torigoe noted at the July 2019 CMC Forum sponsored by CASSS (2).

Manufacturers may reduce ECs requiring regulatory approval through development and submission of a post-approval change management protocol (PACMP) that describes anticipated changes to a product or products. The PACMP would provide the basis for agreement between the applicant and regulatory authority about information required to support certain changes. PACMPs could involve multiple products, as with establishing a new process to improve product sterility assurance, upgrades to a vial wash room, or introducing a new product to a manufacturing facility. FDA is launching a pilot program to gain experience in assessing proposed ECs, with the aim of reviewing nine submissions of new drugs, generics, and biotech products to see how much time and effort is involved in identifying ECs at time of approval.

An approach similar to Q12 already has been established in Japan, pointed out Tomonori Nakagawa, API project manager at Otsuka Pharmaceutical Co., at the CASSS Forum. This initiative by Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) has produced a more efficient program for overseeing a robust change management system, he noted, based on a demonstration of product and process knowledge. And Health Canada is ready to implement ICH Q12, reported senior regulatory scientist Anthony Ridgway at Health Canada’s Biologics & Genetic Therapies Directorate. That agency has issued guidance on categories, conditions, and data expected for different reporting categories, and policies already are aligned to provide flexibility in defining ECs and in justifying reduced reporting. Health Canada encourages adoption of risk-based categorization of post-approval changes that require only notification or listing in an annual report, Ridgway.
said, adding that more work is needed to better define and align with ICH recommendations for PACMPs.

Kavita Vyas, policy lead in the Office of Policy for Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER), described ongoing FDA efforts to prepare to meet Q12 challenges. An agency group is examining case studies related to established conditions and anticipates gaining useful learnings from the upcoming pilot project. Alexey Khrenov, senior staff fellow at CBER’s Office of Tissues and Advanced Therapies (OTAT), noted that training is being developed to familiarize reviewers with Q12 approaches. Greater regulatory flexibility should benefit manufacturers, he commented, although the specifics for defining ECs and for assessing PACMP and product lifecycle management (PLCM) documents remains uncertain.

**Encouraging improvement**

Despite the challenges, manufacturers hope to move forward with Q12 as more products are tested, produced, and distributed in multiple regions, creating complex supply chains that trigger diverse testing requirements and inspection processes. It can take four to six years to add a new site or comply with a new standard for a product that is approved and distributed globally, noted Nakagawa. Similarly, consultant Moheb Nasr, formerly with FDA and Amgen, described how the current system discourages firms from adopting more efficient laboratory test methods and modern production systems.

Many manufacturers look to advance strategies for managing CMC changes under the firm’s PQS, as supported by a series of earlier ICH quality guidelines (Q8–11). Leslie Bloom, executive director of regulatory CMC at Pfizer, described efforts to develop PLCM plans to manage ECs over the product lifecycle even before Q12 is finalized. And ongoing efforts aim to provide more justification for a range of risks related to ECs and non-ECs, especially in process and analytical methods.

Kimberly Wolfram, director of global regulatory affairs CMC at Biogen, described herself as a “realist” in anticipating the benefits from Q12 after years of effort. While she hopes for less confusion in regional adoption of ECs and guidelines, she and others acknowledge challenges in gaining global alignment on change management protocols based on risk assessment to enhance access to therapies.

**References**

2. CASSS, “The Future of Post-approval Changes is Coming—Are You Ready for ICH Q12?” Conference (Gaithersburg, MD, July 2019).
Front-end focus and new approaches are speeding scale-up and reducing costs, while scale-down and scale-out become increasingly important.

Years ago, scaling up the production of a new therapy was a linear, iterative process that demanded patience and deep pockets. Best practices, and more than a little trial and error, moved processes from the bench to the manufacturing floor. Over the past decade, as manufacturing operations have become more complex, engineering advances in modeling, digitalization, single-use process equipment, and process intensification have made scale-up more systematic, for both small and large molecules.

“A decade ago, most scale-up would have been a very linear process with lab-scale going to kilo lab-scale to pilot plant-scale and, for successful products, to an in-house existing batch production facility. Now there are many more nodes of partnerships and equipment choices to be made,” says Joe Hannan, CEO of Scale-Up Systems. “It’s no longer just about getting reaction, workup, and isolation steps to work as best they can in existing multi-purpose equipment, but also about reconfiguring modular components in a continuous process to fit the equipment to the requirements of the chemistry. This is allowing a lot more more innovative thinking and is pushing the boundaries in developing chemistry in ways that were not considered feasible until recently,” he says.

As a result, scale-up is becoming a more finely tuned process, with scale-out and scale-down playing more important roles. “The era of blockbuster production strategies has transitioned into scale-out and even scale-down for most of the bioproduction market,” says Michelle Stafford, global product marketing manager, Enterprise Solutions, GE Healthcare. “Multiproduct production models that utilize single-use technologies are now more common, and scale-out is becoming the norm, where increased flexibility and platform standardization enable faster changeover between batches and faster tech transfer,” she says.

Changing scales during the lifecycle
At the same time, contract development and manufacturing organizations (CDMOs) have assumed a dominant position in scale-up and must master a wide range of scales to meet clients’ needs. “Speed to clinical phases is faster now, and biopharmaceutical manufacturers are targeting smaller patient populations and specialized drugs in order to access the market faster, reach patients, and get financial returns sooner than ever before,” says Stéphane Varray, head of commercial development in Lonza Pharma and Biotech’s mammalian and microbial
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development and manufacturing business unit. “Based on that paradigm shift, manufacturing scale needs to be adaptable along the full lifecycle of the product. Moving from a small scale to a larger—or vice versa—must be done smoothly, in the context of a regulatory framework that is growing more complex,” he adds.

“Overall, the scale-up process remains the same, regardless of the volume of product being produced, but strategies have changed,” says Sebastien Ribault, senior director of MilliporeSigma’s global Bioreliance end-to-end delivery and sales, and managing director of MilliporeSigma’s Biodevelopment Centers, the company’s CDMO division. “We are not using one scale in the lab and another one in the facility anymore, but multiple scales in the facility,” he says. In 2010 and 2011, he says, the company invested in developing models to help its scientists understand how biomolecules behave at various scales, he says. As a result, he says, it has scaled all biopharmaceutical processes up directly (i.e., in one pass) since 2012, where previously, efforts may have required going back to the drawing board.

Solid dosage scale-up

Within the past five years, pharmaceutical manufacturers have become more comfortable with advanced process control and are embracing other advanced manufacturing concepts, says Fernando Muzzio, professor of pharmaceutical science at Rutgers and head of the Center for Structured Organic Particulate System (C-SOPS), which has been focusing on tech transfer and commercialization of continuous manufacturing processes for solid dosage forms.

Hannon, whose company specializes in scale-up simulation software for small-molecule APIs, sees a definite change in the way that manufacturers are approaching simulation. Where five years ago, they might simply require that a unit operation undergo simulation studies and specify the time required, they are now using simulation to couple batch kinetics with continuous equipment characteristics. “They want to operate flow chemistry optimally on the first run,” he says. “We are now seeing more of an appetite for deep process understanding around the reaction and impurity-formation mechanisms to support right-first-time operation in flow on scale,” says Hannon.

More interest in continuous

Branded pharmaceutical and even generic-pharmaceutical manufacturers are increasingly interested in continuous manufacturing, says Muzzio, which allows development and manufacturing to take place at the same scale on the same equipment, eliminating the equipment scale issues that have dogged scale-up in the past. Most new chemical entities (NCEs) that are going from lab to larger scale still face scaling challenges, however, in that the next level equipment is significantly larger than the laboratory equipment, says Hannon. “Sound chemical engineering principles such as mixing and heat transfer must be engineered in for successful operation. And scale-down (i.e., being able to mimic production scale conditions closely in a laboratory setting) remains key to scale-up success, especially when troubleshooting a process,” he says. Beyond troubleshooting, Muzzio sees growing interest in scaling down to smaller lines for continuous solid-dosage form manufacturing. “Some companies are working with 5 kg/h, and a few, with 1 kg/h, which is ideal for products that use very small amounts of powder,” he says.

He recalls one company that opted to start with a very small line and to duplicate that line four times to manufacture a large-volume product continuously. “This approach makes sense, because the integration of process, software, and sensors accounts for a significant fraction of overall costs. If you simply copy one line, the additional capacity will not add too much to overall costs.” However, he notes, scale down must be approached carefully to avoid having to redo scale-up later on. In addition, he says, scale-down can be particularly challenging with powders, which can be much more difficult to transfer and mix at small scale than at larger scales.

Biopharm process intensification

Process intensification is becoming more important in biopharmaceutical manufacturing evidenced upstream by perfusion bioreactors and downstream by continuous chromatography. Tangential flow filtration (TFF) is becoming more prominent. In August 2019, Samsung Biologics scaled up alternating tangential flow (ATF) in a perfusion bioreactor at its manufacturing facility in South Korea. Samsung expects it to reduce processing time by 30%. Pressures to reduce cost of goods sold (COGS) and to meet smaller, specialized market demands are driving use of process intensification. “The goal is to increase productivity per some form of tangible measurement, such as in time, volume, or dollar,” says Andrew Yang, global product marketing leader for upstream bioprocessing at GE Healthcare. By integrating technologies, simplifying operations and offering insights via analytics, he says, it “offers a path to risk reduction and economic global manufacturing in an increasingly fragmented market.”

Scaling down

As Ribault notes, manufacturing scales have come down overall. MilliporeSigma is no longer using 10,000–15,000-L volumes for most of its work. “Now, our facilities are running at 2000 L or below. When we need more volume, we operate with multiples of 2000 L,” he says. The philosophy behind scale-up has remained the same, however. “You still need to understand the platform and the differences not only for downstream but the impact of change of scale for upstream, which means gaining a clear understanding of the impact of agitation and power input, and also the quality of the molecule. Agitation and oxygenation give you a cell that will result in the right level of product quality. That is what
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we focus on when we scale up,” he says.

Modeling and scale-down studies are playing a greater role in providing key process knowledge required for scale-up. AbbVie, for example, used a combination of mass-transfer studies (KLa), computational simulation (i.e., the use of computational fluid dynamics to model shear-rate distribution within the bioreactor), and scale-down (i.e., developing proof-of-concept on a small scale in the lab, then scaling up to 200 L) in one recent project, in which the time required to reach process performance qualification (PPQ) was reduced to 18 weeks (1).

Ribault predicts that the use of digital twin technology will become more important. “In the future, we won’t need to run some steps at the bench and will be able to run process in-silico before running at bench,” he says. Multivariate data analysis is also becoming more important in allowing developers to use production data to determine optimal characteristics for components and equipment parameters and use those characteristics in a model to optimize scale-up and manufacturing, says Stafford.

Coordination with tech-transfer

In general, scale-up success demands coordination with tech transfer, and good project management and documentation are key, says Ribault, who notes that smaller research company clients may need to understand that research data alone cannot move a project to good manufacturing practice (GMP). “We don’t want to rush because we know the bare minimum that is required to scale up without intermediate scale and engineering runs. If we deviate from that bare minimum, we will not be managing the risk properly. In the attempt to save a few weeks, we may wind up wasting a few months, or even quarters,” he says.

To address these challenges, CDMOs and customers together should take a careful and forward-looking approach to planning for commercial supply, says Varray. This should include a clear idea of the scale of development, planning for a biologics license application, and a sophisticated regulatory approach. “This plan may be drafted as soon as Phase I is cleared. External partners can work together with customers to adapt manufacturing set-up and regulatory strategy while the clinical phase is ongoing,” he says.

Scale-up and scale-out merge

Process intensification enables scaling out or building incremental capacity rather than scaling up to larger equipment. As this approach gains acceptance, the distinctions between scaling up and scaling out are blurring. “With the adoption of high titer processes, process intensification including continuous processing, and perfusion, the definition of scale-up and scale-out are synonymous such that requirement for product volumes are lower that can be achieved with single-use technology and replicated with increasing demand,” says Kenneth Dawson Green, manufacturing team leader with Samsung Biologics.

At large scale (15,000 L), utilizing stainless-steel bioreactors, Samsung replicates the number of bioreactors required to achieve the optimal volumetric scale (up to 180,000 L), he explains. However, for single-use, the typical working volume is between 2000–5000 L and replicated to achieve desired scale, he says. Increasingly, single-use and stainless-steel technologies are being used in hybrid systems such that the bioreactor seed train may utilize single use bioreactors, and the production scale utilizes stainless steel. Samsung uses hybrid systems for both upstream and downstream processes, Green says, factoring applicability, cost, ease of operation, operational risk, and waste-minimization into equipment selection, he notes.

It remains to be seen whether scale-out will become the preferred route for biopharmaceutical manufacturing in the future. At this point, both approaches are needed. “Adoption of continuous manufacturing, including perfusion, has led to the requirement for reduced product volumes with higher productivities for some products. The option to scale-out vs scale-up presents lower process risk and enables more efficient tech transfer when processes are transferred at the same scale,” says Green. However, he notes this approach is more practical with single-use technology and clinical products for which capital investment may be deferred. “For larger volume commercial products including biosimilars, large-scale stainless steel equipment will remain the most cost-efficient platform,” Green says.

Cell and gene therapies

Increased cell- and gene-therapy development also poses questions for scale-up. “In cell and gene therapy, we see both forms of scale—up and out,” says Phil Vanek, general manager of cell and gene therapy strategy at GE Healthcare, who says all three approaches are needed. While many of the therapies today are autologous or patient specific, Vanek says, for certain applications (e.g., acute injury or nondurable treatment duration) allogeneic versions of autologous therapies may be preferred for access or cost reasons.

“We use scale up where we can make multiple doses to serve large markets; scale out to meet the needs of patient-specific therapies, and, perhaps most importantly, scale-down in the appropriate high dynamic range platforms to do process development,” Vanek says. Process development can typically be cost-prohibitive, so platforms that mimic large-scale (up or out) systems, but at smaller scale, will allow quicker process optimization, regardless of scale,” he says. At this point, Vanek says, “The jury’s still out on whether scale-out or scale-up will prevail.”

Reference

Explore The BioContinuum™ Platform

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The rapid advance of gene and modified cell therapies and growing interest in viral vaccine therapies are creating significant demand for large-scale viral-vector manufacturing capabilities. Biopharma companies and contract manufacturers alike face a host of challenges as they work to meet this crucial market need, from a limited availability of technology to a lack of standardization to complex and evolving regulatory pathways.

Many significant challenges

There are numerous challenges to sourcing effective large-scale manufacturing solutions for viral vector production. Based on conversations with customers over the past several years, Univercells has identified the major hurdles in large-scale virus manufacture, which include expensive manufacturing facilities, lack of expertise, limitations in the number of scalable manufacturing technologies available in the market, and the high cost of good manufacturing practice (GMP)-grade reagents including transfection mix, plasmids, and bovine serum, according to Thomas Theelen, business development manager at the company.

"Equipment and facility setup using the technology that is available, most of which has been adapted from other therapeutic areas, is very expensive and often does not support product manufacture through different maturity stages including process development, clinical trials, and commercialization. In addition, the level of expertise around developing large-scale manufacturing processes for gene therapies is limited, and the use of flatware for cell culture and sub-optimal downstream processing protocols result in low yields; both factors also influence the overall cost of goods sold (COGS),” Theelen explains.

"Existing manufacturing processes are often complex with hard-to-control unit operations and unfavorable COGS profiles,” agrees Xin Swanson, head of commercial development for viral vector gene therapy, Lonza Pharma & Biotech. As an example, she points to the widely used transient transfection process for associated adeno virus and lentivirus (AAV and LV, respectively) production, which mainly uses adherent cells and lacks scalability and lot-to-lot consistency due to variability in transfection efficiencies. In addition, she notes that many downstream processes for early-stage clinical production often employ gradient centrifugation steps that lack the ability to be furthered scaled.

"Overall the volumetric productivity of virus particles per cell from culture systems and complete virus recovery rates through downstream processing are suboptimal among existing production systems, both of which negatively impacts COGS. As a result, the lack of standardized production platforms that support industrialized scale processes is the leading challenge,” Swanson concludes.

Further complicating the situation is a lack of standardized and advanced analytical methods for vector characterization and release testing (including in-process samples), which makes it difficult to have well-understood manufacturing processes before incorporating process improvement steps, according to Swanson. Other challenges include a lack of automation in key steps of the manufacturing process; immature supply chains, which creates risk and leads to a lack of standardization/innovation of critical raw materials; and rapidly advancing regulatory pathways that are complex to manage among different jurisdictions.

Increasing urgency

Many of these challenges have existed for several years, with some developments occurring along the way. For instance, Theelen observes that novel scalable bioreactor systems, the implementation of continuous bioprocessing, and the introduction of new resins for viral vector purification are having an impact. “Several companies are developing suspension-based processes and implementing stable producer cell lines,” he notes. However, he adds that even though stable cell lines have the potential to significantly reduce COGS, developing robust processes using these stable cell lines is still a challenge. The same is true for suspension-based pro-
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cesses, which currently require significant investments in process development and extend the time to market.

What has largely changed, according to Swanson, is the timeline for overcoming these challenges. "It is critical to meet the clinical and commercial manufacturing needs for these curative therapies, and the need is becoming more urgent due to the rapid advance of clinical progress. The lack of manufacturing scalability has created a vector shortage, and the collection of sufficient vector chemistry, manufacturing, and controls (CMC) information has become a bottleneck during the product development lifecycle," she asserts.

Theelen adds that to ensure that more gene and other next-generation therapies reach patients, reducing COGS is necessary to increase availability, facilitate reimbursement, alleviate the burden on healthcare budgets, and ensure that innovator companies can offer their products at an affordable price while maintaining sustainable gross margins. "Scalable and reliable technologies for cost-effective cell and gene therapy manufacture will reduce the reliance of biopharmaceutical companies on hard-to-acquire expertise and dependence on contract development and manufacturing organizations (CDMOs)," he says.

Additionally, Theelen notes that developing technologies that facilitate process and product development will shorten the time-to-market and reduce development costs, while increasing the number of technology candidates will intensify competition and finally drive down materials and equipment costs.

**Innovation is a priority**

Technology innovation is key to addressing the challenges associated with large-scale GMP viral vector manufacturing, agrees Tânia Pereira Chilima, NevoLine product manager at Univercells. "Solutions that are tailored for gene therapy manufacture and combine a low capital investment, scalability, ease-of-operation, and robustness while maintaining product quality are needed," she comments.

It is also important that these technologies are able to accommodate the manufacture of gene therapy products with low and high annual demands in order to ease the development and commercialization of personalized gene therapies and viral vector-based vaccines. Lowering the capital investment is also necessary for reducing the entry barriers for gene therapy start-up companies.

Swanson adds that all of the major challenges must be tackled concurrently in order to address the manufacturing challenges. "The optimal goal is to deliver products that will meet target product profiles with defined quality attributes while realizing the need to increase process productivity and reduce COGS," she says.

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viral vector production. “Given the fast pace of clinical development timelines and the unconventional demand curve of curative therapies, CDMOs offer competitive advantages not only from a manufacturing technology advancement perspective, but also from a cost perspective with respect to optimizing capital expenditures and better managing operating expenses,” Swanson states.

Pereira Chilima agrees that CDMOs are a major gateway for the adoption of new technologies. “Many established gene-therapy developers rely on CDMOs throughout all stages of product development and even once they reach the commercialization stage. The expertise of CDMOs in large-scale production helps cell therapy developers evaluate different avenues for cell therapy manufacture and select the technologies to be used once they decide to internalize product production,” she explains.

CDMOs are also in the unique position of developing and providing manufacturing platform processes that will allow drug developers to focus on product innovation and significantly shorten the gene-to-product development timeline, according to Swanson.

**Achieving some progress**

One of the most important developments highlighted by Swanson has been the transitioning of cell-culture processes from an adherent format to a suspension format via cell-line adaptation, which is enabling better scalability. Development of stable producer cell lines is also reducing process variability and enabling the adoption of intensified processing solutions. A better understanding of the important qualities of critical raw materials, such as animal serum, plasmids, non-chemically-defined media, and the extractables/leachables associated with single-use technologies has also helped to address some manufacturing challenges.

Incorporating design-of-experiment study principles and use of improved bioprocess control and data analysis software are allowing process development/optimization to be conducted at the multiparameter level, while new analytical methods, such as more accurate viral vector quantitation techniques, provide a better understanding of impurity profiles and allow for better process monitoring. In downstream processing, density-gradient centrifugation is being replaced with chromatography methods for more consistent and efficient operations.

**Lower capital investment will reduce the entry barriers for start-up companies.**

**Collaboration is key**

Collaboration between the different stakeholders in the industry is necessary to build on preexisting expertise and capitalize on academic innovation to help guide technology developers on the gaps that must be addressed in the industry, according to Pereira Chilima. Adds Swanson, “Collaboration between members of the value chain, ranging from innovators, manufacturers, and reagent and equipment suppliers to regulators, as well as close collaboration between academic and industry partners, is critical in driving solution development.”

Pereira Chilima also notes that involving the regulatory bodies and payers early on is needed to reduce regulatory barriers and ensure adequate reimbursement. These types of collaborative efforts are ongoing, she says. Good examples include the efforts made by the Cell and Gene Therapy Catapult and Cobra Biologics to investigate continuous manufacturing. Univercells is also actively discussing promising collaborations with established gene therapy companies with the aim of combing its expertise to develop manufacturing solutions for end-to-end viral vector production for gene therapy applications.

**Platform development**

Lonza has invested substantial internal research and development efforts in platform development, particularly in the area of AAV and LV production. Specific focus areas include scalable suspension-based transient transfection processes and stable producer cell-line technologies, according to Swanson. Concurrently, the company is investing in the development of novel analytical methods and new media formulations with the aim to provide turnkey solutions.

Separately, Lonza has invested heavily in a manufacturing capacity expansion with the opening of its dedicated, 300,000-sq.-ft. cell and gene therapy facility in Houston in 2018. The facility uses an extensive modular design concept and employs single-use technologies to allow clients quick access to scaled-up production capacity based on project needs.

Univercells, meanwhile, has developed the NevoLine platform, a modular and automated manufacturing system delivering affordable viral products such as vaccines and gene therapy vectors. This design of the NevoLine platform relies on a modular approach, allowing for a variety of configurations that provide tailored solutions for a range of products, according to Pereira Chilima. Viral-vector-specific NevoLine platforms can be designed for enabling AAV or LV manufacture for small- and large-scale applications.

At the core of the NevoLine platform lies the scale-X fixed-bed bioreactor coupled with in-line product concentration to intensify upstream processing and deliver large product quantities within a reduced footprint. “Intensification of each unit steps allows for drastic footprint reduction, enabling the entire process to be placed in self-contained modules such as isolators or biosafety cabinets,” Pereira Chilima explains. “The platform aims to minimize the capital investment for gene therapy manufacturers while delivering the low COGS and flexibility required to support the development and commercialization of gene therapy products, eventually ensuring their availability to patients,” she says.
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Oral solid-dosage forms are commonly examined by time-consuming, off-line tests of only randomly chosen samples. This article discusses an alternative, fully integrated, at-line spectroscopic quality control approach for oral solid dosage forms and presents the findings of a case study in this field.

### Benefits of PAT solutions

Process analytical technology (PAT) tools allow process monitoring and process control of the critical parameters during production. Furthermore, in many cases, PAT even provides a better process understanding.

PAT tools are mainly integrated as in-line, on-line, or at-line solutions. In-line and on-line techniques perform frequent measurements directly in the product stream, allowing fast reaction and even process control. The difference between these two solutions is how the PAT tool is integrated into the process; on-line uses a sampling loop while in-line refers to measurements directly in the process stream. These solutions are the methods of choice for detecting short process disturbances. Nevertheless, integration into the process and, in particular, the requirement to find a representative measurement position without disturbing the process, might be challenging.

For at-line PAT tools, the samples are commonly withdrawn out of the process, and the analysis is performed on the defined number of samples in the production environment. Several tests can be performed on exactly the same sample during the manufacturing process, such as measurement of weight and content needed for a content uniformity assay. Therefore, such a system is a good start for the definition of the real-time release (RTR) strategy. Furthermore, as the analysis is performed directly after the manufacturing step (not off-line in the lab), it enables the manufacturer to react immediately to process variations and reduce waste by potentially stopping the process and recapturing the powder.

### Advantages of spectroscopic techniques

Spectroscopic techniques, such as near infrared (NIR) spectroscopy, are non-invasive, non-destructive, and allow fast quality control investigations on higher amounts of samples during the complete manufacturing process. Thus, NIR exhibits great potential as a PAT tool for control of the critical parameters during production and better process understanding. Furthermore, the same NIR measurement delivers information about chemical and physical attributes of the sample. Thus, it is applicable for measurement of API concentration, moisture, density of the sample, and so on.

Two major measurement approaches for NIR spectroscopy, transmission and reflection, are possible. Reflection is the method to choose on moving samples (e.g., powder, tablets) due to its ability to measure at high speed and its low sensitivity to changes in sample thicknesses. One limitation is that the penetration depth of the NIR light has to be taken into account, with a special focus on the ratio of measured volume to the whole sample volume.

For at-line measurement on a static sample, transmission is a better solution; because the light signal travels all the way through the sample (rather than partway through as in reflection NIR), the information within the sample is acquired. Additionally, measurement on static samples brings an advantage of longer possible measurement time, allowing the usage of slower NIR spectroscopy devices with higher resolution.

The combination of measured sample volume, non-moving sample, and higher resolution for transmission...
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Tableting

PUTTING NIR TO GOOD USE IN TABLET FORMULATION AND MANUFACTURE

Oral-solid dosage (OSD) forms remain a popular choice for both pharmaceutical companies and patients. Convenience, ease of manufacture and administration, increased stability, and simplicity for pack and transport—compared with alternative dosage forms—are some of the factors leading to the continued popularity of OSDs.

According to market research, the global OSD formulation market is anticipated to grow by an annual compound rate of 6.5%, reaching a value of US$926.3 billion (€826 billion) by the end of 2027 (1). As tablets comprise a significant proportion of OSD forms, within the pharma industry, tools that can aid in formulation and manufacturing efficiencies are of critical importance.

One such tool that finds use in tablet formulation and manufacture is near-infrared (NIR) spectroscopy. To learn more, Pharmaceutical Technology discussed the technique and its uses in greater detail with Federica Giatti, compression technologist at IMA Active Process Development R&D Laboratory.

Useful in every step

PharmTech: Could you highlight the main uses of NIR specifically in tablet formulation and manufacture?

Giatti (IMA): NIR spectroscopy can be used in every step of the tablet formulation and manufacturing processes. For example, NIR is useful in tasks such as raw material identification, blend homogeneity, tablet characterization, and end-points determination in manufacturing critical process parameters.

Thanks to the efficient and non-destructive method offered by NIR spectroscopy in the detection and quantification of physical and chemical characteristics of tablets, it is possible to quantify many tablet attributes, such as drug content, hardness, and dissolution, non-destructively from a single measurement. Additionally, NIR can be useful for in-line process control, where it can be used to monitor whether or not tabletting is performed to the required quality level over time. The probe can deliver real-time data to prevent process deviations and stop the machine before powder has gone through the process area. Statistical post-process NIR analysis can be also implemented to verify, in a redundant way, the quality of tablets and compare with spectra acquired before.

Considering several variables

PharmTech: Why is it important to analyze materials to be used in tabletting, and how is NIR beneficial for these purposes?

Giatti (IMA): Several variables should be taken into consideration in a common tabletting process—variations in raw materials, deviations in granulation, or handling of all phases of formulation preparation could all affect the quality of the final blend.

Although NIR spectroscopy cannot be the primary analytical method for characterizing raw materials, its sensitivity to certain raw material characteristics (e.g., moisture content) allows for verification of the consistency between each API or excipient batch.

In the granulation process stages, a process analytical technology (PAT) approach based on NIR sensors allows for the simultaneous determination of multiple parameters by measuring on-line residual moisture and particle enlargement during all phases of the granulation process by achieving the desired quality attribute phase-by-phase and not at a predetermined time.

Verification of blend homogeneity is another interesting feature of NIR technology because it can lead to the avoidance of issues caused by chief sampling used in traditional content uniformity testing of powder blends. The spectral information can provide data about qualitative features of the blend (possibility to predict mixing end-point) or quantitative characteristics (API content) for building a specific calibration model.

Furthermore, NIR spectroscopy is useful when trying to keep process variations under control. A big advantage of the technique is real-time optimization of the process parameters by reducing the risk of batch rejection. This benefit is achievable as information about process or material properties can be obtained in a shorter period of time.

Uses for dissolution testing

PharmTech: Can NIR provide significant benefits in dissolution testing?

Giatti (IMA): NIR spectroscopy has been evaluated by numerous investigators for predicting dissolution profiles in a PAT approach. The major benefits provided by the technique are that it is a fast, non-destructive method allowing users to overcome the issues of a potentially long, drawn-out analysis as well as the small sample size that is commonplace in standard dissolution tests.

Moreover, dissolution can be predicted to a certain level of reliability through calibration model development (e.g., partial least squares) when API content is variable. In addition, as NIR spectroscopy can detect the physical characteristics of tablets or a powder blend, tablet hardness variation can be monitored with NIR spectra. It is well known that as strength increases, API release decreases, and so for this reason, if the NIR spectra are studied extensively, dissolution behavior can be accurately predicted.

What might the future hold?

PharmTech: In your opinion, what does the future hold in terms of NIR spectroscopy within tablet formulation and manufacture?

Giatti (IMA): Regarding the future, particularly looking toward continuous manufacturing, NIR spectroscopy can help in the prediction of deviations from a quality gold standard using post-process chemometric algorithms. Through the acquisition of spectra continuously over time, pharmaceutical developers and manufacturers will be able to define specific areas or sections of the process when critical process parameters are under control, and also when out-of-specifications occur. For the latter situation, it could be possible to set up an alarm that can stop the machine and as a result avoid batch rejections.

Reference


—Felicity Thomas
NIR allows measurement of lower API concentrations compared to reflection NIR. However, the thickness of the sample might be a limitation for transmission, because the light needs to propagate through the sample. Tablets less than 9 mm thick are usually accessible by transmission NIR.

At-line PAT solution

To benefit from all the advantages of an at-line spectroscopic PAT solution, the PAT tool should be integrated into the process to allow frequent measurement and control during the process. For example, in an at-line tablet tester, the tablets are automatically sampled after the tableting process and pass individual measurement positions (e.g., tablet weight measured by a scale and API content measured by NIR). Subsequently, these values are transferred back to the process control system. As mentioned, this position is a good choice for the NIR spectroscopy transmission measurement, although there are additional challenges for integration into the process. It is well known that an off-line NIR spectroscopy lab analysis in transmission is a precise and reliable technique, but the positioning has to be as precise as possible, because it influences the signal-to-noise ratio. Additionally, unwanted scatter light, which escapes from the sides of a sample (tablet), also has a high influence on the measurement precision and should be avoided. Therefore, new challenges for an automated at-line PAT solution are precise and repetitive positioning and avoiding scattered light when measuring during the process.

Two of the main goals of at-line analysis are to replace the final analysis in the lab (e.g., high-performance liquid chromatography [HPLC] for the API concentration and content uniformity) or the direct release of batches after production (i.e., RTR). At least four release tests (i.e., identity, assay, content uniformity, and even dissolution) performed by NIR in combination with a scale might be a part of the RTR strategy and thus replace these lab tests. The following case study performed by Bayer in collaboration with Kraemer Elektronik and Fette Compacting shows that this goal is achievable.

Figure 1: The NIR Checkmaster (Kraemer Elektronik / Fette Compacting) is an automated tablet tester.

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Bayer tested a technique using an automated tablet tester equipped with NIR spectroscopy on a formulation with a low API concentration. In this study, the suitability of an integrated at-line transmission NIR spectroscopy solution to predict the API concentration of the sample tablets with an accuracy comparable to HPLC was investigated.

**Methods.** Tablets were produced on a rotary tablet press (2200i, Fette Compacting) with 6-mm round concave punches. The compression force and compression speed were varied to verify the robustness of the model. Tablets with eight different API concentration ratios (in the range of 0–6% API concentration) were compressed. Thereafter, the tablets were randomly assigned to either a calibration or a test set.

**INDUSTRY EXPERIENCES IN CONTINUOUS MANUFACTURING FOR ENCAPSULATION AND TABLETING**

Early adopters of continuous manufacturing approaches shared their plans and some of their experiences at the 11th annual Charles Jarowski Symposium in Industrial Pharmacy on May 6, 2019, at St. John’s University in New York City. Takeda Pharmaceuticals, which acquired Shire Pharma’s continuous manufacturing expertise when it bought the company, has continued continuous research and piloting efforts begun by Shire in 2016, according to Jim Bonner, Takeda’s director of small-molecule drug product, who spoke in the program (1). The company, along with Thermo Fisher’s Patheon, is exploring the use of continuous manufacturing for encapsulation as well as tableting, focusing on the continuous direct encapsulation of Vyvanse (lisdexamfetamine dimesylate), a treatment for attention deficit/hyperactivity disorder that was approved in 2007. Configuring encapsulation equipment for continuous manufacturing has been challenging, he noted.

The company has completed trial runs using near-infrared (NIR) and Raman spectroscopy, which involved scanning 30 different blends three times, then using product of least squares-based chemometric methods on reference gravimetric rather than high-performance liquid chromatography assay data. Extensive design of experiments work has also been done, and the company is anticipating approval of the continuous process by 2020. As Bonner pointed out, these efforts have underscored the need for more robust and economic process analytical technology options and simplified model maintenance. In addition, he believes that FDA should be shown that loss-in-weight feedback data are more accurate than data provided by NIR models.

Andrew Farrington, principal scientist for oral formulation sciences at Merck in West Point, PA, discussed the company’s pilot project, designed to build upon existing expertise in real-time release testing, raw materials monitoring, and quality by design (2). The pilot applies continuous-to-direct compression and film coating using tablet transmission NIR and tablet weighing instead of content uniformity, and hardness and disintegration instead of dissolution. The goals are to produce nearly one billion tablets per year with less than 90-day lead times from formulation to patient in a two-floor installation that is roughly one-third the size of traditional tableting facilities.

The company engaged early in discussions with regulators and is now working on both a continuous product development line, capable of manufacturing 5–20 kg/h of product, and a commercial line, with capacity of 10–90 kg/h. The advantages of the small-scale unit, he said, included a single point of control, facilitating remote equipment operation and potentially allowing operators to be removed from the processing environment. The company has developed a predictive model based on material attributes for continuous feeding and has also tested twin screw granulation. Although the company is optimistic about the role that continuous processes will play in the future, Farrington asserted that a mix of batch and continuous will be better for the industry’s assets and supply chains.

**References**


—Agnes Shanley
Subsequently, the calibration set tablets were measured with NIR Flex N-500 Solids Transmittance (Büchi Labortechnik). The calibration model was calculated with NIRSOL Software (Büchi Labortechnik) and then transferred to the NIR Checkmaster (Fette Compacting/Kraemer Elektronik). The NIR Checkmaster, shown in Figure 1, is a fully automated tablet tester with a built-in NIR Flex N-500 Solids Transmittance spectrometer.

The tablets are withdrawn out of the process and guided by the sampling gate of the tablet press to the NIR Checkmaster. The NIR Checkmaster positions the tablets by the rotating star wheel in front of individual testing stations: weight, thickness, hardness, diameter, and NIR transmission measurement cell, where the measurements are performed. Thereafter, all measured values (including API content measured by NIR transmission) are transferred to the tablet press. The tablet press can take an action based on the results. Furthermore, these results are included into the batch record.

The test set tablets with four different API concentration ratios were analyzed with the NIR Checkmaster, which was operated by the tablet press software. All tablets were measured with HPLC to determine the reference API concentration. Results of the NIR Checkmaster and HPLC were then compared.

Results and discussion. Figure 2 shows that the mean API HPLC values and the NIR Checkmaster values have comparable standard deviations for the four concentrations of the test set. The NIR Checkmaster values include manufacturing process variabilities, such as changes of the compression speed and the compression force. An exact positioning of the tablet using a patented format part tablet holder that always positions the tablet in the same way in front of the sensor was crucial for obtaining accurate results using the tablet tester. In addition, the holder avoids the occurrence of unwanted scatter light.

Conclusion
Based on the results that are shown in Figure 2, the presented at-line spectroscopic solution exhibits a great potential for a robust RTR strategy, because the NIR Checkmaster is able to predict the same concentration values with a comparable standard deviation as HPLC. Additionally, the tablet tester is fully integrated into the process, enabling process control and documentation. This PAT solution already offers several benefits along the road to RTR: process control and reduction of waste batch production, gaining of process understanding and process knowledge, and finally reduction or elimination of the off-line lab analysis.

Acknowledgments
The author would like to thank Dr. Adrian Funke, Reinhard Gross, and Dr. Albert Tulke from Bayer AG for the performance of the study and provision of the results.
Research compared the properties of corticosteroids processed by wet and dry milling for use in inhalation formulations.

WITHIN THE PAST FEW YEARS, MUCH HAS BEEN LEARNED ABOUT CHARACTERIZING THE PARTICLES USED IN INHALATION THERAPIES, WITH THE GOAL OF IMPROVING DRUG DELIVERY TO THE LUNGS. OPTIMIZING THE MANUFACTURING OF THESE THERAPIES REQUIRES AVOIDING PARTICLE INTERACTIONS DURING SIZE REDUCING, BLENDING, AND CAPSULE FILLING, BECAUSE THESE CAN AFFECT THE FINAL PRODUCT’S QUALITY.

IN AN INHALATION FORMULATION, THE PHYSICOCHEMICAL PROPERTIES OF SIZE-REDUCED DRUG PARTICLES STRONGLY AFFECT THE END PRODUCT’S STABILITY AND PERFORMANCE. PREVIOUS STUDIES REPORTED THAT SIZE-REDUCED APIs THAT HAD BEEN MILLIED USING DIFFERENT TECHNIQUES MAY PRESENT SIGNIFICANT DIFFERENCES IN TERMS OF MORPHOLOGICAL AND INTERFACIAL PROPERTIES (1,2). CHARACTERIZING THE PARTICLES’ SURFACE PROPERTIES IS KEY TO UNDERSTANDING API/EXCIPIENT INTERACTIONS AND THEIR IMPACT ON THE FINAL FORMULATION PERFORMANCE.

SELECTING THE MICRONIZATION TECHNIQUE IS CRUCIAL FOR PARTICLES THAT ARE TO BE USED IN INHALATION THERAPIES, BECAUSE IT WILL DETERMINE THE API’S PROPERTIES. FOR INHALATION DELIVERY, A NARROW AND CONTROLLED PARTICLE SIZE DISTRIBUTION (PSD) IS THE KEY TO IMPROVING AND CONSISTENTLY DELIVERING THE AERODYNAMIC PERFORMANCE. WITH A NARROW PSD AND Dv90<5μm, THE FRACTION OF PARTICLES THAT REACH THE LUNGS (FPF) WILL BE HIGHER THAN IT WILL BE IN FORMULATIONS WITH A WIDE PSD.

API/EXCIPIENT INTERACTIONS DEPEND ON PHYSICOCHEMICAL CHARACTERISTICS OF THE PARTICLES, SUCH AS MORPHOLOGY, ELECTROSTATIC CHARGE, CONTACT AREA, SURFACE ENERGY, CARRIER SURFACE ROUGHNESS, AND RELATIVE HUMIDITY. THUS, THE CHARACTERIZATION OF THE PARTICLES’ SURFACE PROPERTIES BECOMES THE KEY TO UNDERSTANDING THEIR SURFACE-BASED PHENOMENA, OFFERING INSIGHTS INTO INTERACTIVE FORCES AND ADHESION AFFECTING THE API, CARRIER AND DEVICE. SEVERAL STUDIES (2,3,4) HAVE SHOWN THE IMPORTANCE OF THE PARTICLE’S PROPERTIES TO THE EFFICACY OF THE FORMULATION AND ITS AERODYNAMIC PERFORMANCE.

THE OBJECTIVE OF THIS WORK WAS TO ANALYZE AND COMPARE PARTICLE ATTRIBUTES (E.G., SIZE, MORPHOLOGY, POLYMORPHISM, AND SURFACE PROPERTIES) OF TWO DIFFERENT CORTICOSTEROIDS THAT ARE INTENDED FOR INHALATION FORMULATIONS. THE MATERIALS WERE PROCESSED BY BOTH WET AND DRY MILLING.
Particle size-reduction techniques

The following size-reduction approaches were evaluated:

**Micronization.** Micronization is a high energy-driven process that may induce changes in the crystallinity of materials and form amorphous domains on the particle’s surface. These amorphous domains, even when present in very small amounts on the particle’s surface, have a significant impact on the material’s physicochemical nature. In addition, they may affect particle-particle interactions.

It is hypothesized that the milling process changes the orientation of molecules on the surface of the powder particles and changes surface energy (2). Additionally, the amorphous regions of the crystal tend to be converted into a more energetically stable crystalline form. The recrystallization of amorphous domains of the particles often leads to particle size growth and agglomeration as a result of molecular rearrangement phenomena occurring at the surface of the particles and, over time, can strongly affect the aerodynamic performance of a pharmaceutical formulation.

**Jet milling.** Jet milling (JM) is widely used in the pharmaceutical industry and remains the leading technology for particle size reduction and to obtain powders within the inhalation size range. In JM, the powder to be size-reduced is fed into a milling chamber where compressed air or nitrogen, usually in a vortex motion, promotes particle-particle collisions. Particle classification is made by inertia, following reduction via impaction and abrasion.

JM is a solvent-free and cost-effective technique capable of yielding an appropriate PSD for simple inhalation applications. During JM process, however, large quantities of energy are employed that may lead to undesired morphological changes, amorphization, and/or conversion in a different crystalline form of the APIs, often requiring post-conditioning steps. The conditions under which the particles are processed to attain lower PSD influence particle morphology and the surface energy of the products.

**Wet polishing.** Wet polishing (WP) is an alternative wet milling technique that circumvents the limitations associated with JM and is capable of generating stable crystalline material. Unlike JM, this technique uses an appropriate antisolvent to produce a suspension during the milling phase that is later removed during a subsequent drying step (e.g., spray drying).

The WP process is easily scalable, more reproducible than JM, and offers a much higher control over PSD, enabling finer PSD customization with narrower spans. Unlike JM micronization, which requires higher levels of energy and may result in a polymorphic form changing, WP requires less energy and maintains the polymorphic form, and, thus, is often considered preferable to JM.

Analysis and experimentation

To determine and compare the effects of various micronization processes, several batches of two APIs that are widely used in inhalation therapies were produced by wet and dry milling. The following methods were then used to evaluate the impact of size reduction techniques on the particles’ properties.

- Scanning electron microscopy (SEM) was used to study morphological properties

<table>
<thead>
<tr>
<th>API</th>
<th>Jet Milling</th>
<th>Wet Polishing</th>
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<tr>
<td>API-1</td>
<td>(a)</td>
<td>(b)</td>
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<tr>
<td>API-2</td>
<td>(c)</td>
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Figure 1: Scanning electron microscope (SEM) images of the two APIs micronized by jet milling (JM) and wet polishing (WP) (10000 X).
X-ray powder diffraction was used to characterize polymeric forms.

Dynamic vapor sorption (DVS), Brunauer, Emmett and Teller (BET) methods, and PSD were used to study physical properties.

PSD was measured using a laser diffraction analyzer (Malvern, Mastersizer 2000); morphology was studied via the scanning electronic microscope (Phenom ProX); specific area was determined using the BET method (Micromeritics, TriStar II 3020); water sorption value was measured using Dynamic Vapor Sorption (Surface Measurement Systems, DVS Intrinsic), and polymorphism was analyzed using a x-ray powder diffraction device (PANalytical, X’Pert PRO).

### Morphological properties

Scanning electron microscopy (SEM). Figure 1 presents SEM images of particles that had been previously micronized by jet milling and by wet polishing for the two APIs evaluated. After micronization, the particles exhibited different morphologies based on technique employed. For both APIs, the particles obtained by wet polishing exhibited a smoother surface and a higher degree of homogeneity than those obtained by jet milling. After the micronization process, API-1 (FF) particles had a plate-shaped appearance, where API 2 particles were of an irregular, rounded shape.

**X-ray powder diffraction (XRPD).** As shown by the diffractograms in Figure 2, both APIs, regardless of the micronization technique employed, exhibited a high degree of crystallinity and maintained the same correspondent polymorphic form.

Nonetheless, for several APIs processed via JM a post-production conditioning step was usually needed to convert the amorphous regions and to achieve a stable crystalline form.

### Physical properties

Table 1 presents the BET and PSD results for both APIs. BET values for API-1 were similar, regardless of the milling technique employed. In contrast, for API-2, the BET value was higher for the particles milled by JM than it was for those milled by WP. In addition, the BET values were higher for API-2 than they were for API-1. These findings can be explained by the particle morphology shown in Figure 1. For API-1 (for both JM and WP particles), a smooth surface translated into a lower BET surface area.

In contrast, for API-2, the particles processed by JM exhibited a rougher surface that translates into a higher BET value compared to the API particles micronized by WP, which presented a smoother and more polished surface and, consequently, a lower BET value.

Regarding the PSD, results showed that it is possible to use both methods to produce particles within the inhalation range. However, WP showed a number of clear benefits when compared with JM: not only can it enable a smaller PSD, it reduces variability between batches. Figure 3 shows the typical variability obtained by JM and WP processes when using the same process conditions. The standard deviation for the Dv90 of JM process is 0.32, while, for the WP process, it is 0.10. For highly dependent PSD formulations, therefore, WP presents a clear advantage to JM.

### Table 1: Brunauer-Emmett-Teller (BET) data and particle size distribution (PSD) of APIs 1 and 2. JM is jet milling and WP is wet polishing.

<table>
<thead>
<tr>
<th>API</th>
<th>BET (m²/g)</th>
<th>Particle size Distribution (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dv10</td>
</tr>
<tr>
<td>API-1 JM</td>
<td>4.96</td>
<td>1.06</td>
</tr>
<tr>
<td>API-1 WP</td>
<td>4.66</td>
<td>0.66</td>
</tr>
<tr>
<td>API-2 JM</td>
<td>9.15</td>
<td>1.009</td>
</tr>
<tr>
<td>API-2 WP</td>
<td>5.65</td>
<td>0.852</td>
</tr>
</tbody>
</table>

### Figure 1: Scanning electron microscopy (SEM) images of particles that had been previously micronized by jet milling and by wet polishing for the two APIs evaluated.

### Figure 2: X-ray powder diffraction (XRPD) imaging of wet polishing (WP) and jet milling (JM) of API-1 (left) and API-2 (right) particles.

### Figure 3: Typical variability obtained by JM and WP processes when using the same process conditions.
DVS results (Table II) show that, in the case of API-1, both samples behaved similarly during the analysis: they gained and released water reversibly without the formation of a hydrate form or the crystallization of an important amount of amorphous phase.

In the case of API-2, the maximum sorption value (at 90%RH) for both samples was quite similar (0.19%/w/w for WP and 0.17%/w/w for JM). During the desorption phase, however, the sample processed by JM lost approximately all the water it had gained, while the sample processed by WP retained part of the water gained. This difference is not significant, though, and both samples are classified as non-hygroscopic.

### Conclusion

The particle size-reduction method chosen to prepare inhalable drugs can strongly affect the PSD, particle morphology, and surface area of the formulation. The choice of micronization method should depend on the critical quality attributes that are desired for the particles in the given formulation. WP enables a finer level of control, reducing variability in the micronized API’s physical properties. This results in more uniform material, improving both batch homogeneity and batch-to-batch consistency. These API properties, in turn, can result in better final product performance (i.e., a formulation that delivers more API to the lungs) and a more stable formulation.

### References


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Container closure integrity (CCI) plays an important role in maintaining the sterility and stability of sterile injectable products. The defects that cause a sterile vial to leak are not necessarily detectable by a visual inspection process. Examples of such defects are those that are hidden by the crimp, microscopic cracks and scratches in the glass, or temporary defects such as stopper pop-up that result in temporary container leakage.

New regulatory guidance has triggered changes in industry best practices in the area of CCI testing (CCIT). This article summarizes the current state of container closure integrity testing in the pharmaceutical and biopharmaceutical industries and outlines possible approaches for developing a CCIT strategy.

Regulatory environment for CCI

Historically, good CCI has been linked to the maintenance of sterility. A container that loses, or does not have, good closure integrity is at risk for microbial contamination. However, the context of CCI has become broader over the years.

An increasing number of formulations have significant sensitivity to oxygen and need to be packaged under an inert atmosphere. Freeze-dried product requires protection against water vapor and is often packaged at a partial vacuum to help with reconstitution and/or seating of the stopper. In these cases, good CCI is necessary not only for the maintenance of sterility but also to maintain critical headspace gas conditions.

Note that, quite generally, a container that is gas-tight will also be tight against microbial ingress. Therefore, the requirement to maintain headspace gas conditions imposes higher standards on CCI than the requirement to maintain sterility.

In light of the importance of CCI for product sterility and stability, regulatory guidance has placed an increasing emphasis on CCI concepts. The current United States Pharmacopeia (USP) <1207> chapter titled Package Integrity Evaluation—Sterile Products was implemented in late 2016 and represents the most thorough guidance document to date on CCI concepts for sterile injectable product (1).

The chapter gives an overview on CCI testing technologies and approaches for CCI control over the product lifecycle. Traditional CCIT methods, such as microbial challenge tests or blue dye ingress tests, are described as methods associated with probabilistic outcomes having some uncertainty in the results which, in turn, makes such methods difficult to quantitatively validate for the detection of critical leaks (1). The chapter also makes clear that CCIT should be performed throughout the product lifecycle. Deterministic CCIT methods based on non-destructive analytical measurements can be used to generate science-based CCI data that, coupled with a risk-based approach, enable informed decisions about a CCIT strategy in commercial manufacturing.

A draft revision of the European Union’s Annex 1 requirements for sterile product manufacturing was released at the end of 2017 (2). CCIT was a popular discussion topic for the revision, and the draft text contains new requirements for CCIT in manufacturing. Other world regulatory bodies, Russia and South Korea for example, have also been putting increasing emphasis on CCI control for finished sterile products. It is clear from these developments that regulators are wanting to see improved industry practices in the area of CCI.

CCI test methods

USP <1207> provides an overview of CCIT technologies and categorizes them...
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as being deterministic or probabilistic (see Table I). The chapter emphasizes that this overview of CCIT technologies is not exhaustive but is a summary of technologies that have been implemented for CCIT in the pharmaceutical industry and that are described by a body of peer-reviewed literature.

It is important to distinguish between CCI technologies and CCI test methods. Once a leak testing technology has been chosen as the basis for a test method, the chapter emphasizes the need to perform method development studies generating data that demonstrate detection of a critical leak for a specific product container configuration using defined test method parameters (1): “After a methodology has been selected for use, the test equipment operation and performance is qualified. Test method parameters are optimized during method development and confirmed during validation. Thus, a final leak test method is specific to a particular container-closure or product-package system.”

Another point emphasized in the chapter is that “no one test is appropriate for all packages or for all leak testing applications.” The chapter and its three subsections describe a framework in which appropriate CCI test methodologies are chosen, optimized per product configuration, and a robust validation of the method for detecting a critical leak is performed. In selecting a methodology, “deterministic leak test methods are preferred over probabilistic methods when other key method selection criteria permit.”

Package integrity data are generated over the product lifecycle and serves as input for an ongoing database of CCI data (the package integrity profile), which then serves as a risk management tool to ensure that CCI of finished product meets the product quality requirements. The framework described in the chapter is currently driving changes in industry best practices for CCI testing, including:

- Implementation of a ‘toolbox’ of CCI test methods optimized and chosen on a per product configuration basis rather than the application of a single legacy test method in a one-size-fits-all approach
- Generation of science-based CCI data in robust method validation studies, which demonstrate the detection of a critical leak represented by various types of positive controls.

### Table I. Overview of container closure integrity testing (CCIT) technologies.

<table>
<thead>
<tr>
<th>Deterministic</th>
<th>Probabilistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical conductivity and capacitance (high-voltage leak detection)</td>
<td>Bubble emission</td>
</tr>
<tr>
<td>Laser-based gas headspace analysis</td>
<td>Microbial challenge, immersion exposure</td>
</tr>
<tr>
<td>Mass extraction</td>
<td>Tracer gas detection, sniffer mode</td>
</tr>
<tr>
<td>Pressure decay</td>
<td>Tracer liquid (blue dye ingress)</td>
</tr>
<tr>
<td>Tracer gas detection, vacuum mode</td>
<td></td>
</tr>
<tr>
<td>Vacuum decay</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from USP 40 <1207.2>

A big topic of current discussion is how much CCIT is required, especially for commercial batches of finished sterile product. Despite the general consensus that CCI is a critical quality parameter for finished sterile product, the industry has historically expended much more effort on testing for particle contamination than for CCI.

Visual inspection to detect particulate contamination has been a requirement for many years with 100% inspection of finished parenteral product being done manually or by automated inspection platforms. In the context of risk to the patient, a loss of CCI would, in general, be assessed as being just as critical as particle contamination.

The current EU Annex 1 guidelines require 100% leak testing for certain types of product containers. “Containers closed by fusion, e.g., glass or plastic ampoules, should be subject to 100% integrity testing” (3). This requirement is a result of the fact that the inherent failure rate of the sealing process for these types of containers cannot be sufficiently controlled.

The ongoing draft revision of the EU Annex 1 guidelines again states the requirement of 100% integrity testing for fused containers and adds the following requirements for all other types of containers. “Samples of other containers should be checked for integrity utilizing validated methods and in accordance with QRM, the frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A statistically valid sampling plan should be utilized. It should be noted that visual inspection alone is not considered as an acceptable integrity test method” (2). If finalized in this form, these CCIT requirements will require the evolution of best practices for CCIT in the manufacturing environment.

Currently, a small percentage of the industry performs statistical CCIT of finished commercial product. Most companies point to the 100% visual inspection process to justify meeting current CCIT guidance, such as the following from the FDA (4), “A container closure system that permits penetration of microorganisms is unsuitable for a sterile product. Any damaged or defective units should be detected, and removed, during inspection of the final sealed product.” The language of the draft EU Annex 1 revision makes clear that visual inspection is not considered an acceptable integrity test method; in other words, the CCI test methods that enable the testing of larger amounts of samples will need to be implemented.

To demonstrate statistical confidence in the process requires the generation of statistical CCI data. However, an argument could be made that a better place to do this in the product lifecycle is in process development and scale-up rather than in manufacturing. The guidance provided in USP <1207> to collect package integrity data throughout the product lifecycle so that a package integrity profile database is built up implies an approach in which a significant amount of CCI data are gener-
ated outside of the manufacturing environment. The generation of robust CCI data providing knowledge of the container and closure system (which then gives guidance to a CCIT strategy in manufacturing) is also implied in the text of the draft revised EU Annex 1, “the frequency of testing should be based on the knowledge and experience of the container and closure systems being used.” Figure 1 outlines a possible approach to generating CCI data that enables the design of an appropriate CCI testing program in manufacturing.

After validation of the fundamental closure system, data need to be generated to understand if the process introduces risk to CCI. To gain statistical confidence in the process, it would be necessary to perform testing on statistical sample sets. This in turn will require the use of non-destructive deterministic test methods because the probabilistic legacy test methods (blue dye and microbial ingress testing) have limited throughput capability. Testing could be done on either a pilot scale or with test and engineering batches from the manufacturing environment. Once a baseline failure rate has been established, process controls could be implemented to improve the process, if necessary.

Product from the improved process would be tested to quantify the residual risk to CCI after which a decision could be made for an appropriate testing strategy in manufacturing. Packages and processes having a high inherent failure rate that is difficult to control would require a heavier inspection process and vice versa. In this way, the decision for an inspection process design is driven by science-based statistically relevant data.

**Summary**

The current environment for CCIT of sterile injectable product is evolving. New regulatory guidance recognizes CCI as a quality parameter that is critical for the maintenance of both the sterility and the stability of finished sterile product. New concepts introduced in the regulatory guidance are changing industry best practices and include the following:

- Generate science-based CCI data throughout the product lifecycle to build up a package integrity profile database that can be used as input for risk management.
- When possible, use deterministic CCI test methods that have been validated to detect a critical leak.
- There is no one-size-fits-all CCI test; a toolbox of CCIT technologies that can be optimized on a per-product package configuration is necessary for a robust CCIT program.

Because industry best practices will evolve as the impact of new guidance becomes clearer, a certain amount of uncertainty in CCIT best practices is to be expected in the near term. However, a general approach that includes the implementation of validated deterministic CGIT methods and the increased generation of science-based CCI data to enable informed risk assessments will help prepare the industry for the future.

**References**

A
luminum compounds have been
used as adjuvants in human vac-
cines for more than 75 years (1),
and they are the most widely used ad-
juvants in both human and veterinary
vaccines. Billions of doses of aluminum
salts containing vaccines have been
administered safely to a diverse popu-
lation of patients globally (2). Despite
their widespread usage, there is little
regulatory guidance or published lit-
erature regarding release and stability
testing of these products. Though there
have been great gains in knowledge of
therapeutic protein chemical and
physical stability, there are few pub-
lished examples of the applications of
bioanalytical stability methods applied
to protein once adsorbed on to the alu-
minum adjuvant. This article provides
an introduction to aluminum adsorbed
vaccines, reviews studies of antigen
stability, and proposes test methods for the analysis
of aluminum vaccine release and stability analysis.

Wendy Saffell-Clemmer and Elizabeth Joseph

The authors provide an introduction to aluminum
adsorbed vaccines, review studies of antigen
stability, and propose test methods for the analysis
of aluminum vaccine release and stability analysis.

Aluminum adsorbed vaccines

Early vaccines were prepared as alum pre-
cipitates, which could be heterogeneous.
Preformed gels of aluminum hydroxide
and, later, aluminum phosphate replaced
alum precipitation and have resulted in
standardized formulations of aluminum-
adsorbed vaccines. Aluminum-based
adjuvants continue to be used in new
vaccine preparations as recombinantly
expressed protein antigens are identified,
which can serve as safer replacements for
inactivated or attenuated pathogens. Ad-
ditionally, vaccines containing combina-
tion adjuvants linking aluminum with
synthetic and natural ligands have been
approved (2). The addition of adjuvants is
often needed to induce a robust immune
response and effective immunization to
protein antigens, which may not possess
strong immunogenicity. The physiologi-
cal mode of action of aluminum adju-
vants, however, is not completely under-
stood (3). Potential mechanisms include
that the aluminum forms a depot at the
injection site from which the antigen is
released slowly; that the particulate form
of the adsorbed vaccine results in uptake
by macrophages, neutrophils, and den-
dritic cells; and the immune system is
stimulated directly. Additionally, it has
been proposed that adsorption of the pro-
tein on the aluminum gel could result in
structural destabilization increasing the
protein’s immunogenicity (4).

There are two common aluminum
salt preparations used in human vac-
cines: aluminum hydroxide (Alhydro-
gel) and aluminum phosphate (Adju-
Phos). The pH at which the net surface
charge of the aluminum adjuvant is
zero is called the point of zero charge
(PZC), which is similar to the isoelec-
tric point (pI) of a protein. The adjuvant
surface is positively charged when the
solution pH is below the PZC and nega-
tively charged when the solution pH is
greater than the PZC (5). Aluminum
hydroxide has a PZC of approximately
11 and aluminum phosphate has a
PZC of 4–5.5 (4), though consideration
should be given to the buffer used in
vaccine formulation as substitution of
ions at the surface may lower the PZC
and impact the adsorption of the anti-
gen (5). For many proteins, antigen ad-
sorption is best in pH intervals between
pI of the protein antigen and PZC of the
aluminum adjuvant because it is in this
pH range that the protein antigen and
the adjuvant will have opposite electric
charges (1). For this reason, lysozyme, which has a pI of 11.35, has been used as a model antigen in studies of aluminum phosphate. Bovine serum albumin (pI of 4.7) and ovalbumin (pI of 4.5) bind more efficiently to aluminum hydroxide (4). Generally, Alhydrogel has a higher adsorption capacity than Adju-Phos, and the adsorption capacity of Alhydrogel decreases as its particle size increases and as the molecular weight of the proteins increase (6).

The correlation of strength of adsorption to vaccine effectiveness is related to the adsorption mechanism.

The adsorption mechanism of proteins to aluminum adjuvants is not completely understood (6) and is likely a combination of physical phenomena including “electrostatic attraction, hydrogen bonding, apolar interactions, ligand exchange, and van der Waals’ forces” (4). Studies of model proteins found that electrostatic interactions were the major mechanism for adsorption of lysozyme, human growth hormone, diphtheria toxoid, a monoclonal antibody, and PEGylated growth hormone, but that for one protein, ovalbumin, adsorption involved ligand exchange (6). The predominant mechanism for adsorption of HBsAg by aluminum hydroxide was determined to be ligand exchange between the phospholipids in HBsAg and the surface hydroxyls in aluminum hydroxide adjuvant (7). HBsAg was found to bind more tightly to an aluminum hydroxyphosphate sulfate adjuvant when the concentration of phosphate buffer was increased (8). The correlation of strength of adsorption to vaccine effectiveness is related to the adsorption mechanism. Phosphorylated proteins adsorbed via ligand exchange have an inverse relationship between high adsorption strength and poor antigen presentation and immune response (9). Studies of a trivalent Pneumococcal protein vaccine demonstrated differences in immunogenicity resulting from selection of adjuvant impacted immunogenicity and found that lower microenvironment pH at the antigen surface and decreased strength of adsorption improved antigen stability (10).

Antigen stability following adsorption

A significant challenge in vaccine formulation development is the understanding of the antigen stability following adsorption. While aluminum-precipitated and aluminum-adsorbed vaccines have been in use for 75 years, it has only been in the past 15 years that studies investigating the impact of adsorption on protein structure and stability have been reported, presumably as new techniques developed to characterize recombinant proteins were applied to vaccine research. In a review of the subject, Clapp and colleagues describe how the environment of the protein at the adjuvant surface differs from that in solution, potentially driving structural change (11). Specifically, studies of the rate of acid-catalyzed hydrolysis of glucose-1-phosphate (G1P) adsorbed to aluminum hydroxide concluded that the pH of the microenvironment at the surface of the adjuvant was approximately two pH units higher than that of the bulk solution (12). Differences in polarity and charge density on the adjuvant surface may also result in structural changes in the bound protein (11).

Spectroscopic methods have been applied to the study of protein structural perturbations resulting from adsorption. Techniques have been well described in the literature and have included fluorescence spectroscopy (13), transmission Fourier-transform infrared (FTIR) spectroscopy (14), FTIR spectroscopy using an attenuated total reflectance (ATR) cell (13, 14, 15), and circular dichroism (CD) (15). Differential scanning calorimetry (DSC) has also been applied (13, 16). In studies of model vaccines, structural changes by FTIR–ATR, fluorescence spectroscopy techniques (13, 15), and DSC (13) were observed by following adsorption. Studies using transmission FTIR (14) concluded that no structural changes resulted from adsorption in studies of six model proteins. Overall, a review of studies indicates that variation in the buffer concentration, buffer pH, and properties of the antigen itself may influence the structure of the adsorbed
There is little general guidance on release and stability test methods for aluminum adsorbed vaccines. In studies of a hepatitis B vaccine, the interaction between the antigen and aluminum hydroxide adjuvant was modified by optimizing the phosphate ion concentration and could possibly ensure that the native concentration of the antigen was maintained (17). While no structural information was presented, the authors concluded that a formulation containing 40 mM phosphate had improved thermal stability by in-vitro antigen reactivity. Additionally, FTIR–ATR studies determined that the structural changes were dependent on the amount of protein adsorbed, with more native protein observed in samples with maximum adsorption (17). The authors theorize that at lower adsorption concentrations, a monomolecular layer is formed in which the confirmation of the adsorbed protein is affected by the properties of the adjuvant surface and are more denatured. At higher adsorption levels, the protein is more weakly linked and may retain the native structure. While the focus of aluminum-adsorbed vaccine characterization studies has protein antigen structure, questions remain about the applicability of studies to individual vaccine formulations and the impact that antigen structural perturbations may have on vaccine effectiveness and stability throughout the shelf life of the product.

Regulatory guidance for vaccine stability studies
There is little general guidance on release and stability test methods for aluminum adsorbed vaccines. The FDA document, Guidance for Industry, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (18), states that identity, purity, and potency should be included in drug product release specifications but does not provide specific test methods or guidance. United States Pharmacopeia (USP) Chapter <1235> Vaccines for Human Use–General Considerations (19) does not provide specific recommendations for release and stability tests beyond general requirements of testing for potency, general safety, sterility, purity, identity, and constituent materials. There was only one aluminum-adsorbed vaccine USP monograph available as an example (Anthrax Vaccine Adsorbed), but this was deleted as of August 2018 (20). The monograph includes tests performed on the sterile filtrate which does not include aluminum. Tests performed on the sterile filtrate include Identity by Western Blot, total protein by using a Bradford assay per USP <1057> (21), and 83kDa Protein using sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS–PAGE). Finished product tests are in-vivo relative potency, concentration determination of aluminum by atomic absorption spectroscopy, safety, sterility, pH, sodium chloride by ion-selective probe, benzethonium chloride by titration, and a limit test for formaldehyde using UV-Vis spectroscopy.

While there is not specific guidance on the inclusion of test methods that are potency-indicating, there are parallels that can be drawn from International Council for Harmonization (ICH) Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their manufacturing process (22). The guidance states that “the manufacturer should consider the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change.” However, it also states, “In cases where the biological assay also serves as a complement to physicochemical analysis (e.g., as a surrogate assay for higher order structure), the use of a relevant biological assay with appropriate precision and accuracy might provide a suitable approach to confirm that change in specific higher order structure has not occurred following manufacturing process changes.” While the intent of this analysis is to assess stability rather than manufacturing change, this guidance can be extrapolated to stability test methods. If potency methods lack sufficient accuracy and precision to detect small physical and chemical changes occurring during storage, additional methods may be required to provide early indication of loss of potency and expiry.

Test methods
Ideally, test methods to provide stability data for adsorbed vaccine products would not require extensive sample preparation or desorption of the antigen from the adjuvant. There are a variety of different mechanisms suitable for desorption but all share disadvantages. The desorption procedure itself may result in structural changes or additional modifications or impurities in the protein antigen. For analysis in most test methods, desorbed samples will require a buffer exchange step, which will result in solutions with an unknown concentration, which must be determined using a separate assay prior to analysis by stability indicating methods. Lastly, desorption recovery may vary and recovery can decrease in aged samples (15, 24).

The measurement of unbound antigen by its definition is performed on
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While Western Blots are not a practical method, the use of dot or slot blots allows for identification or, in some cases, quantitation without desorption. Generally, slot or dot blots eliminate the separation step. In a slot blot or dot blot method, the finished drug product (FDP) without desorption. The intention of the test is to measure the amount of free protein that was not adsorbed or has desorbed from the aluminum adjuvant. Samples are prepared by centrifugation, and the supernatant is removed for analysis. Typically, chromatography is utilized to quantify the amount of free protein in the sample against a standard curve of the same protein. Chromatographic methodologies vary and may include size-exclusion chromatography (SEC) (25) or reverse-phase high performance liquid chromatography (RP–HPLC). Typical methods can be based on those used for analysis of the antigen bulk drug substance (BDS), which are then optimized for sensitivity and validated using a low-level standard curve.

Some immunological test methods are feasible in the presence of Alhydrogel or aluminum phosphate and may be used for identification or, in some cases, quantitation without desorption. While Western Blots are not a practical alternative because SDS–PAGE cannot be performed on FDP, slot blots and dot blots eliminate the separation step. In a slot blot or dot blot method, the product is applied directly to a membrane and may be pulled through the membrane using a microfiltration apparatus and vacuum. Additional rinses may be performed as needed to ensure no surface residue remains on the membrane. Following application of samples, standards, and controls to the membrane, the membrane is removed from the apparatus and immunoblotted using standard procedures. Though no published procedures were identified describing the use of dot or slot blots for the analysis of aluminum adsorbed vaccines, the technique was used to quantitate the Hemagglutinin and Neuraminidases in influenza vaccine (26). An advantage of dot and slot blots is that multiple samples can be analyzed simultaneously, and membranes can be cut into strips for immunoblotting using multiple antibodies allowing for the identification of multiple antigens simultaneously. Zhu demonstrated the feasibility of a direct Alhydrogel formulation immunoassay (DAFIA) for the determination of antigen identity and content (27). In the method, the FDP is added to wells of a black multititer plate. Following centrifugation and washing, the wells are blocked, then probed with primary antibody followed by a secondary antibody tagged with fluorescein. Signal is read with a fluorometer at 485nm/535 nm.

Concentration measurement of the aluminum adjuvant can be determined directly, using inductively coupled plasma atomic emission spectroscopy (ICP–AES). Traditional methods for protein quantitation such as UV-Vis spectroscopy or RP–HPLC are not suitable for bound antigens. Method 6 of USP <1057> utilizing o-phthalaldehyde (OPA) (21) has been applied to Alhydrogel vaccines. The OPA reacts with N-terminal amine groups or the amine groups on the side-chains of lysine and results in a fluorescent signal at 340nm/455 nm. Protein concentration of the FDP is compared to a standard curve. The OPA method was applied to Malaria vaccine candidates containing Alhydrogel, and it was determined that for accurate results Alhydrogel must be included in standards at an equivalent concentration as samples (28). Accuracy was 87–100%, and linearity, though protein dependent, ranged from 25–400 μg/mL. In internal studies, the method had a range of 20–250 μg/mL using a non-linear curve fit and resulted in accuracy of 98–110% and repeatability of ≤2% for samples (see a representative standard curve in Figure 1).

HPLC is not suitable for the analysis of intact aluminum-adsorbed FDP because the vaccine molecules would be filtered by the column frit or, if they do pass into the column, would result in column clogging and increased back-pressure. RP–HPLC has been applied to concentration measurement, and to a limited extent, chemical stability of vaccines after desorption (10). While a desorption step is required to perform chromatographic analysis of the intact antigen, peptide mapping provides a powerful tool to verify the identity of FDP as well as evaluate the chemical stability of the antigen following adsorption and during stability. In peptide mapping, the protein is digested with an enzyme such as Lys C or Trypsin to produce a set of peptides. The resulting mixture of peptides can be separated chromatographically and compared visually to a control or the BDS or it can be analyzed by mass spectrometry and compared to the expected masses of peptides based on the primary sequence. The peptide mixture can also be analyzed without separation using matrix-assisted laser desorption mass-spectrometry with time-of-flight detection (MALDI-
TOF). Lys C digestion of the desorbed antigens followed by MALD–TOF analysis of a trivalent botulinum vaccine containing Alhydrogel detected oxidation and deamidation reactions in all three protein antigens and reaction rates were accelerated in the presence of the adjuvant (29). Initially a 250 mM succinate buffer, pH 3.5 was utilized to desorb samples, but following incubation, desorption became more difficult, and use of a 4 M Urea pH 7.5 buffer was required. The desorption itself complicates the analysis because, first, it may not be completely reproducible, especially for aged samples, and, second, it may result in additional degradation. In unpublished studies, trypsin was used to successfully digest the antigen bound to Alhydrogel without desorption. Standard digestion procedures of incubation in Tris/HCL buffer, pH 8.0 for four hours at 37 °C were followed by RP–HPLC using an ACN/TFA mobile phase and C18 column. Visually, chromatograms (Figure 2) from digested FDP closely matched those of digested BDS, indicating the non-desorbed peptide mapping is a feasible method for the evaluation of antigen stability in FDP. With the increased availability of high mass accuracy/high resolution mass spectrometers, peptide mapping has evolved into multi-attribute methods (MAM), which can replace multiple electrophoretic and chromatographic stability indicating methods for therapeutic proteins (30). The application of MAM to aluminum-adsorbed vaccines has the opportunity to further understanding of protein-antigen stability and improve analysis to support quality by design (QbD) development as well as quality control (QC) release.

MAM has the potential to replace the electrophoretic and chromatographic stability indicating methods that all require desorption prior to analysis. Desorption methods range from the use of phosphate buffer pH 7.4 (25), phosphate buffer and Zwittergent (9), 250 mM succinate buffer pH 3.5 (29) to harsher conditions such as 20 mM sodium dodecyl sulfate (SDS) or 20 mM cetylpyridium chloride in citrate-phosphate buffer (31), and up to 4M Urea (29). Multiple investigators have noted that desorption is more challenging in aged samples (14, 24). Therefore, development of desorption procedures for stability indi-
cating methods should be performed with aged samples when possible. The selection of desorption method will vary depending on the adjuvant used as well as the intended analysis method and compatibility with the desorption solution. For example, SDS would be a good choice for desorption buffer when preparing samples for methods utilizing SDS in the procedure, such as SDS–PAGE or CE–PAGE. Additionally, SDS does not significantly interfere with RP–HPLC procedures. Urea is often used in sample preparation for imaging capillary electrophoresis (ICE) procedures and is a preferred buffer for preparation of samples for charge separation methods such as ICE and ion-exchange chromatography (IEX). A standard protocol for desorption using SDS involved the following steps:

- Mix buffer, SDS, and vaccine FDP and incubate at 70 °C for 10 minutes.
- Centrifuge, remove supernatant, and determine protein concentration using RP–HPLC. Ensure that SDS concentration in the reference standard matches that in the samples.
- Concentrate using spin-filters and desalt with water wash. Utilize volume to determine approximate concentration prior to analysis.
- Dialyze samples to reduce urea concentration.
- Repeat RP–HPLC analysis to determine concentration, concentrate using spin filters and desalt with water wash.
- Perform ICE or IEX analysis.

Following desorption, SDS–PAGE can be performed using standard procedures and commercial gels and reagents. The analysis of a model vaccine pictured in Figure 3 utilized a precast gel (Thermo Invitrogen NuPAGE 4–12% Bis–Tris) with recommended sample and running buffers (NuPAGE LDS Sample Buffer and NuPAGE MOPS SDS Running Buffer). The gel shows results from analysis of SDS-desorbed model vaccine samples that had been stored at 37 °C for 0 to 5 days. Samples are reduced prior to loading the gel and stained using a Coomassie blue stain (NuPAGE Colloidal Blue Staining Kit). Gels were analyzed by densitometry (Bio-Rad GS–800 Densitometer with Quantity One software).
ON-DEMAND WEBCAST: Aired Thursday, September 19, 2019

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

Event Overview
Biologics analytical testing is rapidly evolving as new testing protocols become available and companies seek to expedite current methodologies. Learn about the latest cell-based bioassays and binding assays, including applications, advancements, and outlook. The discussion will focus on a variety of assays including antibody-dependent cellular cytotoxicity, Octet, AlphaLISA, and Host Cell Protein (HCP), as well as the potential application of automation.

In this webcast, a panel of four industry experts will unravel the science and dive into some specific applications, providing useful information for both novices and experts. The presentation will be followed by a roundtable discussion, where the panel will discuss registrant-submitted questions and address current issues and trends within bioassays and binding assays.

Register now to submit a question for the experts!

Key Learning Objectives
- Fundamentals on how various assays work, when they should be used and what questions they answer
- Differences between various bioassays and binding assays
- Application of immunochemistry-based platform technologies to analyses of biologics

Who Should Attend?
- Scientist/Manager/Lab Manager/Technician/Director/VP/SVP/Procurement for large molecule analytical testing and strategy

Presenters
Michael Sadick, Ph.D.
Principal Scientist, Biologics Analytical Development
Catalent

Dan Papa, Ph.D.
Group Leader, Biologics
Catalent

Eric S. Bishop
Vice President of Research & Development
Cygnus Technologies, LLC

Jeff Dixon
Field Application Specialist
PerkinElmer

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions or concerns, email kmoore@mmhgroup.com.
Quality

Figure 3. Model vaccine sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS–PAGE) gel for heat-treated samples. MW = molecular weight marker, RS = standard, C = control sample, T0–T5 = days stored at 37 °C, B = blank, S = sensitivity standard.

Figure 4. Imaged capillary electrophoresis (ICE) electropherogram overlay for urea-desorbed samples that had been stored at 37 °C for up to five days.

for presence of additional bands due to degradation as well as % purity. Purity of the main band ranged from 96% for the Day 0 sample to 90–91% at Days 4 and 5, therefore demonstrating that the desorbed SDS–PAGE method is stability-indicating.

ICE analysis of a model BSA-Alhydrogel vaccine was performed using an imaged capillary electrophoresis system with detection at 280nm (ICE280 and ICE3 systems, Protein Simple). Samples were prepared using urea desorption and dialysis as described previously and then concentrated using spin filters. Samples, reference material, and a control sample were diluted in a diluent consisting of a mixture of pharmalyte 4–6.5, pharmalyte 3–10, 1 g/mL urea, 0.7% methylcellulose, and pI markers 5.12 and 6.61. Analysis was performed using acidic anolyte (0.1% methylcellulose, 0.08 M H3PO4), basic catholyte (0.1% methylcellulose, 0.10 M NaOH), and separation for 10 minutes at 3000V. The resulting electropherograms were analyzed (ChromPerfect 7 software) for isoform purity. Samples of model vaccine were stored at 37 °C for 0 through 5 days prior to analysis. See Figure 4 for an electropherogram overlay showing the isoform profiles for each sample. The main peaks are observed at pI 6.1 and 6.2 in non-degraded samples, but a significant shift toward more acidic isoforms is observed with longer storage at 37 °C. The desorbed ICE method is stability-indicating for detection of changes in isoform profile.

Conclusion

The nature of aluminum adsorbed vaccines presents challenges to the application of traditional bioanalytical methods commonly used for stability studies of therapeutic proteins. While studies have demonstrated structural and chemical modification of the protein antigen resulting from adsorption, and that adsorption may impact stability, little regulatory guidance is provided beyond the recommendation to include identity, purity, and potency in drug product release test-
ON-DEMAND WEBCAST: Aired Tuesday, September 17, 2019

Register for this free webcast at: http://www.pharmtech.com/pt_p/packaging

Event Overview
The webcast on “Considerations in Primary Packaging Component Selection for Parenteral Drug Delivery” will guide the audience through the process of selecting the ideal sealing solution components for safe and effective drug delivery. Beginning with an introduction to parenteral packaging, technical experts will discuss common industry concerns when selecting components and how these issues can be mitigated through a risk-based approach. The presentation will focus on the following topics:

- Common concerns in the pharmaceutical industry surrounding parenteral packaging
- Introducing sealing solutions for various delivery applications and therapies
- A quality-by-design approach to manufacturing for best-in-class components mitigating industry concerns
- Analytical tools utilized to ensure packaging integrity and product quality

Key Learning Objectives
- Understand the risks that face the pharmaceutical industry today from a drug packaging perspective, and strategies to mitigate these risks.
- Review solutions for manufacturing high-quality packaging components to meet the needs of the pharmaceutical industry.
- Understand future trends for the pharmaceutical industry and how parenteral packaging suppliers are working to meet these needs.

Presenters
- Rahul Thakar, Ph.D.
  Technical Key Account Manager
  Datwyler
- Eugene Polini
  Technical Key Account Manager
  Datwyler
- Felicity Thomas
  Editor
  Pharmaceutical Technology

Who Should Attend?
- Formulation scientists and packaging engineers
- Device development engineers and managers
- Technical functions surrounding drug delivery systems
- Extractable and leachable experts
- Quality/regulatory personnel in parenteral drug delivery
- Procurement professionals
ing. Potency methods may not have the necessary accuracy and precision to predict vaccine effectiveness and stability throughout the shelf life of the product. Instead, a panel of tests adapted from traditional therapeutic protein analysis is proposed in Table I. Though historically, antigen characterization was performed following desorption, most of the methods proposed can be performed on the FDP directly. As MS-based peptide mapping methods, such as MAM, continue to grow in popularity, the need for desorption followed by electrophoretic and chromatographic methods for the determination of fragmentation or chemical modification may be eliminated.

References
Implantable Systems and Microparticle Depots: Meeting the Formulation and Manufacturing Challenges of Long-Acting Drug Delivery

ON-DEMAND WEBCAST  Aired September 11, 2019

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

A growing number of APIs suffer from poor water solubility, low bioavailability, and insufficient stability. As more BCS class II–IV compounds enter the drug development pipeline, formulators must look to advanced drug delivery systems to achieve a desired therapeutic effect and protect APIs from degradation.

Long-acting dosage forms such as microparticle depot injections and implantable systems—both biodegradable and biodurable—offer tunable designs that help overcome these challenges. However, successful development and optimization of these complex drug products requires specialized knowledge, equipment, and facilities to properly execute.

This webinar will explore key considerations in developing long-acting drug products, including a comparison of design options, polymers, and manufacturing methods for both depots and implants. Experts will investigate some of the common challenges in these areas and explain how long-acting dosage forms are characterized with real-world case studies.

Key Learning Objectives

- Explore the growth of long-acting drug delivery with an emphasis on microparticle depot injections and implantable systems
- Review long-acting dosage form selection, design choices, polymer options, and manufacturing techniques
- Investigate common challenges and solutions for developing, manufacturing, and characterizing long-acting drug products—including a review of in vitro release testing and measuring particle size distribution
- Provide real-world case study data to demonstrate how long-acting drug products can be customized to achieve a specific therapeutic effect

Who Should Attend

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

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Technology is changing more than just healthcare’s latest therapeutic modalities and pharmaceutical advances. It’s also disrupting the design and implementation of the facilities that create them. Building information modeling (BIM) is at the helm of this digital disruption. BIM is a 3D, digital facility model that can be optimized to include schematic drawings, product information, engineered data calculations, estimation, and automated instrumentation. When retrofitting, scanning equipment can capture an existing facility’s space and provide a cloud of data that is easily converted to a full, 3D BIM model.

Whether new construction or retrofit, BIM streamlines workflow coordination, allows late submittals to be facilitated more quickly and easily, permits building owners and operators to offer real-time feedback during early design, and can automate and optimize equipment specification.

**Improved process efficiencies**

From the design team to equipment vendors and subcontractors, when the entire building team works from a single, digital model, efficiencies are championed. Unfortunately, late submittals are a rule rather than an exception in today’s building design process. As project schedules become more fast paced, equipment specification and delivery moves more in parallel to construction, and sometimes even beyond. Final coordination isn’t possible until all submittals are in. BIM can be used for clash detection, and it facilitates late design submittals, avoiding common, costly change orders.

As a case in point, during the construction of a large biologics manufacturing facility, a last-minute design submittal came through. The transfer panels (i.e., wall-mount piping assemblies) in fabrication took up more space in the facility than initially anticipated. The design team had to determine the best solution, weighing long-term operating effects against the short-term cost/schedule changes to modify plans. BIM allowed the design team to digitally test all the potential building layout scenarios this change posed without making any costly mistakes in the field (see Figure 1). Without BIM, this change would have easily cost the project an additional two to four months of construction time.

**A new project view**

With a 3D BIM model of the facility, clad with equipment specifications; mechanical, electrical, and plumbing infrastructure; and architectural design, building owners, operators, and other end-users have a unique opportunity to “walk through” a building, room by room, using virtual reality software and goggles. This technology provides an avenue for real-time feedback during the early project design phase.

Engaging end-users is often complicated by their day jobs. But when they have a chance to review a 3D image of the facility prior to subcontractor fabrication models, their participation soars and the feedback is received in enough time to actually influence facility design rather than modifying it. Pulling the design review phase forward saves time and reduces the project’s overall bottom line. While redesign can’t be avoided, it can be moved forward to ensure that everyone—including lab managers/operators, maintenance personnel, and even C-suite executives who take an interest in daily operations—is on the same page faster.

As an example, during the design phase of a manufacturing facility, end users that reviewed the 3D model had a number of very practical change requests. One group of end-users wearing virtual reality glasses noted that they wouldn’t be able to reach a valve. Another group pointed to an area above a lab station and suggested a window be placed there. In
both scenarios, designers were able to go into the BIM model and annotate it in real time. Later, designers went back to the comments tagged to alter the design.

The facility owners continue to use the 3D images created via BIM during design to give visitors a virtual tour of their facility. This technique allows them to give access to the facility without a visitor having to gown up to enter clean or secure spaces. BIM models can also be used to train operations staff or aid maintenance.

Streamlined equipment coordination

Three-dimensional, digital design allows facility designers to solve their project challenges in creative ways. Designers can work with existing tools or create new ones. On one complex project, for example, the design team was tasked with tackling a large amount of equipment design—10,000 instruments all together—in a short amount of time. Because there wasn’t another efficient way to do so, the CRB team designed an automated instrumentation design and specification tool to coordinate with the BIM model. What would have taken weeks instead took hours to specify with the new tool. Using the tool, designers were able to create a template specification for each type of instrument, review it with the owner for approval, and then populate each unique instance for that instrument within BIM. When expanded beyond instrumentation, the tool can also manage the information associated with equipment, such as physical location, and it can facilitate the generation of datasheets, lists, etc. All process data are linked with the schematic design. The instrumentation tool streamlined the design, layout, and construction of the facility, helping owners with facility management, maintenance routines, and more.

Next-generation biotech facilities

Shorter project timelines, increased demand for sustainability, and the availability of big data are driving forces in facility design. BIM pushes the envelope of design, resulting in better processes, optimized workflow, reduced cost, and ultimately, the next generation of biotech facilities. PT

Tips for BIM Optimization

• Consider the speed of your computers, network, connectivity. How much computing horsepower do you have?
• How will you manage accessibility for your users; who needs to access the model, from where, and on what platforms? Making the information accessible is an important part of keeping projects on track. New advancements in the cloud can aid with this as well.
• Update the BIM model frequently so building team members aren’t working on an out-of-date model. Consider linking in real time, or at a minimum at close of business daily.
• When working with other trades, anything not modeled is a potential risk to be uncoordinated. Often times, a trade may opt not to model, or trades will choose not to model below three quarters of an inch. This is important to communicate to the entire building team.
• Make a BIM execution plan for each project, including what to model and what tolerances to use.
Identifying and Solving Scale-up Challenges in the Synthesis and Formulation of Small-Molecule APIs

ON-DEMAND WEBCAST: Aired Thursday, September 12, 2019

Register for this free webcast at: http://www.pharmtech.com/pt_p/identifying

Event Overview
Pharmaceutical developers are under pressure to rapidly advance products to the next clinical milestone. In early development, decisions are made regarding how much should be invested in API process development, characterization, and other parts of the workflow. Not making the right decisions can lead to challenges with drug-product formulation and even clinical data. This webcast will focus on:

- Setting the correct balance between cost and process development
- Knowing what and when to invest at different stages of development
- Establishing a firm foundation to allow scale up to an efficient process that will benefit later phase and commercial manufacture

Key Learning Objectives
- Learn how to develop a medchem API synthesis into a scalable process
- Understand how to apply state-of-the-art manufacturing technologies to avoid manufacturing problems during scale-up

Presenters
Dr. Peter Poechlaur
Innovation Manager,
Small Molecule API
Thermo Fisher Scientific

Rita Peters
Editorial Director
Pharmaceutical Technology

Who Should Attend?
- Pharmaceutical companies with API needs from pre-clinical to phase III
- VP
- Director
- Manager
- CMC Head
- Researcher/Developer
- Scientist/Chemist/Analyst

For questions or concerns, email kmoore@mmhgroup.com.
pharmaceutical operation and, in particular, for sterile manufacturing ones.

References

More on quality
For more about quality control, visit PharmTech.com to read the following:
- Best Practices in the QC Micro Laboratory
- Effective Root Cause Determination
  www.pharmtech.com/effective-root-cause-determination

Your opinion matters.
Have a common regulatory or compliance question? Send it to shaigney@MMHGroup.com, and it may appear in a future column.
Providing regulators with a holistic approach to addressing deficiencies is the best response to an inspection, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

A recent inspection of our facility resulted in several observations, including insufficient hand sanitization by personnel in the sterile filling area, deficient gowning in the microbiology laboratory, and use of wooden pallets in the cold storage area. Before concluding, the inspectors told us that they want us to address these deficiencies holistically. Can you give some advice on how to do this?

It is correct that all too often, companies address each and every inspection observation individually, rather than address fundamental flaws or gaps in the systems, processes, or organizations. The regulators want the industry to find the true root causes for their compliance lapses. This is why your inspectors want to see the issues they identified addressed holistically. For example, they want you to clearly identify the functional relationship between the parts that lead up to a compliant operation and the whole.

Looking at the examples you cite, it seems that you would be best served by preparing a contamination control strategy (CCS). Control strategies are an increasing requirement in the European Union good manufacturing practice regulations (EU GMPs) and expected to be referenced in the next revision of EU GMP Annex 1 (1). The draft text, which is likely to be adopted in the final version, reads:

‘Quality assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A contamination control strategy should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed. This assessment should lead to corrective and preventative actions being taken as necessary. The strategy should consider all aspects of contamination control and its life cycle with ongoing and periodic review and update of the strategy as appropriate.’

In your case, the CCS should consider all the integral elements of sterile product manufacturing, including quality risk management (QRM) principles and supporting risk assessments for contamination control and monitoring (detectability of contamination event) (2). How should or could you develop this CCS? First, you need a complete process flow description of all materials and personnel. This will allow you to identify points of critical risk of contamination and points of inherent risk of contamination.

Regulators want the industry to find the true root causes for their compliance lapses.

If we take the examples provided by your inspectors, you will need to identify where there is a risk for contamination (e.g., the operators) and how you control this risk of contamination (e.g., gowning and barriers, such as isolators and disinfection). Next, you need to determine whether these control measures (individually and as a whole) are sufficient to reduce the risk to an acceptable level. For example, is hand sanitization performed often and sufficiently, and is the procedure following industry best practices (3)? Are your personnel suitably trained and are they following the prescribed procedure? Have you collected sufficient data (e.g., from swabs and dabs) that prove the efficiency of the sanitizing regime? Once you have performed this risk assessment, you will have sufficient information and data to understand, whether:

• Your hand sanitizing procedures are adequate and effective
• Your personnel training and personnel following procedures is correct
• Your contamination control strategy for all points of risk of contamination from gloved hands is appropriate and sufficient.

If not, you should be able to immediately identify corrective action and preventive action (CAPA) measures to reduce the risks to an acceptable level.

The CCS will bring all these assessments together and provide a holistic view of your approach to contamination control. The CCS is not only needed for responding to the inspection observations, it is an essential document for any

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