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**COVER STORY**

14 New Biotherapies Push Technological Innovation Forward

The emergence of new biotherapeutics is both the driver and result of innovative drug development technologies.

Cover Design by Maria Reyes
Images: ipopba - Stock.adobe.com

**FEATURES**

**DEVELOPMENT**

20 Assessing Risk and Production of Potent Substances
In addition to ADCs, other types of highly potent biologics require specialized manufacturing skills.

22 Moving Beyond Particle Size Control
Particle engineering is a vital tool in overcoming many formulation challenges, and technological advances are enabling developers to achieve the full potential of pipeline molecules.

**MANUFACTURING**

26 Considering Robotics for Drug Compounding
Automation offers benefits for sterile manufacturing in 503B outsourcing facilities.

30 Cleaning Continuous Manufacturing Equipment
Consider best practices for manual or clean-in-place procedures.

**ANALYTICS**

44 Prioritizing Cleaning Validation
As recent COVID-19 vaccine facility citations make clear, failure to meet cleaning and sanitization requirements puts patients, facilities, and operators at risk.

**OUTSOURCING**

48 Developing a Method for Success through Partnerships
Outsourcing method development offers multiple benefits to companies, including access to experience and expertise, streamlined costs, and development time efficiencies.

**PEER-REVIEWED RESEARCH**

**PEER-REVIEW RESEARCH**

34 Using Quality by Design to Develop Fixed-Dose Combination Tablets
In the present investigation, the fixed-dose combination (FDC) tablet of Atorvastatin calcium and Ezetimibe was prepared by a quality-by-design approach using $2^3$ factorial design.

Continued on page 6
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NEWS & ANALYSIS

FROM THE EDITOR

10 A “We are the World” Vaccination Effort?
Bio/pharmaceutical manufacturers have made a good first step toward global vaccination through pledging doses at no- to low-profit rates.

REGULATION & COMPLIANCE

REGULATORY WATCH

12 Pandemic Highlights Need for Advanced Pharma Manufacturing
Expanded interest in advanced drug manufacturing and continuous production methods calls for more flexible production systems and regulatory policies.

ASK THE EXPERT

54 The Facts About Filing Drug Applications
Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, answers some commonly asked questions about regulatory filings.

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In the past 16 months, the public gained some insight into the complexities of drug development. The rapid development and emergency approval of the Pfizer/BioNTech and Moderna COVID-19 messenger RNA (mRNA) vaccines should not, however, give the impression that these tasks were easy. These innovations were built on years of research, with setbacks and successes.

The development of new drug modalities, such as mRNA vaccines, push researchers to develop bespoke technologies, methods, and processes to meet scientific, safety, regulatory, characterization, and manufacturing requirements for innovative treatments.

The cover story for this issue examines how researchers developing emerging biotherapies must address unique challenges associated with cell therapies, intranasal vaccine delivery, and virus-like particles, as well as the cold-chain limitations of mRNA vaccines. The solutions to these innovation hurdles will have implications for the success of future new biotherapeutic modalities and can set the stage for future life-saving treatments.

Some innovations are happening at the particle level, as formulators look for ways to engineer APIs to improve solubility, permeability, and release profiles to better target drug delivery using milling, spray drying, and other processes. The emergence of potent biologic drugs creates the need for risk assessments for operator exposure and manufacturing containment requirements. Learn how these challenges are being addressed in the Development articles in this issue.

Maintaining quality
As the pandemic-related headlines fade, the routine of bio/pharma development and manufacturing continues, with efficacy, safety, and quality at the forefront.

The potential for cross contamination is a major concern in multi-use drug manufacturing facilities; cleaning and cleaning validation are frequent targets of regulatory inspections. This issue looks at best practices for cleaning continuous manufacturing systems as well as recommended cleaning validation strategies.

In addition, the editors report on ways drug compounding facilities are turning to robotic technology to reduce the risk of human error, streamline operations, and improve good manufacturing practices.

Emerging technologies and improving basic operations will continue to be bio/pharma industry themes and will be the ongoing focus of coverage in Pharmaceutical Technology. 

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The importance of a flexible, efficient infrastructure able to produce critical, high-quality drugs and medical products quickly and reliably has been heightened this past year by the soaring demand for medicines to combat COVID-19. Recent events have expanded interest in advanced drug manufacturing and continuous production methods able to provide needed therapies and prevent shortages that could compromise public health. Heavy reliance on foreign suppliers for necessary medical equipment and APIs similarly has increased concerns about supply interruptions as nations limit exports to protect the health of domestic populations. The result is a resounding call for more flexible production systems and regulatory policies able to respond quickly to supply disruptions and heightened demand for new preventives and treatments.

FDA officials have long pressed bio/pharma manufacturers to step up investment in advanced manufacturing technologies, as seen in multiple statements and proposals from Janet Woodcock during her many years as director of FDA’s Center for Drug Evaluation and Research (CDER). Former FDA Commissioner Scott Gottlieb urged added funding in 2018 to support continuous drug manufacturing and 3D printing to ensure steady output of finished drugs. And Former Commissioner Stephen Hahn highlighted in August 2020 how advanced drug manufacturing techniques could help address manufacturing and supply chain problems generated by the pandemic (1). There has been some progress, as seen in CDER’s report on drug product quality for 2020, which notes that FDA approved the first application utilizing a continuous biomanufacturing process in 2020 and semi-continuous processes for two other products (2).

The Biden administration has acknowledged the importance of reliable advanced drug and vaccine production to ensure access to treatments for COVID-19. A White House executive order early this year sought sufficient supplies of vials and needles, as well as APIs, to support expanded vaccine supply and distribution. And the administration included pharmaceutical and biotech products on a list of key industries important for enhancing supply chain resiliency (3).

A related goal by federal officials has been to expand drug manufacturing in the United States to reduce reliance on foreign sources and global supply chains. An early executive order from the Biden White House supported “Buy American” policies by calling on federal agencies to contract for American-made products before purchasing imported goods. The government also has funded retrofitting of US biopharma facilities to boost domestic production of COVID-19 vaccines. While some experts consider added tax incentives and financial support key for encouraging more domestic biopharma production, other analysts note the value of geographic diversity in supply to reduce the risk of disruptions in any one place from hurricanes and other natural disasters.
to modernize pharmaceutical manufacturing to ensure reliable access to high-quality drugs, particularly in response to disruptions caused by the pandemic (4). While the report identifies several important manufacturing innovations on the horizon, the expert panel recognizes that adopting new methods and systems is costly, especially for companies with already approved facilities.

A notable finding of the report is that drug regulatory policies pose a barrier to innovation, in that manufacturers looking to adopt continuous or other advanced manufacturing methods first must gain FDA review of any new technology, a process that can delay approval of a new drug application. And implementing new technology for a marketed drug involves submitting a post-approval changes application, an equally perilous and time-consuming oversight process. Varying regulatory expectations and policies among international health authorities, moreover, further complicate prospects for implementing new technologies for both new and established medicines.

The NASEM experts note that CDER has taken steps to foster manufacturing innovation with its Emerging Technology Program and Emerging Technology Team (ETT) to assist firms in evaluating and documenting new production approaches. But to provide more support and expertise to advance modern manufacturing, the panel advises FDA to clarify further what data are required in regulatory filings to demonstrate the identity, safety, purity, and potency of a drug produced with innovative technology. More consistency in evaluating residual risk to product quality from modern manufacturing methods, and greater harmonization in regulatory requirements across regions, is crucial for effective risk-benefit evaluation of new manufacturing methods.

References

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The emergence of new biotherapeutics is both the driver and result of innovative drug development technologies.

Joe Foster, chief operating officer of Mogrify, a UK-based cell therapy company, adds that all medicinal products have strict manufacturing and quality standards to follow to deliver safe and efficacious treatments to patients. In situations where the active pharmaceutical ingredient is biological, variation in the raw material and manufacturing process is difficult to eliminate entirely, which challenges the scalability of manufacturing biological modalities. “In cell therapy,” Foster notes, “the most clinically successful cell type, T cells, currently follows a highly standardized ad-hoc manufacturing process where the quality of the final product is subject to the quality of the source cells initially isolated from the patient.”

“While ad-hoc protocols are associated with high costs and limited scalability, a challenge more broadly encountered in the translation of cells into safe and efficacious cell therapies is the need to modify, expand, and maintain cells in ex-vivo conditions, evident in the scant number of cell types that have been delivered to the clinic,” Foster adds.

Challenges

The challenges to creating new biotherapeutic modalities stems from technical, scientific, and clinical advances that are resulting in a wider range of these modalities. This wider range of biologic modalities has led to a frequent requirement for bespoke development and characterization on a product-by-product basis to ensure that all possible interests, concerns, and compliance requirements of the international regulatory authorities have been considered and addressed, points out Margaret Temple, business development director of SGS.

“For example,” Temple explains, “Novel cell therapies have very limited or no downstream purification, which leads to a requirement to conduct very detailed safety testing and characterization of the cell bank and clinical product.”

“The development of COVID-19 vaccines in 2020 required an enhanced focus on documentation and study timelines to ensure lot-by-lot data [were] available in a coordinated and timely manner, whilst ensuring full compliance with the product release criteria,” she adds.
Cover Story: Emerging Therapies

Challenges such as these are what have driven the innovation being seen in drug development and manufacturing technologies. For example, it is expected that the rapid development and regulatory authority approval of several COVID-19 vaccines will lead to a shorter timeframe to develop and approve new biologics, says Temple. This shortened timeframe will be aided by developments in the availability of more rapid testing and techniques, such as in-vitro toxicity and next-generation sequencing, she adds.

Meanwhile, translating new technologies to commercial-scale production poses its own challenges. “Scaling up of cell culture is a continued challenge in the application of stem and primary cells as therapeutics when compared to the scale up of, for example, stable cell lines such as [those derived from] CHO [Chinese hamster ovary] cells (1),” says Temple.

“In scaling up new technologies, manufacturers are expected to account for the requirements to generate sufficient clinical material and additional material for testing and stability study purposes,” Temple emphasizes.

Another potential challenge, Temple says, is clarifying the chemistry, manufacturing, and controls (CMC)-related studies that must be performed if a novel technology (e.g., novel equipment, novel manufacturing process, and/or novel biological substrates) is used, as there is little or no precedence to follow. However, on the positive side, innovations in the use of synthetic raw materials and disposable equipment are expected to enhance manufacturing process development, she says.

Next-generation modalities
Intranasal vaccines: the challenges. The furious pace with which COVID-19 vaccines were developed has shone a spotlight on the need for more agile responses to health emergencies, including the need for quicker and easier administration of vaccines. While not necessarily a new technological idea, intranasal vaccines is one potential answer to addressing the need for global administration. US-based Meissa Vaccines is working to develop an intranasal live attenuated vaccine (LAV) for COVID-19, with Phase I trials already underway (2). Meissa’s vaccine candidate can be manufactured cost-effectively with single-dose immunity to meet global demand, according to Marty Moore, founder and CEO of Meissa Vaccines.

“In scaling up new technologies, manufacturers are expected to account for the requirements to generate sufficient clinical material.” —Margaret Temple, SGS

Meissa is overcoming traditional challenges in attenuating a live virus for use in an intranasal vaccine. “The attenuation of a virus to produce a vaccine must balance reducing its virulence while retaining its ability to stimulate an effective immune response, or immunogenicity,” says Moore. The company started out to develop a pediatric vaccine for respiratory syncytial virus (RSV). “Natural RSV infection does not stimulate a robust immune response, and immunity following SARS-CoV-2 infection wanes, so vaccine technologies, such as our AttenuBlock platform, that enhance immunogenicity are required,” Moore explains.

The traditional processes for making live attenuated vaccines involve serial passage, gene deletions, or other mutation strategies, he notes. “These strategies, however, typically affect the viral replication machinery, which can compromise immunogenicity of the vaccine candidate.”

Intranasal vaccines: call to innovation.
In Meissa’s case, the development of its intranasal live attenuated recombinant vaccine also carries important opportunities as an end game vaccine for COVID-19. Moore uses the example of the live oral polio vaccine, which was successful in its ability to block transmission. Compared to the inactivated polio vaccine, the oral live attenuated (replicating) polio vaccine provided strong immunity and blocked transmission well. This example motivated the company in its development of an intranasal vaccine candidate.

“That’s our goal for our COVID-19 recombinant live attenuated vaccine: provide strong immunity with a single dose that’s intranasal with a high potential to effectively block transmission,” Moore states.

Meissa’s proprietary platform, known as AttenuBlock, uses synthetic biology to generate live attenuated RSV vaccine candidates designed to increase antigen expression and decrease or eliminate the expression genes that counteract the immune response. “The AttenuBlock platform incorporates 10 years of research and development at Emory University, where researchers employed rational and precise codon deoptimization and other genetic strategies to produce hundreds of targeted mutations into the RSV genome, providing exquisite control over viral protein expression,” Moore explains.

“We used codon deoptimization to reduce the efficiency of translating viral mRNA [messenger RNA] into proteins. By carefully selecting and replacing commonly used codons with nonpreferred codons in viral genes that inhibit the immune response, the translation of these viral mRNAs into proteins becomes inefficient. This approach results in heavy attenuation, optimized immunity, and genetic stability,” Moore further states.

For COVID-19, Moore points out that it is important to note that Meissa’s vaccine candidate is not a whole SARS-CoV-2. “Ours is designed as a live attenuated RSV backbone that expresses a fully functional SARS-CoV-2
spike protein, in place of the RSV antigen. The reason we did that is because coronaviruses, as a family of viruses, have a high rate of recombination, and viruses like RSV do not. We viewed that with relatively high productivity of viruses like RSV do not. We viewed that with relatively high productivity of
terary pathogens is fairly new, VLPs have

tal manufacturing technologies, Moore says.

“Meissa’s vaccine candidates grow well in cell culture to support manu-
facturing. Furthermore, Meissa’s single,
low-dose vaccine candidates allow for a
smaller manufacturing footprint and fewer batches to support production,”
Moore states.

Virus-like particles: the challenges. When the pandemic began, Icosavax, a US-
based biotechnology company pursuing VLP technology applied its technology platform to develop a vaccine candidate against COVID-19. The company’s vaccine program is supported by a $10 million grant from the Bill & Melinda Gates Foundation and $6.5 million from Open Philanthropy, a US-based research and grantmaking foundation (3).

“Although the application of VLP technology to the prevention of respira-
tory pathogens is fairly new, VLPs have been around for a long time,” says Adam Simpson, CEO of Icosavax. “In fact, li-
censed VLP vaccines are extremely effective. For example, naturally occur-
cing VLPs have delivered effective licensed vaccines, including against human papillomavirus and hepatitis B.”

Simpson explains that VLP-based vaccines present key parts of the patho-
gen in a symmetrical and repetitive way, similar to how a virus would pres-
ent itself. Meanwhile, the immune sys-
tem has evolved to detect things that are presented thus as a danger signal and to react strongly to them. “However, reworking naturally occurring VLPs has been difficult to do for the display of proteins from certain pathogens, including those with complex heterologous antigens, such as RSV and SARS-CoV-2,” he states.

“That’s our goal for our COVID-19 recombinant live attenuated vaccine: provide strong immunity with a single dose that’s intranasal.”

—Marty Moore, Meissa Vaccines

In Icosavax’s case, the company’s technology is designed to enable the use of VLP vaccine technology for a broader array of pathogen targets. Nat-
urally occurring VLPs have historically induced strong, broad, and durable immu-
nomgenicity and protection, Simpson asserts. “However, naturally occur-
ring VLP vaccines have limitations in displaying complex heterologous antigens. Our technology is designed to overcome this limitation to enable the incorporation of a broad array of complex heterologous antigens into VLP structures,” he says.

Virus-like particles: call to innovation. The idea behind Icosavax’s technology is based, not on reliance on molecules that naturally form VLPs, but rather on starting from scratch and using the power of computational protein design to create fully self-assembling proteins, Simpson explains. “We do not have to rely on the limits of what we see in nature, and we can optimize the particles accordingly via our technol-
ogy,” he says.

Icosavax’s computationally designed VLP technology is designed to solve the problem of constructing and manufactu-
ring VLPs displaying complex antigens. “The technology generates computationally designed proteins that separate the folding of individual protein subunits from the assembly of the final macromolecular structure. The individual proteins are expressed and purified using traditional recombinant technologies and then self-assemble into VLPs when mixed,” Simpson illustrates.

“We often describe our VLP technology as a soccer ball. The black parts are at the base of the antigens (e.g., the prefusion structure of the RSV F glycoprotein or the SARS-Co-V receptor binding domain) and the white parts are there as the second piece to help create an icosahedral particle in the middle of the vaccine. When mixed, the black and white parts self-assemble into the soccer ball, displaying the antigens in a repetitive fashion, much like a virus,” Simpson says.

However, the translation from lab-scale to commercial-scale production can be challenging if the technology was not designed with large-scale manufactur-
ing processes and purification methods in mind, Simpson cautions. In addition, he adds, new technologies often have stability challenges at temperatures above sub-zero, which can lead to commercial distribution challenges.

“Our technology utilizes self-assem-
bling of two protein components that can be manufactured using traditional recombinant protein manufacturing techniques. The technology is designed to be highly scalable and distribut-
able,” Simpson says. Icosavax can use off-the-shelf technologies available at many recombinant protein contract manufacturers, he assures. “Both key intermediate components for IVX-411 [the company’s VLP COVID-19 vac-
cine candidate] have high manufactur-
ing yield, and all data gathered to date support a competitive cost-of-goods. In

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Cover Story: Emerging Therapies

addition, our final vaccine product is expected to be stable at 2–8 °C,” he adds.

Cell therapy development: the challenges. Mogrify, meanwhile, has developed a proprietary suite of platform technologies that utilize a systematic big-data approach to drive the speed, efficiency, and maintenance of cellular reprogramming. Its platform technologies have applications in generating the scalable source of functional cell types required to underpin the development of ex vivo cell therapies and also the potential to pioneer a new class of in vivo reprogramming therapies for indications of high unmet clinical need in immuno-oncology, ophthalmology and other disease areas.

The main hurdle for a new technology such as this in its translation into viable biotherapies is proving clinical benefit and safety in vivo, Foster says. “In cases of innovative treatment modalities, especially, there is limited experience and historic data to refer to,” he emphasizes. In terms of the development of allogeneic cell therapies, for example, clinical efficacy has been proven through autologous cell therapies, but the use of pluripotent cells as a starting material and the integration of genetic modification requires thorough risk assessment for tumorigenicity and genetic instability, he explains.

Cell therapy development: a call to innovation. “To deliver safer, more efficacious, and scalable cell therapy to patients, particularly in immunotherapy, developers are aiming to reduce toxicity-inducing factors, shift toward allogeneic cell therapies, and expand the range of clinically viable cell types,” says Foster.

He points out some current developmental trends, such as the use of gene-editing tools to remove immunogenic components, incorporate safety switches, and reduce the expression of cytokines associated with severe adverse events. He explains that the expansion of therapeutic cell types has seen progress in the increase of alternative cell types reaching clinical trials, such as natural killer cells and macrophages. This progress is accompanied by continuous efforts into the characterization of rare subtypes with high levels of desired functionality, such as gamma delta T cells, and the discovery of new cell types through single-cell innovations.

“Taking inspiration from [K. Takahashi et al.’s] discovery of the OKSM [OCT4, SOX2, KLF4 and MYC] pluripotency-inducing factors (4), the field has been working to generate a universal induced pluripotent stem cell (iPSC) source for the derivation of any cell type of interest,” Foster says.

“The technology generates computationally designed proteins that separate the folding of individual protein subunits from the assembly of the final macromolecular structure.”

—Adam Simpson, Icosavax

“Considerable effort has been invested into the development of off-the-shelf cell therapies derived from iPSCs; however, progress has been limited by the field’s ability to identify and recapitulate developmental pathways to freely differentiate target cell types from iPSCs whilst also acquiring and maintaining their required functional maturity for therapeutic purposes,” Foster adds.

In the meantime, with the increasing availability of high-throughput bioinformatics data, researchers have developed innovative computational approaches to systematically tackle the challenges posed by cellular reprogramming.

Platform technologies, such as MOGRIFY, utilize transcriptomic and regulatory network data to predict the key regulatory factors and small molecules that direct cellular reprogramming, Foster explains. Using the data in this way enables the transdifferentiation of any target cell type from any source cell type. Other complementary technologies, such as epiMOGRIFY, deploy epigenetics to predict optimal xenogen-free culture conditions for cell maintenance and to support cell reprogramming.

“When combined, such techniques provide a unique opportunity to enhance existing stem-cell-forward reprogramming methods or bypass development pathways altogether, allowing the direct reprogramming of the scalable source of functional cell types required to transform the development of ex vivo cell therapies, and furthermore, the exploration of new classes of in vivo reprogramming therapies, which offer the potential to introduce cell reprogramming in situ,” Foster emphasizes.

Unmet needs and future direction
The future direction of drug development technologies may largely follow the near-term results of biotherapies currently in development and how they are handled. For example, the long-term prospects for mRNA vaccines are contingent on improving on the current cold temperature requirements for storage and shipment. “If this is feasible, it would be expected that development of nucleic acid-based technologies progresses to develop products with other applications for healthcare, such as protein-based therapeutics. The international regulatory authorities have been supportive of advances in molecular biology, both with regard to product analysis and testing and with regard to product application, and this would be expected to continue,” Temple says. She further adds that it is not unreasonable to suggest that more product and clinical data and data analysis may be required to answer the question of what
direction RNA-based therapeutics may take in the future, and to compare the application of nucleic acid technology with, for example, the application of cell-culture derived viral vaccines, which have been developed and approved for a significantly longer time.

Intranasal vaccines generate both mucosal (IgA) antibodies in the nasal cavity and antibodies that circulate in the blood (serum), providing an alternative to injected vaccines, which typically do not do a sufficient job in blocking transmission, points out Moore.

“In contrast, injected vaccines typically induce circulating but not mucosal antibodies. While circulating antibodies are important for preventing serious lung disease, mucosal antibodies are important for blocking infection and transmission of respiratory viruses,” he states.

“We believe that end-game vaccines for COVID-19 need to be able to do both: prevent disease and block transmission,” Moore adds.

The preclinical data for Meissa’s COVID-19 recombinant LAV candidate shows that the vaccine induces a SARS-CoV-2-specific mucosal IgA response, causes the generation of serum-neutralizing antibodies, and provides efficacy against challenge, Moore emphasizes.

“With the current injected vaccines, we are going to need boosters for both durability and protection against variants. A real mucosal transmission-blocking vaccine could put a tight lid on SARS-CoV-2 and be an important end-game strategy to really put this to bed and get back to normal. That’s why we need intranasal vaccines,” Moore concludes.

Moore says that Meissa’s vaccine candidate has the potential to deliver a single-dose of $10^8$–$10^{10}$ plaque-forming units (PFU)/dose compared with multiple doses of $10^6$–$10^7$ PFU/dose of non-replicating vaccines or multiple milligrams for subunit vaccines. “The footprint for manufacturing live attenuated vaccines is significantly smaller and does not necessitate single use technologies,” he also adds.

Meanwhile, an aging population also poses a challenge for traditional vaccine technology because the older a person gets, the more difficult it is to induce a robust immune response. “We believe that a technology that induces higher neutralizing antibody titers will have the best chance of optimal and lasting protection in older adults,” says Simpson.

“When combined, such techniques provide a unique opportunity to enhance existing stem-cell-forward reprogramming methods or bypass development pathways altogether.”

—Joe Foster, Mogrify

“Our vaccine candidates have shown a strong immune response in preclinical models, and we believe that our candidates could become important for older adults, where immunosenescence plays a role in the effectiveness and durability of other vaccine technologies,” Simpson states.

“Furthermore,” he continues, “from a global health and access perspective, the high yield and stability of the assembled VLPs suggest that manufacture of VLP vaccines will be highly scalable, and our final vaccine product is not expected to require subzero storage.”

The advantage of Icosavax’ technology is that it was designed to be highly scalable and distributable, according to Simpson. “That said, COVID-19-related efforts have resulted in near-term shortages in materials, and, with the number and scale of existing vaccine manufacturing efforts worldwide, there are limited openings and manufacturing facilities. Right now, the biggest challenge we face is similar to many vaccines and therapeutic manufacturers in the current environment: access to facilities and materials needed for manufacturing and fill and finish at a large scale,” Simpson says.

“Currently, there are a small number of cell types that have been successfully delivered as therapies to the clinic, due to the limited capacity in directing cell fate and cell conversion,” says Foster, speaking from a company translating cell reprogramming into viable cell and gene therapies.

Mogrify is currently in the preclinical proof-of-concept stages of development, so discussion of commercial-scale aspects is early at this point; however, with the broad opportunities offered by the company’s proprietary technology platforms, its biggest challenge to date has been the identification, consolidation, and prioritization of the disease areas of focus, says Foster.

“We have chosen to focus on immuno-oncology and ophthalmology because they are both areas with clear regulatory pathways, and building on known therapeutic potential, will allow us to deploy our novel science and progress our lead assets within a well-defined clinical roadmap,” Foster states.

References
In addition to ADCs, other types of highly potent biologics require specialized manufacturing skills.

Highly potent compounds are typically associated with small-molecule APIs, except perhaps antibody-drug conjugates (ADCs) that include a cytotoxic chemical API linked to an antibody. ADCs have received significant attention due to their ability to provide targeted delivery of their cytotoxic payloads, affording higher efficacy with dramatically reduced side effects. There are, however, several other types of biologic drugs that are potent and require specialized facilities and equipment and highly trained operators to ensure protection of personnel and the environment.

Highly potent drug substances—and drug products—are generally considered to have occupational exposure limits (OELs) of <10 μg/m³ and require a low dose to generate a pharmaceutical effect, according to Iwan Bertholjotti, director of commercial development for bioconjugates at Lonza. “While the majority of these drugs are based on small molecules, some biologics fall into this class due to their potential to be sensitizers, including monoclonal antibodies (mAbs) and ADCs as well as non-oncology drugs such as hormones, narcotics, and retinoids,” he says.

Meinhard Hasslacher, director of CMC for SOTIO, adds that some highly potent conjugates are derived from mAbs, such as antibody fragments, diabodies, and single-chain variable fragments, while additional non-antibody scaffolds include affibodies (from Staphylococcus Protein A) and fibronectin Type III.

Other types of bioconjugates may also be highly potent, notes Gregory A. Sacha, senior research scientist with Baxter BioPharma Solutions. He points to peptide drug conjugates (PDCs) in development for cancer therapy. “These modalities are attracting attention given their potential to provide improved homogeneity of conjugation and more predictable pharmacokinetics than ADCs, combined with the possibility of designing PDCs with the ability to cross the blood brain barrier,” he explains.

It is important to keep in mind, notes Hasslacher, that highly potent does not necessarily mean toxic. “A protein that is active at the milligram or microgram level in a body—like hormones, insulin, clotting factors, or even some vitamins—are highly potent. High potency in combination with a toxic compound adds another level of complexity, which is what we see with ADCs,” he observes.

Assessing potency
As with highly potent small molecules, it is important to assess the potency of new biologic compounds with the potential to be classified as highly potent, which can be challenging for new drug substances with little available toxicity data. “Potency is assessed considering the indicated dose and pharmacological and toxicological aspects,” comments Bertholjotti.

Baxter BioPharma Solutions, according to Sacha, uses information provided by its clients, including safety data sheets and OELs, to evaluate the exposure control category. “In addition,” he says, “risk evaluations are conducted prior to the introduction of a new product to ensure there is no risk of cross contamination.”

The risk assessment of both potent substances and their production processes ultimately defines how these substances will be handled to protect operators and the environment. Waste management is also an important topic and needs to be appropriately defined, Bertholjotti adds. “Based on experience and similar substances handled in the past, it is possible to identify a catalog of standard protection measures,” he states.

Once preclinical animal data are available, SOTIO uses this information to determine values for the lowest observed adverse effect level and no observed adverse effect level, says Hasslacher. With this information in hand, it is possible to calculate the permitted daily exposure. In combination with
Accurate determination of potency is crucial for establishing the appropriate level of containment that will protect personnel during manufacturing and subsequent product handling, waste management, and equipment cleaning. “Once the risk assessment described above is completed, required measures are implemented according to company policy, local legal requirements, and other potential considerations,” Hasslacher says.

The handling of highly potent drugs requires defined concepts to protect operators and the environment, agrees Bertholjotti. It also necessitates the proper safety culture, he asserts, which can present a challenge that is essential for companies to overcome before they introduce highly potent processing into their facilities. “To establish a safety culture, time and investment in people and infrastructure are both required,” he explains.

Once the containment concept is defined, operators must then be trained. In some cases, Lonza also conducts surrogate studies to confirm that the containment approach delivers the level of protection expected. At that point, there is assurance that highly potent drugs can be handled safely, Bertholjotti says.

Unlike many small-molecule processes, which require the use of organic solvents, highly potent biologics are often processed in aqueous solutions at neutral pH and room temperature. For these reasons, Hasslacher notes that containment requirements tend to be less onerous than those required for small molecules.

High-molecular-weight highly potent biologics such as ADCs may pose less risk to operators than highly potent small molecules because they are less bioavailable via absorption and inhalation, according to Sacha. Both, he adds, can be manufactured in dedicated or disposable direct product contact equipment.

Lyophilization, Sacha notes, which is not often required for small-molecule drugs, is often necessary for biologics and presents different containment requirements. “Although they represent indirect equipment and do not come in direct contact with the product, lyophilizers must be included in a robust equipment cleaning validation program,” he comments.

Manufacturing challenges

Many of the manufacturing challenges faced by highly potent biologics are the same as those for any biologic drug substance/drug product. For instance, microbial contamination, sterility, and endotoxin issues are similar, notes Hasslacher.

There is a possibility of forming aggregates if the molecule is sensitive to interfacial interactions such as the formation of foam during mixing or interacting with container surfaces. Most of these can be prevented by using stabilizing agents or surfactants, according to Sacha.

In addition, a highly potent biological drug must, like other drugs, be stable for several days up to several weeks in the human body at 37 °C once administered, observes Hasslacher. Stability studies must also be performed to determine storage conditions, such as the container type and whether the product must be freeze-dried or can remain in the liquid state and whether light protection is required.

“For cryopreservation, the primary package needs to be clean, tight, and suitable for use with highly potent biologic,” Bertholjotti comments. Proper processes also need to be defined and implemented also for drug product manufacturing processes.

The added challenges posed by highly potent biologic molecules relates to the need to prepare the formulation in an isolator, agrees Sacha. “There is often less space for work in an isolator and all materials needed for manufacturing must be either sterilized during sterilization of the isolator or transferred into the isolator using transfer ports,” he explains.

In addition to these containment measures, cleaning of multipurpose facilities represents a further challenge when working with highly potent biologics. “The mindset that a biotechnology process is bio and not highly potent while a chemistry process always is hazardous can be misleading,” states Bertholjotti. He concludes that the combination of biosafety, occupational hygiene, and good manufacturing practice requirements create challenges not faced by non-potent biologics.

Advances in various types of equipment are helping manufacturers of highly potent biologics overcome some of these challenges. Sacha points to new types of equipment that are fully contained, where preparation of the formulation and filling into containers occur all in the same space, such as the Vanrx system, acquired by Cytiva in February 2021, and the VersA-Tech system from the Bausch Group.

“Containment in the last decade has been influenced by the recognition that it is not possible to sufficiently protect workers using only personal protective equipment anymore; additional technical solutions are needed to contain the increasingly highly potent drug substances and ensure adequate protection of operators and the environment,” Bertholjotti states.

Bertholjotti points to single-use systems available today that enable the implementation of single-use process concepts for closed manufacturing.

Essential medicines

Despite the manufacturing challenges associated with the production of highly potent biologics, pursuit of their development and commercialization is important to the advance of new therapies. “Highly potent drugs tackle various life-threatening diseases, and the necessary capacity must be available to prevent drug shortages,” assert Bertholjotti.

“The manufacturing of these drugs requires knowledge, experience, and special attention to ensure operators and the environment are protected to deliver these drugs safely and sustainably to patients,” Bertholjotti continues. Fortunately, much progress has been made in our understanding of the best practices for highly potent biologics manufacturing. In addition, both drug developers and contract manufacturers are committed to advancing technologies to achieve ongoing improvement of existing solutions. PT
Particle engineering is a vital tool in overcoming many formulation challenges, and technological advances are enabling developers to achieve the full potential of pipeline molecules.

Particle engineering plays a vital role in optimizing a drug’s effectiveness. The size of a particle will have an effect on the delivery of a drug, the route of administration—particularly in cases where an inhaled formulation is being developed—and will impact the rate at which a drug is metabolized in the body.

“In formulation and development, both active and excipient particles can be engineered to tailor the performance/efficacy of the drug product,” confirms Jamie Clayton, operations director, Freeman Technology (a Micromeritics company). “A relatively simple example would be controlling the particle size of an active to influence dissolution rate and by extension bioavailability.”

Additionally, particle size, along with other properties, influences bulk powder properties, Clayton continues. “Therefore, particle engineering is equally important for achieving desirable bulk powder properties, properties associated with the consistent manufacture of a drug product of acceptable quality, for example, a tablet with the required hardness,” he says.

“With drug particles or particle assemblies being the crucial component of solid dosage forms, which represent the vast majority of all medicines, it has become clear that ‘drug particles are of the essence’ when designing quality, safe, and efficacious medicines,” agrees Peter York, chief scientist at Crystec-Pharma.

Critical attributes, such as a drug’s solid state, particle size, and morphology, all impact a drug’s bioavailability, remarks João Henriques, group leader—Drug Product Development, Hovione. As a vast proportion of the development pipeline is now incorporating compounds with low aqueous solubility and permeability, addressing bioavailability is forming a significant part of development approaches.

“Particle engineering plays a pivotal role in addressing bioavailability issues,” says Henriques. “By modulating the solid state, particle size, or morphology, one can increase both the solubility and dissolution rate of a drug. The former is generally required when dealing with solubility-limited compounds and can be achieved by particle engineering techniques, such as spray drying and nano-milling.”

Furthermore, for downstream operations, particle engineering will dictate the processability of a drug, adds Henriques. “Even in the absence of bioavailability challenges, particle engineering can be used to mitigate processing problems, from avoiding segregation to improving flow and compactability,” he reveals. “Particle engineering is therefore an essential tool for formulators to enable successful pharmaceutical development programs of challenging drugs.”

“The importance of particle engineering and particle size analysis take on an even stronger role in the development of therapeutics with more novel routes of delivery, such as inhalation,” York notes. “Here, the particle properties not only dictate the pharmacokinetic performance of the drug, but also the amount of drug that reaches the targeted site of administration.”

**Common challenges**

A major challenge with particle engineering is access to the information needed to guide the process, Clayton explains. “The goal is to determine robust correlations between manipulable particle properties, process variables, and critical quality attributes of the drug product,” he adds. “Bulk powder properties are often vital in elucidating such correlations, but with a wide range of analytical techniques to choose from, it can be difficult to identify those of most value.”
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Recently published collaborative studies have demonstrated the drive for industry to refine analytical strategies (1–3). Clayton continues, “These [studies] focus on the potential of material property databases to accelerate the identification of critical material attributes, support process optimization, and improve supply chain management. Such work is equally helpful for those learning how to efficiently gather information to support particle engineering,” he confirms.

“A particle engineering technology should ideally be built upon an understanding of the mechanical, physical, and/or chemical events taking place during particle formation,” adds York. “For drug substances, the requirements of good manufacturing practice (GMP) and regulatory specifications must be embedded into the engineering and operation of the process.”

Traditionally, particle size reduction methods are approached in a ‘top-down’ way, so, reducing the size of larger crystalline drug particles uses high-energy impact mills, York explains. “This method continues to be widely used as a ‘first approach’ in solving the dissolution challenge; however, the high energy applied, and uncontrolled fracture and breakage of particles frequently imparts negative features to the milled drug particles such as changes in the solid state and causing highly charged, static particles, which are difficult to process downstream,” he says. “These factors, as well as the need for particle engineering tools that address not only the issue of low drug dissolution, but also potential physicochemical and biopharmaceutical challenges, have provided the basis for innovation in drug particle engineering and new concepts and approaches in drug particle design and delivery.”

To ensure the desired characteristics have been achieved through particle engineering, it is necessary to employ analytical tools, highlights York. “Whilst particle size and size distributions are a key property to be measured, the wide range of effects of particle size reduction methods on drug substance structural chemistry necessitates additional analytics to determine whether the process has led to any detrimental changes in solid state, physicochemical properties and, in the case of biotechnology substances, the biochemical and potency characteristics,” he states.

The size of a particle will have an effect on the delivery of a drug, the route of administration, and will impact the rate at which a drug is metabolized in the body.

Other common challenges encountered with particle engineering and size analysis are related to process scale-up, asserts Mafalda Paiva, group leader—Analytical Development, Hovione. “Particle size methods are product and size specific, and method development should be performed with lead process candidates,” she says. “A change in process scale is often accompanied by an increase in size that can translate to challenges in measuring the desirable primary particles. Attention is required when analyzing this data, for instance, employing an orthogonal technique such as scanning electron microscopy (SEM) to ensure the employed method is still fit for purpose.”

Further challenges can arise with particle engineering as a result of solid-state changes, emphasizes Paiva. “The use of particle engineering can often lead to changes in the solid form,” she reveals. “These [changes] may be as simple as residual amorphization upon high energy milling operations and the emergence of different polymorphs after spray drying.”

The hurdles associated with new drug candidates are numerous and varied, particularly when accommodating different routes of delivery, York continues. “By far the major current challenge is the low aqueous solubility of drugs, which constrains the dissolution and thereby subsequent bioabsorption of drug particles when administered to patients,” he notes. “Incorporating micron sized drug particles in the medicine provides a high surface area and drives up the rate of solution of the drug, which in some cases is sufficient to provide an efficacious product.”

Henriques concurs that low aqueous solubility of new chemical entities represents the most common challenge facing formulators that requires the use of particle engineering. “The increasing number of BCS [biopharmaceutical classification system] class II compounds means that the interest and demand for such technologies is also increasing,” he says.

BCS class IV actives, which have both low solubility and low permeability, represent one of the toughest formulation challenges, remarks Clayton. “Gastroretentive (GR) oral solid dosage forms can be the answer, with floating, sustained release tablets the most common approach,” he adds. “Engineering such tablets is a complex task and calls for an array of analytical insight, with particle morphology, blend flowability, and porosity information all of proven value (4).”

Another trend of note, highlights York, is the increasing prevalence of biotherapeutics entering the development pipeline. These compounds are typically more sensitive to high energy processing techniques that are used in conventional particle engineering, he explains.

“Emerging technologies enable particle engineering to be conducted
in low temperature and chemically benign environments, providing opportunities to engineer particles of biological substances with high levels of retained biological activity and targeted particle properties to enable specific target product profiles to be achieved,” York stresses.

**Novel and alternative approaches**

There are many established particle engineering techniques that are being used for commercial supply of API programs, Henriques specifies. Techniques such as spray drying, hot-melt extrusion, and co-precipitation are commonly encountered, but there are also new methodologies emerging within academic and industrial initiatives, he comments.

“One [such technique] is the use of mesoporous silica for the impregnation of APIs,” says Henriques. “[This technique is providing formulators with the opportunity to overcome some of the limitations of amorphous solid dispersions and is providing opportunities for the formulation of challenging compounds.”

A lot of interest over the past 20 years has been given to alternative approaches to ‘top down’ particle formation technologies, such as hot-melt extrusion and nano-milling, emphasizes York. “However, the converse strategy of ‘bottom-up’ particle formation techniques has proved a particularly fruitful area for particle engineering. In this approach, a solution of drug substance is subjected to a drying or solvent extraction process to yield drug particles, ideally in a single step operation,” he notes. “Manipulation of targeted particle characteristics, such as particle size, by means of varying process conditions delivers the ambition of particle engineering.”

An example of an innovative approach that is finding success in terms of drug particle engineering includes supercritical fluid (SCF) based technologies, which are available through specialist service providers, such as CrystecPharma, York states. “In supercritical anti-solvent (SAS) configurations, where the supercritical fluid (typically carbon dioxide due to its low critical point) acts as a powerful antisolvent, the solvent from a feed of drug solution is rapidly extracted in a pressure vessel, and dry drug particles precipitate almost instantaneously,” he notes. “The versatility of this technology is impressive in terms of excellent intra- and inter-batch reproducibility, as well as the ability to ‘tune’ the characteristics of the engineered drug particles, for example size, solid state and surface properties. Also, the low processing temperatures possible using supercritical carbon dioxide enable particles of delicate biotech drugs, from peptides to monoclonal antibodies, to be produced.”

As a vast proportion of the development pipeline has low aqueous solubility and permeability, addressing bioavailability is significant.

Additionally, SCF is being used for wider process and formulation simplification, beyond ‘pure’ drug particle engineering, York continues. “Composite dry particles containing a second drug and/or functional additives can readily be manufactured in a single step—a feature termed in-particle design. Here, solution feed lines containing drug and/or excipients, in addition to the primary drug solution, feed into the pressure vessel to form dry composite particles upon contact with the SCF,” he explains. “Each particle contains a final composition equivalent to that of the sum of the solutes in the feed solutions. The scope and options provided by this feature are vast, and excipient inclusions can be diverse with tunable composition ratios. Added excipients could, for example, be for aiding drug stability, dissolution, absorption, or for modulating drug release profiles.”

The quantification of particle morphology—both particle size and shape—provides more in-depth information than just measuring size alone, a fact that is highlighted when developing a GR tablet, asserts Clayton. “Flowability data adds value here because the agents used to impart buoyancy tend to compromise flow properties,” he says. “Dynamic flow properties measured with a powder rheometer were helpful in identifying optimal formulations. This application also highlights the value of mercury porosimetry, which provides detailed information about pore size, pore size distributions, pore volume, and other metrics, thereby elucidating buoyancy behavior (4).”

“In modern pharmaceutical product development, particle engineering has moved beyond the simple concept of particle size control. Innovative technologies and approaches to particle design and engineering allow molecules to meet their full therapeutic potential, while streamlining development processes, simplifying formulations, and building novelty into products,” York concludes. “In addition to providing opportunities for enhanced intellectual property, cost of goods savings and added process efficiencies, a thoughtful approach to particle engineering can enable the development of therapeutics that better serve the needs of patients and healthcare providers.”

**References**

“If errors are reduced, process reliability and quality improve,” he explains.

Despite these advantages, uptake of robotics is slow, and many 503B outsourcing facilities continue to have technicians working in laminar flow hoods or biological safety cabinets to handle beakers and flasks for solution compounding and fill vials manually using syringes, notes Smalley. He points out that some large teaching hospitals have adopted robotics for large-volume parenterals and for oncologic compounding and filling. “Smaller hospitals that focus on a specialty, such as orthopedics or oncology, appear to be the second wave,” Smalley adds.

An early example of a hospital compounding facility that adopted automation was the overall winner of the International Society for Pharmaceutical Engineering (ISPE) Facility of the Year Awards in 2019 (2). The Kantonssapotheke Zurich (KAZ) supplies oral, dermal, and parenteral formulations to the Canton of Zurich hospital system under current good manufacturing practice (CGMP) conditions. Exyte, the engineering firm for the project, said in the award announcement: “This facility raised the bar for quality performance to CGMP levels, which had never been done before in a hospital compounding facility” (2).

Challenges and considerations

Although robotic systems have many advantages, one of the challenges is designing and programming for flexible operations. Since it takes time to set up the systems to manage different material combinations, speed can be limited. “For a compounding combination that requires a lot of flexibility, such as handling a wide range of materials to prepare one compound, the system will need more time to process materials,” says Fraatz. “In many cases, humans are typically able to handle different types of materials and combinations faster than robotics, but contamination risks are higher.” He explains that planning ahead is important for using robotics, so that the right tools, equipment, and programming instructions are ready for a specific process.
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“The user requirements need to be clearly and completely defined,” agrees Smalley. “Robotics can only work with the tools that they are constructed with, for instance vacuum-assisted suction cups, pincers, barcode scanners, syringe operators, and the like. Additionally, they can only perform tasks that were included in their programming. Refitting and reprogramming can be problematic.”

Another challenge is the need to have barcodes that can be identified by the automated system. “Not all vials have barcodes, and new products or new brands of generic drugs result in barcodes not in the robot’s database. Software updates are constantly needed,” notes Smalley.

New developments are focusing on improving software and improving material handling. “Changes are being made to software to enable the robot to operate more smoothly and efficiently, as well as to make the user interface more intuitive. For material handling, some robotics manufacturers are focusing on loading cells, while others are looking at the ‘hands,’ as it were, trying to make the way the robot grasps items more securely without the danger of breaking the item,” reports Smalley.

A best practice for robotics users is periodic service by the equipment manufacturer that includes maintenance and adjustment, as well as software updates to address operational and security needs, notes Smalley.

“Routine maintenance and attention are absolutely required for robotic automation in the compounding space,” agrees Fraatz. In his experience, various hospitals tend to be familiar with using high-tech equipment such as robotics (as in some surgical settings), but the overall compounding industry is not yet as aware of how process automation can be used in compounding environments.

In particular, integrating robotics inside isolators is a relatively new technology for the compounding environment, says Fraatz. “True isolators have become very common in the pharmaceutical processing industry, and are the safest containment solution available for the compounding market as well,” he says. “From a best practice perspective, compounding organizations need to evaluate and adjust their quality risk management philosophy, including process and validation protocols for this type of automation. Evaluating [the use of isolators and robotics] is a multi-department effort, as there are also facility considerations in terms of what they may need, concerning cleanroom design or availability of utilities, for example.” Fraatz notes that it is also important to evaluate the process flow, including how materials are introduced to the compounding environment and handled after compounding. He points out that robotic equipment can be designed to be compatible with cleanroom conditions.

“Cleanroom conditions require easy to clean tools, low particulate generation, and equipment designed to respect the clean airflow required,” notes Fraatz.

Robotics in compounding facilities

A pharmaceutical manufacturing company adopting cutting-edge robotic technology for its CGMP 503B operations is Nephron Pharmaceuticals in South Carolina. The company, which specializes in producing generic respiratory medications using a fully automated process with blow-fill-seal (BFS) technology, launched its division for sterile compounded drugs in 2017 and began with manual operations, in which pharmacy technicians worked inside laminar-flow hoods to fill parenteral solutions coming from sterile filtration into intravenous (IV) bags or syringes. Now, Nephron is moving to robotic systems inside of the laminar-flow hood to perform these fill/finish operations. The company worked with the University of South Carolina (UofSC) and Clemson University in two separate projects to custom design robots for this application. In April 2021, Nephron validated the UofSC system and began commercial production, says Lou Kennedy, CEO of Nephron. A second robot is already being built, and more are planned. “We’re producing drugs on FDA’s drug shortages list, and this 503B space is growing,” she says. Robotic systems will improve productivity, reduce the burden of repetitive physical work for operators, and provide better accuracy and precision. Future projects will seek to increase speed of the robots to obtain higher throughput.

In addition to being used in commercial production at Nephron, Kennedy would like to see the robotic systems licensed to hospital compounding facilities.

“What I love about both the Clemson and UofSC projects is that as we collaborate with both undergraduate and graduate students, we’re helping develop future industry employees,” says Kennedy.

Preparing the workforce

Although a common fear is that robots will eliminate people’s jobs, Kennedy says this concern is unfounded. “Robotics is not eliminating people; it’s teaching people to have new skills to operate automation,” she notes. “Operators need to learn how to service the robot and work with it, to solve a jam or replenish components, for example. Operators are also needed for quality functions.”

Kennedy notes that Nephron sees a need for more pharmacy technicians, and the company works closely with local schools to help develop the future workforce. For example, Nephron built a sterile compounding lab on the nearby UofSC campus that is used to train pharmacy students at the university as well as two-year students from the local technical college in using robotics in sterile compounding.

Both developing an understanding of how robotics works and specific training with the equipment and its functions are key, adds Fraatz. “It is a new approach, which means trust needs to be gained, starting from education and understanding, so people can appreciate the purpose of robotic automation. Once they believe in the purpose, they can grow their familiarity and comfort with it.”

References

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ers would need to work closely with equipment vendors to develop such a system for a full process train. Hovione’s contract development and manufacturing facility in New Jersey has been running continuous solid-dosage drug manufacturing equipment for a few years and working to streamline the manual cleaning process. “The magnitude of the task of changing over a continuous manufacturing rig from one product to the next is very large,” explains Santos. “From a unit operation standpoint, there are no major differences from batch equipment, and in most cases the equipment is exactly the same at the unit operation level. The differences between continuous and batch have to do with the transition sections in between [the integrated] unit operations. Depending on the actual setup of the continuous rig, these transitions can be comprised of large pipe sections, in some cases with pass-through connections between floors. Also, such transitions might comprise large number of PAT instruments to measure, for example, powder level or quality attributes of the material being processed. Thus, continuous rigs have additional parts to be cleaned. If the continuous manufacturing line is entirely ‘clean-out-of-place,’ the extra equipment also poses the added challenge of keeping track of many equipment components of all different sizes as they move through the cleaning operation and subsequent reassembly; the learning curve associated with these operations may be much longer than comparable operations of individual batch manufacturing units.”

Santos notes that, “While in batch, each unit operation is operated independently, in separate rooms, and typically staggered in time; in continuous, the full set of equipment is used during manufacturing, typically with higher asset utilization. Hence, from a planning standpoint, the cleaning of continuous rigs requires significantly more resources, effort, and cleaning capacity (e.g., additional wash rooms and footprint for parts staging and storage) to address the full set of equipment with-

Consider best practices for manual or clean-in-place procedures.

When running manufacturing equipment continuously, rather than in batch mode, operators should consider what cleaning practices need to be adjusted. FDA’s draft guidance for continuous manufacturing of small-molecule, solid oral drug products notes time between equipment cleanings can depend on a variety of factors, such as running time or amount of product (1).

When considering equipment running continuously, cleaning might be automated with clean-in-place (CIP) elements or involve full disassembly with manual cleaning, say Paul Lopolito, senior manager, and Beth Kroeger, senior manager, in Technical Services at STERIS. “Using cleaning agents or cleaning tools requires a cleaning validation to demonstrate removal of these elements to acceptable limits. The calculation of accepted limits may utilize traditional uniform carry-over models or non-uniform residue or stratified residue models,” say Lopolito and Kroeger. These models are used because residue can become concentrated as it moves through the connected equipment (2). Other considerations with continuous manufacturing are addressing microbial issues and process intermediate degradant residue. “These residues may present a cross-contamination risk to the next lot or batch of product. If these hazards exist, then it is warranted to perform the appropriate level of cleaning and cleaning validation to mitigate the risk,” they conclude.

Most lines for continuous manufacturing of solid-dosage drugs today are cleaned in a “clean-out-of-place” mode, but a complete CIP solution would improve cleaning turnaround times, notes José Luís Santos, director of Hovione’s Continuous Tableting Center of Excellence, who suggests that end-us
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Manufacturing

Hovione was to allocate enough resources to address the manual cleaning process—including a large team of operators and enough space to do the cleaning—and then to optimize with shop-floor operational excellence tools, says Santos. “In our experience, the use of Lean tools brought not just the acceleration of the operation, but also an increase of the comfort levels of the team members involved with the cleaning. An otherwise huge challenge could be decomposed into smaller, more manageable, blocks of work, with a clear visibility of how the work was progressing during each day of the operation,” he explains.

Another best practice, says Santos, is to maintain control of the organization of equipment components from disassembly through assembly. “For example, use specific bins to contain disassembled components from specific (predefined) sections of the line so that those components, which make up those specific line segments, stay together throughout the cleaning process. Organization is critical to reduce lost and mixed-up equipment components among thousands of such components,” he explains.

Considerations for cleaning biopharmaceutical process equipment

In biopharmaceutical manufacturing, process intensification can change the way the equipment is used and thus affects cleaning methods. “Process intensification continues to influence trends, such as higher-titers in bioreactors, greater binding capacity in resins, improvements in upstream clarification, and other advances in technology and equipment design,” notes Beth Kroeger, senior manager for Technical Services at STERIS. Manufacturers that take advantage of these technology advances, however, should also consider how cleaning can be affected. Kroeger and Paul Lopolito, senior manager for Technical Services at STERIS, shared some points to consider in an interview with Pharmaceutical Technology.

Equipment design

PharmTech: How have changes in biopharmaceutical equipment use affected cleaning requirements?

Lopolito and Kroeger (STERIS): One area we see a change to equipment design, as a result of process intensification advances, is in the use of inline conditioning skids and inline dilution where buffers are prepared from buffer concentrates. Use of buffer concentrates meets an obvious need to mitigate the amount of storage space required for several large volume tanks and bags. However, the use of buffer concentrates along with the increase in throughput lead to a change in how buffer tanks should be cleaned and maintained. In the past, based on solubility of buffers, water has been suitable for cleaning buffer tanks. This industry practice was confirmed during a benchmarking session at a CIP [clean-in-place] Technology and Industry Summit where 90% of the participants indicated water was used to clean some part of the process, with an acid detergent to prevent micro-pitting and untimely corrective passivation testing. The concept of predictive modeling within laboratory testing methods has been useful in modifying routine cleaning procedures to better predict cleaning frequencies, preventing failures due to residue buildup, loss of passive surface characteristics, or microbial contamination. Testing may include measurement of conductivity by trending drift in conductivity results; total organic content; bioburden; in-line ultraviolet spectroscopy measurements; and bacterial endotoxin testing. In addition to determining equipment cleaning frequencies based on data, routine stainless-steel maintenance frequencies could also be determined based on iron-monitoring testing, non-viable particulate monitoring, and surface passivation testing. The concept of predictive modeling within laboratory test methods has been useful in modifying routine cleaning procedures to mitigate risk or fine-tune preventive maintenance activities. About six years ago, we worked with one biopharmaceutical company that monitored a solution hold time in tanks, and, after a preset time, the tank was passivated with an acid detergent to prevent micro-pitting and timely corrective action activities. Another biopharoma site confirmed that final acid rinse temperature was not sufficient to maintain the corrosion resistant passive layer and that increasing the temperature and lowering the concentration would prevent the micro-pitting and unscheduled equipment downtime.

References

ON-DEMAND WEBCAST
Aired: Wednesday, June 23, 2021

Accelerate Time to Market via Virtual Formulation Design: A Step-By-Step Approach

Register for this free webcast at:
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Event Overview
Learn how to design your next drug product considering the three pillars of pharmaceutical formulation development: functionality, safety, and cost-of-use. Leverage virtual formulation assistants to reduce development costs and expedite time to market and rationally select ingredients by considering material properties, checking for incompatibilities before stability, and leveraging price discussions to guide purchasing decisions.

Key Learning Objectives
• Using virtual formulation assistants, learn how to predict blend tabletability
• Learn about the top five formulation incompatibilities
• Guide raw material purchasing decisions by communicating cost-of-use advantages

Who Should Watch
• Formulators
• Scientists
• Chemist
• Investigator
• R&D associate
• R&D manager
• Technical services manager/director
• Research fellow
• Process engineer

For questions email kbarry@mjh lifesciences.com
Hyperlipidaemias is an elevated amount of lipids in the blood, a major modifiable risk factor for the development of cardiovascular disease. Reducing the amount of low–density lipoprotein (LDL) cholesterol in each patient’s blood is a primary treatment goal. Statins are 3–hydroxy–3–methylglutaryl coenzyme reductase inhibitors, considered to be the most powerful class of drugs for reducing serum LDL levels. Although they are usually effective in reducing cholesterol, the number of patients who wind up meeting lipid goals is still less than it could be. Moreover, a higher dose of statins results in only a small reduction in the LDL cholesterol level and has been correlated with an increased occurrence of side effects. These issues are driving greater interest in novel compounds or combination drug therapy using currently available drugs (1–9).

Ezetimibe (EZE), a novel cholesterol absorption inhibitor, is recommended as a monotherapy or in conjunction with statins to treat primary hypercholesterolemia. Various studies have indicated that the combined therapy of ezetimibe with variable statins has resulted in reductions in LDL cholesterol levels up to 12–19% and, in some cases, eventually led to substantially lower cardiovascular risk. Therefore, combined treatment with ezetimibe and statins can not only produce gradual reductions of LDL cholesterol but may also boost the cardiovascular outcomes (10–17).

Fixed-dose combinations (FDCs) are one of the many reformulation techniques used in drug lifecycle management to achieve such a combined effect in a single unit dosing form such as tablets. FDCs are known for their ability to reduce patients’ pill burden and to reduce the risk of side effects. They have shown success in treating a number of conditions, such as cardiovascular diseases, diabetes, HIV/AIDS, tuberculosis, and malaria (18–22).

In this investigation, FDC tablets of Atorvastatin calcium (ATC) and Ezetimibe were prepared using a quality-by-design (QbD) approach to better understand the relationship between critical formulation and process parameters to critical quality attributes (CQAs). The effects of critical formulation parameters viz. the concentration of PVP K-30 (binder),...
ON-DEMAND WEBCAST
Aired: Tuesday, June 22, 2021

Presenter

Carina van Eester
Global Platform Leader, Prefilled Syringes and Cartridges
Datwyler

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Parenteral Packaging for Cartridges in Drug Delivery Devices

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

Event Overview
As drug companies seek innovative ways to improve the delivery of drugs and patient compliance, the demand for cartridge-based drug delivery devices—such as pen injectors and on-body injectors—has increased. As new devices and delivery methods become available, it is important that device and drug developers have a wide selection of parenteral packaging for these cartridge applications, as well as an understanding of the components and applications.

This webcast will introduce the audience to packaging components for cartridges used in drug delivery devices today and explore future trends that are emerging in the market.

Topics will include:
• An introduction to parenteral packaging for cartridges used in drug delivery devices
• An overview of common challenges in the market, featuring case studies on packaging drug delivery devices
• A look at emerging drug delivery trends, such as large-volume, on-body injectors

Key Learning Objectives
• Understand the common cartridge applications for drug delivery devices available on the market today
• Learn through case studies and best practices what parenteral packaging components are available for these applications and how to select the ideal cartridge components
• Understand future trends for drug delivery devices and how parenteral packaging suppliers are working to meet future market needs

Who Should Watch
• Quality/regulatory personnel in parenteral drug delivery
• Formulation scientists and packaging engineers
• Device development engineers and managers
• Technical personnel involved in drug delivery systems
• Extractables and leachables analysis experts
• Procurement professionals

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amount of alpha TPGS (antioxidant), and amount of poloxamer 188 (solubilizer) on the physicochemical properties of prepared FDC tablets were investigated by executing design of experiments (DoE) using 2^3 factorial design.

Materials and methodology

Materials. ATC and EZE were received gratis from Cadila Healthcare Ltd., Ahmedabad, Gujarat, India and Sun Pharmaceutical Ltd., Vadodara, Gujarat, India, respectively. Pluronic F-68, Alpha D- Tocopheryl Polyethylene glycol Succinate 1000, MCC PH101, Aeroperl R-300, Kyron T-314, Acryflow – L were donated by Hi-Media Ltd., Isochem India Pvt. Ltd., Sigachi Plasticizers Pvt. Ltd., Evonik Industries, Coral Pharma Chem, and Coral Pharma Chem, respectively. The rest of the chemicals required for this research were purchased from Hi-media Pvt Ltd.

Methodology

Drug excipient compatibility studies. A Fourier Transform Infra-Red (FTIR) spectrophotometer (NICOLET 6700, Thermo Scientific) was used to study the interaction between APIs and excipients. The dosage forms were pelletized. Samples of the drugs (ATC and EZE) and the best prepared batch (F8) were taken separately with KBr, and pellets of each API were formed by pressure. Pure KBr powder was used as background and for baseline correction, considering its transparent nature in the infrared region. The sample was put in a sample holder and scanned with an FTIR spectrophotometer in the region of 4000-5000 cm^{-1}.

QbD approach (23–26). The target product profile (TPP) describes the application, safety, and efficacy of the product that initiates the development strategy. To understand the CQA, the quality TPP (QTPP) for orally dissolving tablets was studied in detail. The initial CQAs were defined from QTPPs to identify a satisfactory level of quality for the product. The critical material attributes (CMAs) and critical process parameters (CPP) were derived from identified CQAs for the formulation of FDC tablet.

By applying a QbD approach to tablet formulation, concentration of binding agent (PVP K-30), the amount of antioxidant with solubilizer (alpha TPGS), and the amount of lubricant (poloxamer 188) were identified as most critical independent variables. The levels of these independent parameters were as follows:

- X1 (concentration PVP K-30 at 3 and 4%)
- X2 (amount of alpha TPGS at 0.5 and 1.0%)
- X3 (amount of Poloxamer 188 at 5.0 and 10.0%).

The percentage cumulative drug release at 10 min (Y_1) and 20 min (Y_2) were identified as the dependent variables. Based on this selection, a 2^3 full factorial design was applied using Design Expert 7 software to generate eight experiments (Table I).

Table preparation. Wet granulation was used to prepare the tablets. Table II describes the composition of optimized tablet formulation. Accurately weighed PVP K-30, poloxamer 188, and alpha TPGS were dissolved in a sufficient volume of isopropyl alcohol (IPA) in a glass beaker. To this solution, accurately weighed ATC and EZE (10 mg of each) were dispersed to form a granulating fluid.

Initial mixing was performed between the 70% solid mass (comprised of Avicel PH101 and Starch 1500 DC mixture) and the granulating fluid, using double-cone blender. Final mixing was done by adding the remaining amount of Avicel PH101, Starch 1500, Kyron T-314, and Aeroperl 300 to above initial mixture. The resulting mass was then passed through sieve No. 20 (with pores of 841 microns in diameter) and the received granular mass was subjected to drying at room temperature (30 ± 2 °C). Finally, Acryflow-L was added, and the blended granular mass was compressed using the 6-mm flat-faced round punches on a Rimek MINI PRESS-II MT tablet machine (Karnawati Engg. Ltd., Mehsana, India), after a thorough evaluation had been made of physicochemical properties such as dimensional uniformity, weight variation, breaking force, friability, content uniformity, and dissolution. The total weight of the tablet was maintained at 100 mg.

Evaluation of prepared granules (pre-compression) (27). Percentage yield. The prepared granules were collected and weighed.

Table I. Design matrix table for 2^3 factorial design.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>X_1</th>
<th>X_2</th>
<th>X_3</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F2</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>F3</td>
<td>-1</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>F4</td>
<td>+1</td>
<td>+1</td>
<td>-1</td>
</tr>
<tr>
<td>F5</td>
<td>-1</td>
<td>-1</td>
<td>+1</td>
</tr>
<tr>
<td>F6</td>
<td>+1</td>
<td>-1</td>
<td>+1</td>
</tr>
<tr>
<td>F7</td>
<td>-1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>F8</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
</tbody>
</table>

Table II. Optimized batch composition.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity/tablet</th>
<th>Functional category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1 (ATC)</td>
<td>10 mg</td>
<td>API</td>
</tr>
<tr>
<td>Drug 2 (EZE)</td>
<td>10 mg</td>
<td>API</td>
</tr>
<tr>
<td>Alpha TPGS</td>
<td>1.0 mg</td>
<td>Antioxidant as well as solubilizer</td>
</tr>
<tr>
<td>PVP K30</td>
<td>4.0 mg</td>
<td>Binding agent</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>10.0 mg</td>
<td>Solubilizer (dissolution enhancer)</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>0.5 mL</td>
<td>Granulating agent</td>
</tr>
<tr>
<td>Kyron T-314</td>
<td>4.0 mg</td>
<td>Super disintegrant as well as pore former</td>
</tr>
<tr>
<td>Avicel pH 101: Starch 1500 DC</td>
<td>15.9 : 37.10 (mg)</td>
<td>Diluents</td>
</tr>
<tr>
<td>Aeroperl 300</td>
<td>6.0 mg</td>
<td>Adsorbent and lubricant</td>
</tr>
<tr>
<td>Acryflow-L</td>
<td>2.0 mg</td>
<td>Glidant and lubricant</td>
</tr>
</tbody>
</table>

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Table III: Statistical analysis. CDR is cumulative drug release.

<table>
<thead>
<tr>
<th>Factors</th>
<th>% CDR at 10 min</th>
<th>% CDR at 20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>X₁</td>
<td>2.18</td>
<td>0.0091</td>
</tr>
<tr>
<td>X₂</td>
<td>2.26</td>
<td>0.0088</td>
</tr>
<tr>
<td>X₃</td>
<td>2.11</td>
<td>0.0094</td>
</tr>
<tr>
<td>X₁X₂</td>
<td>1.87</td>
<td>0.0107</td>
</tr>
<tr>
<td>X₁X₃</td>
<td>3.03</td>
<td>0.0066</td>
</tr>
<tr>
<td>X₂X₃</td>
<td>-1.34</td>
<td>0.0148</td>
</tr>
<tr>
<td>R² value</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>Adjusted R² value</td>
<td>0.9998</td>
<td></td>
</tr>
<tr>
<td>Predicted R² value</td>
<td>0.9978</td>
<td></td>
</tr>
<tr>
<td>Adequate Precision</td>
<td>223.997</td>
<td></td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.96</td>
<td>81.51</td>
</tr>
</tbody>
</table>

The weight measured was divided by the total quantity of components that were used for the preparation of tablet (100 mg). Percent yield (% Yield) was determined using Equation 1.

\[
\% \text{Yield} = \left( \frac{\text{Practical weight}}{\text{Theoretical weight}} \right) \times 100
\]  

Determining drug content. Accurately weighed granules (equivalent to 10 mg of ATC and EZE) were subjected to extraction with methanol, and the resulting extract was then filtered through Whatman filter paper. The extract’s absorbance was measured using an ultraviolet (UV) spectrophotometer at 246 and 232 nm after suitable dilution with methanol. A standard calibration curve equation was used to calculate drug content.

Measuring the angle of repose. The angle of repose is the largest angle possible formed between the powder surface and the horizontal plane. It is a direct measurement of powder flow and, hence, mimics material flow (e.g., the flow from processing equipment such as a tablet press hopper to the die.) The angle of repose for the prepared granules was determined by fixed funnel method. The granules were taken and allowed to pass through a funnel with its tip held at a height of 2 cm onto a flat surface until they formed a conical heap, which touched the tip of the funnel. The height (h) and mean radius (r) of the base for the granule cone were measured and the angle of repose (θ) was estimated using Equation 2:

\[
\theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Bulk density, tapped density, and Carr’s Index. The powder’s bulk density is the ratio of its overall mass to the volume it occupies and is expressed as g/mL. Tapped density of the powder is the ratio of the total powder mass to the volume of powder observed post tapping. Bulk and tapped density were estimated using tapped density tester United States Pharmacopeia (USP) method-II (ETD-1020, Electrolab, India).

Carr’s Index, which shows the flow characteristics of the powder, is calculated as Equation 3:

\[
\text{Carr’s Index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100
\]  

Evaluation of prepared FDC tablet of ATC and EZE (post compression). Various evaluation parameters were determined for the prepared tablets (e.g., dimensional uniformity, weight variation, breaking force, friability, dissolution, and stability (28, 29), as follows:

Dimensional uniformity. Five tablets from each formulation were taken and their diameter, as well as thickness, were determined by using a calibrated digital Vernier caliper.

Weight variation test. Twenty tablets were picked up randomly from each batch, their weights were noted down and percentage deviation from target weight was calculated.

Breaking force test. Hardness reveals a tablet’s capacity to handle mechanical shocks. A Monsanto tester was used to determine the hardness (kg/cm²) of the tablet. In all instances, the average of five replicates was taken.

Friability test. Tablet samples (equivalent to 6 g weight, i.e., 60 tablets) were accurately weighed, dedusted, and placed in the Roche friabilator. The drum was rotated 100 times at 25 rpm, and the tablets were then removed and reweighed. The percentage friability was calculated according to Equation 4.

\[
\% \text{Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100
\]  

Tablet friability levels of less than 1% are considered acceptable.

Content uniformity. Ten milligrams of ATC and EZE from finely-powdered tablets were accurately weighed and transferred to a 100-mL volumetric flask. Methanol was added to the powder mixture to yield a suspension, which was then filtered. Methanol was used to dilute the resulting liquid, and the resulting solution absorbance was measured with a UV spectrophotometer at 247 nm and 233 nm.

In-vitro dissolution studies. The in-vitro drug release study was performed using a USP XXIII paddle apparatus (Dissolution test apparatus TDT-08L, Electrolab, Mumbai) using 900 mL 0.1 N HCl with sodium lauryl sulphate (0.45%, pH = 1.2) at 75 rpm at 37 ± 0.5°C. The samples were withdrawn at predetermined time intervals for up to 60 min. The withdrawn samples were filtered through 0.45μm Whatman filter paper, diluted, and analyzed at 243 nm and 232 nm for ATC and EZE respectively, using UV-visible double beam spectrophotometer (Shimadzu1800).

Data analysis. For optimization purpose, a State-Ease Design Expert Version 7 software was used. Polynomial models,
Peer-Review Research

including all interaction and polynomial terms, were generated for all the response variables, and analysis of variance (ANOVA) was applied. The general shape of the model is represented by Equation 5:

\[
Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1^2 + \beta_4 X_2^2 + \beta_5 X_1 X_2 + \sum_{i=1}^{2} \beta_i X_i X_{2i} X_{22}
\]

[Eq. 5]

Figure 1. Fourier Transform Infra-Red (FTIR) spectra of pure ATC (1a), pure EZE (1b), and tablet formulation (1c).

where \(\beta_0\) is the intercept is the arithmetic average of all quantitative outcomes of nine runs, \(\beta_i\) to \(\beta_n\) are the coefficients from the observed experimental values of \(Y\). While \(X_1\) and \(X_2\) are the coded levels of the independent variable(s). The terms \(X_i X_j\) and \(X_i^2\) are the interaction and polynomial terms, respectively.

ANOVA was used to determine the statistical validity of the polynomials and MS Excel was used to draw tri-dimensional response surface graphs and contour plots from data obtained by the State-Ease Design Expert Version-7 software. The resulting experimental results were compared quantitatively. Predicted values and linear regression plots were obtained using MS Excel, forcing the line through the origin.

Stability studies. An optimized batch (F8) of ATC and EZE was wrapped in alu-alu foil and subjected to stability studies as per guideline Q1A(R2), established by the International Council for Harmonisation (ICH) at 40°C ± 2°C and 75% RH ± 5% RH. Tablets were placed in the stability chamber and periodically (i.e., on the 30th, 45th, and 60th days of the research project), samples were removed for evaluation. Various physicochemical parameters (e.g., breaking force, drug content, and dissolution at 10 min and 20 min) were checked for those samples.

Results and discussion

Preformulation studies. The interaction between the excipients and APIs (ATC and EZE) was evaluated using FTIR spectroscopy. The FTIR spectra of pure ATC, pure EZE, and FDC tablets (F8) are shown in Figure 1a, b, and c, respectively. The FTIR spectra revealed a negligible difference in the functional groups’ peaks of the selected batch (F8) as compared to that of the pure drugs. Hence, it was inferred that no drug excipient incompatibility occurred.

Quality-by-design approach. The type of formulation and manufacturing process decide the QTPP of each pharmaceutical product, and QTPP elements were estimated based on a review of preliminary studies, literature data, and researchers’ experience. The CQAs, in turn, were derived from the QTPP, based on the criticality derived from previous information, literature evaluation, and several preliminary studies. CMAs and CPPs were additionally extracted from the identified CQAs.

Granule parameters. Prepared granulated mass was evaluated for various physicochemical parameters. Good yield (98–100%) and high drug content (99–103%) passes the standard limits. Prepared granules were found to have excellent-to-good flowability considering the angle of repose (20–28 degrees) and Carr’s index (16–29).

Tablet parameters. White, circular and flat-faced tablets were observed. The weight of tablets ranged between 99.5 and 102.0 mg. Thus, the percentage weight variation was within the USP limits (with individual tablet weight deviation of less than 7.5%) and met the criteria. In all lots, the mean thickness and diameter of tablets (n=5) ranged between 2.50–2.60 mm and 6.08–6.02 mm, respectively. The
Figure 2. The dissolution profile of ATC (2a) and EZE (2b) in 0.1 N HCl with 0.45% sodium lauryl sulphate (SLS).

Figure 3. Linear correlation, 3-D surface, and contour plots.

dimensional uniformity of materials in individual lots and between tablets in different lots was therefore observed. The breaking force measured between 30 to 40 N, ensuring good handling characteristics for all batches. For all formulations, the % friability was in the range of 0.31 and 0.77, ensuring that the tablets were mechanically robust.

**In-vitro dissolution study.** Studies on drug release for the FDC tablets containing ATC and EZE were performed and the cumulative dissolution chart was drawn up (Figure 2). Table III addresses data obtained for the dependent variables treated with ANOVA and analysed with statistical software Design Expert.

**Statistical analysis at 10 min.** A mathematical method was used to extract the relation of the dependent variables (response) to the independent variables. The ANOVA results (p-value) of the effect of the independent variables on dependent variables is given in Equation 6.

\[
Y_1 = 40.96 + 2.18 (X_1) + 2.26 (X_2) + 2.11 (X_3) + 1.87 (X_1X_2) + 3.03 (X_2X_3) - 1.34 (X_3X_1)
\]  

[Eq.6]
From the Design Expert software and the linear correlation plot between the predicted value and actual value at 10 min, it was found that the predicted R-Squared value of 0.9978 was in reasonable agreement with the adjusted R-Squared value of 0.9998.

“Adequate Precision,” which measures the signal-to-noise ratio, should ideally be above four, and the resulting ration was 223.997, indicating an adequate signal. The model can also be used for concept space navigation. Thus, the model can be used to navigate the design space. Figure 3 ($Y_c$) shows the linear correlation plot, 3D- response surface graph, and corresponding contour plot. At the fixed value of $X_a$, it has been found that the increase of $X_a$ to a high level (1 level), along with the increase of $X_b$ to a high level (1 level) a better drug release at 10 min. The linear correlation plots drawn between the predicted and the observed responses demonstrated higher values of $r^2$ (ranging between 0.964 and 0.977), indicating excellent fitting of the model ($P<0.001$).

**Statistical analysis ($Y_e$) at 20 min.** The full model equation was found to be as follows in Equation 7:

$$Y_e = 81.51 + 0.53\ (X_1) + 2.34\ (X_2) + 2.15\ (X_3) + 3.81\ (X_1X_2) + 1.63\ (X_2X_3) + 0.29\ (X_3X_1)$$

[Eq.7]

From the Design Expert software and the linear correlation plot between the predicted value and actual value at 20 min, it revealed that the predicted R-Squared value of 0.9555 was in reasonable agreement with the adjusted R-Squared value of 0.9951.

The signal-to-noise ratio, which tested “adequate precision,” found a ratio of 54.145, well above the cut-off point of four. Thus, the model can be used to navigate the design space.

Figure 3 ($Y_e$) shows the linear correlation plot, 3D- response surface plot, and corresponding contour plot. It was found that at the fixed value of $X_c$, increase $X_a$ up to high level along with increase $X_c$ up to high-level results shows better drug release at 20 min. This has been found to be linear between predicted and observed responses and gave higher values of $r^2$ (ranging between 0.9555 and 0.9778), indicating excellent fitting of the model ($P<0.001$).

**Figure 4** provides the individual desirability, the overall desirability D, and predicted value. The factors obtained at the maximum points of $Y_1$ and $Y_2$ (target: 45 % and 85%, respectively) were calculated as $X_1=3.79$, and $X_2=8.36$, which are known as an estimated condition.

**Stability studies.** The selected formulation (F8) was studied for stability using hardness (SD±0.049); drug content (SD±0.303 for ATC and EZE); disintegration (SD±0.417), drug release at 10 min (SD±3.447 for ATC and 1.715 for EZE), as well as drug release at 20 min (SD±2.064 for ATC and 3.447 for EZE). Stability studies for prepared FDC tablet formulation suggested that no significant changes were observed in any of study parameter during a two-month stability study at 40 °C ± 2°C and 75% RH ± 5% RH. The results showed that the optimized formulation (F8) is stable.

**Conclusion**

In the research described above, QbD allowed three factors to be identified from material attributes and a further 2^3 factorial design was used to prepare an optimized batch. From the statistical analysis and contour plots generated, all three independent factors showed a significant effect on dependent variables. The optimized batch of FDC of ATC and EZE (F8) exhibited the selected dissolution criteria. Thus, FDC of ATC and EZE based on wet granulation is suitable for the formulation of FDC tablets. The drug release rate obtained also met the selected dissolution criteria.

**Acknowledgement**

The authors would like to thank Ramanbhai Patel College of Pharmacy, Changa, for providing the necessary facilities and resources to carry out this research.
ON-DEMAND WEBCAST
Aired: Tuesday, June 15, 2021

Presenters
Gary Zoccolante
President
Plymouth Rock Water Consultants

Patrick Buzzell
Product Manager
Evoqua Water Technologies

Moderator
Jennifer Markarian
Manufacturing Editor
Pharmaceutical Technology

Transforming Water to Meet Strict and Consistent Microbial Control While Reducing OPEX

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

Event Overview
With defined criteria for conductivity, total organic carbon, and bacteria, purified water is a critical ingredient and processing aid for many pharmaceutical companies, cosmetic manufacturers, makers of medical devices, and personal care products. Learn how your facility can achieve consistent high purity quality water while reducing total maintenance and operating costs.

Key Learning Objectives
• Review the common challenges and opportunities with high purity and water for injection applications
• Learn about Electrodeionization technology and how it compares to traditional solutions
• Understand Electrodeionization technology and its ability to attain tight and consistent microbial control
• Review considerations when making the switch to Electrodeionization, the ROI and potential savings in maintenance and operating costs
• Hear case studies of how facilities are improving microbial control while reducing OPEX

For questions email kbarry@mjhlifeiences.com

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Peer-Review Research

References
10. E. Dembowski, M.H. Davidson, Curr Opin Endocrinol 16 (2) 183-188 (2009).
30. To whom all correspondence should be addressed.

Manufacturing —
Contin. from page 32

close communication and planning in order to keep operations running efficiently,” he says.

“Sensitive and fragile analytical equipment such as near infrared (NIR) probes require careful and experienced handling in order to prevent damage,” adds Santos. “Developing and controlling standard procedures with the right level of details and mistake-proofing become even more critical in the context of preventing damage to such sensitive components during handling and cleaning.”

“When cleaning equipment with internal sensors, consideration should be given to the material of construction to ensure compatibility with the chosen cleaning agent. Typical substrates may include glass, titanium, or polymeric material,” note Lopolito and Kroeger. If using a CIP cleaning method, they recommend working with the PAT vendor to check compatibility to determine if there will be any impact to the sensors through chemical exposure, high-pressure steam, foaming, build-up of residue on the probes, or through any interaction of materials. Another concern with sensors in a CIP process is determining how well the cleaning and rinse solution flows in and around the sensor and whether there is a significant change in the flow dynamics through the piping. “Coverage testing can be confirmed using riboflavin, and flow dynamics can be assessed through computer modeling, Reynold’s number calculations, or inspection with a borescope,” they explain.

It may be possible to use the existing PAT (which measures process variables when the process is running) to also monitor a CIP cleaning process, says Lopolito. “An example would be an ultraviolet (UV) or Fourier Transform Infrared (FTIR) spectroscopy sensor (to monitor drug active) that can also be used to detect trace levels of cleaning agent in rinse water and stop the rinse process when a target limit is achieved within a specified time,” he explains.

FTIR is also being investigated as an approach to cleaning verification, using a handheld instrument to detect and quantify surface contamination. One of the challenges for manual cleaning is the difficulty of standardizing across a wide range of equipment components with different degrees of product exposure or adhesion, notes Santos. “New technologies such as handheld FTIR can certainly bring a level of simplicity to this process, either in terms of an in-process control to determine the endpoint of cleaning of a component or to eliminate dependence on analytical samples altogether,” he concurs.

References
1. FDA, Draft Guidance for Industry, Quality Considerations for Continuous Manufacturing (CDER, February 2019).
Enabling Formulations of Poorly Absorbable Drugs with Capsule Solutions

**Event Overview**
As the pharmaceutical developers transition from blockbuster APIs to niche busters, they are facing new challenges with formulating poorly absorbable APIs. This webcast will provide a brief overview of the market dynamics and discuss in detail possible oral dosage form solutions to help overcome challenges with bioavailability and absorption of complex drug formulations.

**Key Learning Objectives**
- Provide a better understanding of lipid-based formulations and how they help improve bioavailability.
- Discuss amorphous solid dispersions and how it can improve absorption.
- Review possible oral dosage form solutions and tips on how to choose the right capsule to meet development requirements.

**Who Should Watch**
- Research and development scientists, formulation scientists

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**Presenters**
- **Matt Richardson, PhD**
  Manager Pharmaceutical Business Development
  Capsules and Health Ingredients, Lonza
- **Vincent Jannin, PhD**
  Head of Applications Lab
  Capsules and Health Ingredients, Lonza
- **Feliza Mirasol**
  Editor
  Pharmaceutical Technology

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**Register for this free webcast at:**
www.pharmtech.com/pt_p/capsule

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**ON-DEMANDWEBCAST**
Aired: Tuesday, May 18, 2021 & Tuesday, May 25, 2021

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For questions email kbarry@mjlifesciences.com

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**Presented by**
Pharmaceutical Technology
As recent COVID-19 vaccine facility citations make clear, failure to meet cleaning and sanitization requirements puts patients, facilities, and operators at risk.

Keeping pharmaceutical facilities clean and germ free seems an obvious prerequisite for any company that manufactures medicines. However, regulatory citations suggest that pharmaceutical manufacturers and contract manufacturing and development organizations (CDMOs) may take cleaning and cleaning validation for granted.

An April 2021 Form 483 issued by FDA to the Maryland-based CDMO, Emergent Biosolutions, which is under contract to Johnson & Johnson (J&J) and AstraZeneca to manufacture their COVID-19 vaccines, showed how deeply rooted this problem may be (1). J&J and AstraZeneca use very different manufacturing processes, but both involve the use of viral vectors.

FDA inspectors found fundamental deviations from good manufacturing practices (GMPs) at the facility. Among the observations noted were failure to maintain clean and sanitary conditions; lack of written procedures for cleaning and decontamination of the vessels used to transport and store materials at the site; and no formal requirements to clean and sanitize these vessels after each use.

In addition, no tests were conducted to determine how long viruses used in a client’s production process remained viable on equipment surfaces in one area within the facility.

**Casting the first stone?**

If these omissions seem basic, it might be helpful to remember that in pre-pandemic 2019, the last full year when FDA performed routine site inspections, roughly 60% of FDA 483 regulatory observations involved deficiencies in cleaning and sanitization and their validation.

This fact was presented by Matt Cokely, senior global technical consultant manager for Ecolab Life Sciences in a best-practices webinar presented by the International Society for Pharmaceutical Engineering (ISPE) on April 9, 2021 (2). The most often cited problems, he said, were the lack of procedures for preventing contamination, deficiencies in cleaning, failure to keep cleaning records, and inadequate standard operating procedures (SOPs).

Cleaning validation consultant Rich Forsyth agrees. “Problems often boil down to a failure to follow procedures. Either people are doing something that is not in the SOP or there’s something in the SOP that they aren’t doing,” he says. For example, Forsyth notes, many procedures fail to specify cleaning frequency, or the amount of time that should be spent to clean a piece of equipment using documented procedures and materials. This forces operators to take the unprovable position that ‘it’s not clean until it’s clean’, he says.

**Active training needed**

Cleaning and cleaning validation practices need to be reproducible, Cokely noted, and employees must be trained, not only in the basics of microbiology and hygiene pertaining to cleaning, but in cleanroom procedures and gowning and in understanding potential risks and safety hazards. “They need to understand not just how, but why they are performing a task, and to be trained to actually perform it,” he said, rather than simply being given a pile of SOPs to read and sign off on. Given the trend to outsource cleaning and sanitization activities, Cokely noted, this training must be given to contract cleaning workers as well.

Elaborating further, Cokely noted that written instructions in SOPs should specify who is responsible for the duties, and set a schedule of frequency for cleaning, describe the ma-
Event Overview:

The bio/pharma industry is turning to proven digital technologies used in other industries to plan, develop, and monitor manufacturing processes, as well as in quality, training, and regulatory oversight. In this event, experts discuss how artificial intelligence, remote monitoring, digital twins, and other technologies can be applied to modernize bio/pharma processes and systems. Lessons learned from the pandemic will be shared.

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Analytics

Materials and techniques to be used in detail, and the preparation and storage of cleaning materials. In addition, documentation must include the names and signatures of staff performing the work, as well as the product batch number, cleaner expiry date, and disinfectants used. Cokely also noted that disinfectants with different modes of action should be rotated. Care must also be taken, he said, to avoid interactions between different cleaning chemistries that might inhibit microbe-killing mechanisms and promote the buildup of cleaning solution residues.

Varying amounts of material may be left on the equipment when cleaning officially begins.

The basic problem, Cokely noted on the webinar, is that cleaning and disinfection are undervalued in the pharmaceutical industry, despite their importance to patient and overall safety. “At some companies, cleaning procedures have been used for years, or the facility may have inherited practices that have never been reviewed or scrutinized,” he said.

Regulations for cleaning and its validation abound, supplemented by best practices circulated by ISPE, the Parenteral Drug Association (PDA), and now the American Society for Testing and Materials (ASTM), which has set standards for pharmaceutical cleaning operations and validation. Risk-based standards for cleaning validation, set in 2018 (3) began to establish a more scientific basis for practices at individual facilities.

These standards have had a positive impact, notes Forsyth, getting pharmaceutical companies to go beyond thinking simply about products, equipment, and detergents in their cleaning operations. “Risk-based standards forced people to formalize their risk assessments. Many of them began to consider peripheral risks that they hadn’t factored in before, such as the air-handling system’s impact or the material and equipment traffic in the facility,” he says.

However, in the end, some companies may view having a formal cleaning validation program and strategy as involving too much work. “Companies pay a lot of attention to their cleaning and cleaning validation programs when they get cited by regulators for those programs’ failings,” Forsythe says. But establishing a program or updating one that hasn’t been reviewed in several years, takes commitment, he notes, and it generally requires a year to do because everyone has their regular jobs to do, too. “Often, shepherding a cleaning validation project through to its end becomes more problematic the longer the projects continue. At many companies the success or failure of a cleaning and cleaning validation program may rest on one champion supporting it,” Forsyth says.

Multiproduct facility challenges

Today, multiproduct facilities, and particularly biopharmaceutical facilities, pose several cleaning validation challenges, Forsyth notes. “You worry more about bioburden in a biological plant than in a small-molecule facility, but generally if you have an effective cleaning validation program, you’re fine,” he says.

However, setting cleaning limits can be tricky because traditional methods fail to consider some of the most significant differences between biopharma and small-molecule facilities. “The most notable difference between the two types of plants is that biopharmaceutical facilities start processes using equipment with large surface area but generate small batches, both of which require the use of lower cleaning limits, so if you use the entire equipment train, your limits may, at first, appear to make no sense,” Forsyth says. Single-use systems and equipment have eliminated some of those problems, but they persist for hybrid plants still using stainless steel equipment.

Another question is how batches are finished and whether pre-cleaning equipment preparation processes are consistent from one batch to another. If they are not, varying amounts of products may be left on equipment surfaces after each run. “Some types of equipment will empty completely, but others won’t,” Forsyth says.

He recalls one of his first experiences working on cleaning validation in a pharmaceutical development lab. “We were concerned about pouring active ingredients down the drain, so we wound up scraping equipment and then vacuuming it before cleaning. By the time we started cleaning that equipment, it was almost visually clean,” he says, noting that this type of approach reduces the risk of cleaning failures and compliance problems. At some companies, varying amounts of material may be left on the equipment when cleaning officially begins.

Other CDMO challenges

CDMOs that focus on clinical trial drug manufacturing face unique challenges in setting cleaning limits. “For clinical operations, you are not making a lot of batches of the same thing, so you don’t make enough batches of any single product to validate the cleaning methods using standard approaches,” says Forsyth. “In this case, it is usually best to work with a more general model, establish a worst case, and then evaluate each new product coming in. However, this approach increases the effort and justification required to maintain the model, and a lot of CDMOs don’t do this very well,” says Forsyth.

Specific approaches are needed to prevent cross-contamination in multiproduct facilities, Forsyth says. “Best practices call for calculating the amount of residue that can safely be carried over for every product. For a multiproduct facility that makes 10 products, that means calculating the limit of one product versus those of the other nine, taking the lowest number and then using that, and then following the same procedure for the rest of the products,” he says.

Contin. on page 52
Challenges with Verification of Compendial Chromatographic Methods

Event Overview

Compendial verification is a regulatory requirement in various phases of drug development. The technical merits of a robust review of the written method and the value of demonstrating fit for purpose in your laboratory is often overlooked.

This webcast will discuss a series of case studies that illustrate the importance of performing robust compendial verification in your laboratory. Experts will describe the technical challenges encountered, while evaluating a variety of active pharmaceutical ingredients and excipients and explaining how those challenges were resolved.

Challenges include:
- Sample preparation methodology that led to ruptured vials
- High-purity reference standards unavailable from commercial sources
- Reference standards of uncertain purity or potentially contaminated
- Standard preparation methods that may be hazardous or present safety concern

Key Learning Objectives

- Understand the value added by performing compendial verification to demonstrate suitability under the actual conditions of use in your laboratory.
- Assess why compendial verification data is needed to ensure potential technical and safety issues are identified.
- Identify analytical details and techniques that may not be included in the compendial procedure but are essential for a robust method.

Who Should Attend

- QC chemists
- R&D chemists
- QC laboratory management
- Quality assurance personnel

For questions email kbarry@mjlifesciences.com

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

ON-DEMAND WEBCAST
Aired: Thursday, May 27, 2021

Presenters

James Joslin
Raw Material Chromatography Area Supervisor

Adam Ketola
Senior Scientist

Patricia Thul
Director of Method Development and Validation for Small Molecules

Desmond Bauer
Associate Scientist III

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

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Developing a Method for Success through Partnerships

Felicity Thomas

Outsourcing method development offers multiple benefits to companies, including access to experience and expertise, streamlined costs, and development time efficiencies.

The market for outsourced pharmaceutical and biotechnology services is expected to experience healthy growth and is forecast to reach $91.4 billion by 2028 (1). Factors influencing this market swell include rising pressure on drug prices, increasing drug development costs, higher rates of failure, regulatory hurdles, and deficient internal capabilities of sponsor companies, all leading to an increased demand for outsourced solutions (1).

Method development is an evident area where pharma companies can gain an economic benefit from outsourced services, particularly when there are limited to no capabilities for these services in-house. As an integral facet of drug development, optimization and selection of the most appropriate methods can help save on costs and reduce development times.

“The importance of method development cannot be understated,” says Emma Leishman, manager, Advanced Analytics, Avomeen. “Methods are the backbone of being able to answer scientific questions. Advancements in technology, as well as tighter regulatory needs, are driving methods that are more targeted, efficient, and sensitive. Spending time on method development upfront will build a solid foundation for validation and subsequent sample testing.”

Factors for consideration

“Method development and evolution of a drug product are continuous processes that progress in parallel with one another,” explains Alex Wheeler, senior technician at Wickham Laboratories. “It can be assumed that as the life cycle of a drug product progresses, overall knowledge of the drug product increases as should the robustness of the analytical tests that are being performed.”

Any analytical tests that are due to be performed must relate to the type of drug being developed and are required to comply to any regulatory requirements, continues Wheeler. “During method development, full transparency of the procedure performed is imperative so that when the information is presented to the relevant market authority, it is clear, accurate, and concisely conveys what has been done,” he says. “Investing in robust analytical tests to be established during the method development process will help to ensure that costs are kept down during the further stages of the drug development program.”

Factors for consideration in method development are dependent upon the molecules being developed, agrees Vincent Thibon, technical development lead, RSSL. “For developing methods for small molecules, the analytical method should be developed by looking into the factors such as pH, ionic strength, mobile phase composition, sample preparation, column technology, type of detection, [liquid chromatography–mass spectrometry] LC–MS compatibility, robustness, speed of [quality control] QC, length of time required for stability indication, cost effectiveness, and whether the method is easy to run,” he states. “For developing methods for large, protein-based molecules, the method should be developed by looking into factors such as sample preparation, sensitivity of technique, time to achieve results, complexity of method, and so on.”

A structured method development procedure is vital to ensure the intended methods are fit for the phase of drug product development, they provide the data required for product development support, and they can be validated to the correct product phase following industry guidelines, such as those from the International Council for Harmonisation.
Event Overview

Excipient manufacturing and process development for its use in drug production must meet GMP compliance. The suitability of pharmaceutical excipients for their intended use is defined by critical quality attributes (CQAs) such as identity, strength, and purity, which can pose numerous analytical challenges due to the complex nature of excipients.

The United States Pharmacopeia–National Formulary (USP–NF) provides continued guidance on how to specify excipient composition, including control of impurities. Further efforts from the International Council for Harmonization (ICH) are needed to set guidelines relating to the control of impurities in excipients. In this webinar, we will cover:

- Challenges associated with the control of impurities in excipients
- Analytical techniques used for the characterization of pharmaceutical excipients
- Software technology driving 21 CFR Part 11

Key Learning Objectives

- Use of analytical technologies to drive the control of impurities in excipients
- Understand the regulatory framework for excipients testing, with a viewpoint on the USP stimuli article, titled The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities
- Detect possible genotoxic impurities in excipients
- Achieve data integrity by using software compliant to cGMP and 21 CFR Part 11 for FDA-regulated industries.

Who Should Attend

- QA/QC scientists
- QA/QC managers
- Head of QA/QC
- CRO and CMO laboratory personnel
- QA auditors responsible for laboratory quality and data integrity
Outsourcing

(ICH), for the release of the product to clinic or market, asserts Amanda Curson, head of Analytical Development, Tredegar, PCI Pharma Services. “The method should be well developed at the start with the view of having a long life-cycle without major changes,” she says. “Redevelopment later can be time consuming and have an impact on regulatory submissions.”

For Jerry Mizell, senior director, Analytical Services, Metrics Contract Services, developing a ‘QC ready’ method is the most critical aspect in the method development process. “Having a method QC ready implies that it is very robust, [and the] rigorous challenging of the method will also establish a stability indication to ensure the quality of API or drug product over time,” he comments.

“Throughout development, methodologies are challenged with stressed and design-of-experiment samples to demonstrate performance. Design space creation is also used to determine the range of chromatographic performance and cover multiple formulation compositions for the product,” Mizell continues. “This approach sets a project up for success if there are future changes to the drug product as the developed method will be suitable for use.”

Outsourced offerings and benefits

“Outsourcing method development can give a drug developer access to a more experienced or advanced skill base with minimal delay than it is able to access internally,” highlights Anders Mörberg, analytical chemist at Recipharm. “As a dedicated specialist in method development, the outsourcing partner can provide dedicated expertise to deliver a much higher quality service than a developer may be able to achieve alone.”

It is fundamental that an outsourcing partner has solid insight into regulatory guidelines and expectations, in addition to being able to provide access to industry-standard separation equipment, Mörtberg notes. “Access to structure elucidation techniques for impurity identification is also advisable in an outsourced partner, as this is often necessary in method development,” he states. “Resources to provide computer-aided method development is desirable, as this can help the partner provide guidance on reducing labor and laboratory costs for method development.”

The three ‘E’s’—equipment, experience, and expertise—are important aspects for consideration when seeking an outsourcing partner for method development services, confirms Leishman. “Equipment should be up-to-date and able to meet dynamic regulatory needs. A wide range of equipment is a plus, since the most suitable instrumentation can be applied, and many methods can be developed at the same time,” she says. “Experience of the company and their scientists is a strong indicator of future success. Ideally, the company has experience with similar analytes and matrices. Aside from the scientific experience, having regulatory experience with method development and validation minimizes risk.”

Choosing an outsourcing partner with a broad range of expertise, which is somewhat dependent on experience, and scientists on staff who are subject matter experts is advisable, Leishman continues. “Method development sometimes requires a creative approach, [therefore] adequate expertise can ensure that even the most challenging methods are successfully developed in a timely manner,” she emphasizes.

A desirable outsourcing partner should be able to offer a range of modern, but widely available equipment and should have an experienced technical team with vast method development experience and knowledge, concurs Rebecca Coutts, general manager, Tredegar, PCI Pharma Services. “A company can benefit by working with an outsourced services team that has in-depth knowledge and experience with a range of dosage forms, particularly with dosage forms that can sometimes prove to be more troublesome for method development, such as ointments, creams, suspensions, or very low-dose potent products,” she says. “Using an outsourcing lab that has previous experience on method development, validation, and quality assurance specialist support will ensure the client is guided through the process required to ensure the method is ready for use to release clinical product, and for stability testing.”

For Mizell, development experience represents the most critical capability of a potential outsourcing partner. “Development chemists are not created overnight as it is a learning process that takes time—and there’s no substitute for that,” he asserts. “Knowledge is built upon with every successful development project, especially where technical challenges must be overcome.”

In terms of instrumentation capabilities, Mizell agrees that an outsourcing partner with multiple means of detections in-house, such as diode array, ultraviolet–visible, charged aerosol detection, and LC–MS, are beneficial. “Environmental chambers are also great to have for stressed studies,” he adds.

“Some outsourcing partners can also provide training programs to assist in clients’ learning of regulatory requirements, which would be particularly useful to smaller start-up companies,” confirms Thibon.

Oftentimes, contract research organizations (CROs) are employed for method development due to the wealth of knowl- edge they can offer in specific aspects of analytical tests relevant to the drug development and approval process, comments Wheeler. “An established CRO will operate facilities that are purpose built for analytical testing, maintained to a high standard, often utilize the most cutting-edge technologies, and already have validated and compliant in-house procedures,” he says.

Single versus multiple provider

Whether a single provider or multiple providers of outsourced services are used is dependent on the project and its specific requirements, specifies Curson. “For example, it may be possible for most of the method development to be carried out by one provider; however, there may be individual specialized analysis required, such as X-Ray powder diffraction, particle size analysis or Franz cell analysis, which is more unique and may require a specialized provider to perform method development for one aspect of the analysis,” she explains.
PPD Laboratories’ Suzhou, China Lab Virtual Grand Opening

**Register for this free webcast at:**
www.pharmtech.com/pt_p/opening

**Event Overview**
Join us for a virtual/live grand opening event that will share a first look at PPD Laboratories’ new multi-functional lab in Suzhou, China. This significant expansion will enhance PPD’s bioanalytical, biomarker and vaccine service offerings to support global clinical trials for both China-based and global pharma and biotech customers. The event will include introductory remarks from key laboratory leaders, a virtual tour of the new lab, highlights from the in-person event in China earlier this month, and a live Q&A.

**Key Learning Objectives**
- Attendees will learn about the service offerings of PPD Laboratories’ new multi-functional lab in Suzhou, China.
- Attendees will learn about PPD Laboratories’ strategies and goals for growth in China.
- Attendees will learn about PPD’s commitment to global drug and vaccine development and how our lab in Suzhou, China supports these goals.

**Who Should Attend**
- Director or above, Research and Development – Pharma and Biotech
- Director or above, clinical development – Pharma and Biotech
- Outsourcing/procurement – Pharma and Biotech

**Presenters**

**Chris Fikry**
Executive Vice President
Global Laboratory Services
PPD Laboratories

**Ding Ming**
Vice President and General Manager
PPD, China

**Patrick Bennett**
Vice President
Laboratory Strategy and Operations
PPD Laboratories

**Di Cindy Wu**
Executive Director
PPD Laboratories
Asia-Pacific

**Moderator**

**Kaylynn Chiarello-Ebner**
Managing Editor of Special Projects
Pharmaceutical Technology

For questions email kbarry@mjhlifesciences.com
Outsourcing

It is beneficial to choose a main provider of services—one that can perform the majority of the method development and validation and outsource any specialized aspects of the analysis to a partner laboratory when required—adds Curson. “The main provider would have overall responsibility for the project requirements with one or two outsourced specialized aspects undertaken by a lab with more specific specialized technical experience or available equipment required for the individual analysis,” she says.

According to Thibon, a clear advantage of using a single provider is the fact that all communication between the client and provider can be streamlined, which can mean that a good relationship can be built. “If using multiple providers, then the key thing is that all providers communicate clearly and on time and are willing to collaborate to achieve the goal,” he notes. “Regulations ensure that methods are consistent across providers, but using a single provider for all method development requirements could introduce efficiencies and reduce costs overall.”

“Using multiple providers will add complexity and may result in reduced efficiency due to coordination losses,” stresses Mörberg, who highly recommends opting for a single supplier that is capable of providing all required resources for a project, wherever possible.

A single point of contact is undoubtedly advantageous, as it can allow for easier access to the specific project manager at the CRO, timelines are generally clearer and more consistent, and all the information is presented in the same style, concurs Wheeler. “However, there are some risks as well such as the potential for a greater impact on the stages/ phases of testing if an issue should arise,” he says.

“By using multiple providers, it could be possible for multiple aspects and stages of testing to be performed concurrently if working with strict timelines, but this would generally require more internal coordination on the part of the client in such cases,” states Wheeler.

“A different approach is to use one provider to coordinate a multi-site study, therefore coordinating all testing, tracking of timelines, and compilation of results,” continues Louise Rigden, technical documentation officer at Wickham Laboratories. “This [approach] means the client still only deals with one point of contact for any information required and results can be reported in a consistent fashion.”

If a single provider has all the necessary equipment and expertise, then that approach can be ideal for a client, comments Leishman. There are time and cost efficiencies that can be gained through the use of a single provider, such as employing one sample preparation technique for multiple methods or employing a singular outsourcing lab to do an entire stability program, and in some instances, volume discounts for work can be applied, she adds.

“By reducing the number of outsourcing partners, a stronger relationship can be established with the single provider,” Leishman says. “However, a niche application or a method that needs a state-of-the-art instrument may benefit from a specialist provider.”

Mizell believes that selecting a single contract development and manufacturing organization (CDMO) that can provide all the required development needs provides a multitude of benefits. Not only does it ensure effective communication between the client and provider but can also lead to reduced meeting frequency and eliminates the need to ship API and/or drug product from site to site for different development activities, he asserts. “When working with a single CDMO that a sponsor has established a working partnership with, they can have greater confidence that the development being performed will meet all project requirements and timelines,” Mizell summarizes.

Reference

Analytics — Contin. from page 46

Statistics and instrumentation
ASTM standards have been focusing on use of statistics, which are important after a cleaning program has been validated and needs to be maintained, says Forsyth. Maintenance requires trending data. “The basic statistics needed for trending are fairly straightforward, and more advanced statistics can also be applied, but it has been difficult to motivate some companies to do that in the current environment,” he says.

More work is also being done to use analytical methods to reduce the subjectivity of visual inspection, but Forsyth hasn’t seen any consistently effective methods coming into general use. The best way to remove subjectivity from inspections has been to qualify those who must perform those inspections, a step that most regulatory agencies now require.

“I advise clients to set visual limits for residues and have staffers who might be assigned to perform visual inspections go through specialized training to recognize clearly what various levels of residues look like on equipment, compared with images of surfaces with residues that meet safe carryover limits. It’s important to have exercises in place that will allow people to visually recognize cleanliness levels to avoid patient safety risks,” Forsyth says.

Cleaning is not a popular activity, Cokely noted in his presentation, but it is essential. Taking cleaning and sanitization validation programs for granted only puts facilities and people at risk and increases the likelihood of costly noncompliance.

References
1. FDA, Form 483, Emergent Biosolutions, FDA.gov, April 20, 2021.
the world to see if they could reach agreements on what the best industry practices are for pharmaceutical products. They have created internationally recognized guidelines for quality, safety, and efficacy requirements and other topics categorized as multidisciplinary. The founding members of ICH included the European Commission, FDA, and the Japanese Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency. The list of guidelines produced by ICH is impressive and covers the critical elements a company should include when considering applications to manufacture and produce a new drug. Following the recommendations of ICH can only improve your chances of having a smooth filing and approval process globally.

References
6. FDA, Guidance for Industry. Refuse to File: NDA and BLA Submissions to CDER (CDER, December 2017). PT
The Facts About Filing Drug Applications

Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, answers some commonly asked questions about regulatory filings.

Q. What’s the difference between an IND, NDA, ANDA, an a BLA?

A. Companies need to get approval from FDA to market a new drug in the United States by submitting either a new drug application (NDA) or a biologics license application (BLA). An investigational new drug application (IND) allows a new drug that is being researched for potential medicinal use as part of a clinical trial to be shipped across state lines without marketing approval. The information contained in an IND application will become part of the NDA when the clinical trials are complete and the drug is ready to be reviewed and approved for use in the general population. The abbreviated new drug application (ANDA) is used when a pharmaceutical product’s patent has expired and another company wants to enter into the market with a generic version of the drug product. The BLA is used when seeking approval for products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

Regardless of the regulatory filing category, the company must prove that the drug product is safe and effective for the proposed use, the benefits of taking the drug outweigh the risks (side effects) associated with the drug, the product labeling contains the necessary information about the drug (dosage strength, storage conditions, lot number, expiry date, etc.), and the manufacturing methods used produce products with the proper identity, strength, quality, and purity (1–4).

Q. What's a regulatory filing in Europe called?

A. The regulatory filing in the European Union (EU) is called a Marketing Authorization. The European Medicines Agency (EMA) is responsible for approving regulatory filings before medicines can be marketed in the EU. EMA has three procedures for gaining approval: the centralized procedure, the decentralized procedure, and the mutual-recognition procedure. Regardless of the regulatory filing process used, the company must prove that the drug product is safe and effective for the proposed use, the benefits of taking the drug outweigh the risks (side effects) associated with the drug, the product labeling contains the necessary information about the drug (dosage strength, storage conditions, lot number, expiry date, etc.), and the manufacturing methods used produce products with the proper identity, strength, quality, and purity (5).

Q. What is a refusal-to-file notification?

A. Companies can occasionally provide insufficient data supporting their NDA or BLA filing. When this happens, FDA will issue a refusal-to-file letter with the company (6). There are many reasons FDA may issue a refusal-to-file letter. These include, but are not limited to:

- Inadequate chemistry, manufacturing, and controls (CMC) data resulting from formulation issues
- Incomplete stability data
- Procedural (i.e., missing or incorrect use of the official FDA forms, electronic submission rules not followed, patent certification is inadequate, etc.)
- Failure to submit environmental assessment
- Failure to provide accurate and complete English translations for parts of application not in English
- The drug product that is the subject of the submission is already covered by an approved application on file and the applicant of the submission either has an approved application for the same drug product or is merely a distributor and/or re-packer of the already approved drug product.
- The application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and eligible for approval under section 505(j).

Q. How does following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) help me with my global filing requirements?

A. ICH (www.ICH.org) was founded in 1990 with the mission of bringing together regulatory authorities from around...
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