New Biotherapies Drive Innovation

Development
- HPAPI Risk Assessment
- Building a Better Particle

Manufacturing
- Automating 503B Facilities
- Continuous Cleaning

Quality/Regulations
- International Pharmacovigilance

Analytics
- Cleaning Validation

Outsourcing
- Method Development

Peer-Review Research
- QbD for Fixed-Dose Combination Tablets
Faced with an increasing demand for the production of vaccines, tighter schedules and a growing focus on safety, IMA Life works alongside the pharmaceutical industry’s leading names to achieve efficiency, flexibility and quality. Implementing isolation technologies and advanced robotics, the integrated aseptic processing lines are designed to address specific requisites and all technical aspects are tailored to achieve the performance each customer demands.

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Optimizing Tablet Production through Established Maintenance Methods
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 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.

Formulation of any drug requires a thorough assessment of its critical attributes and manufacturing parameters. In this month’s peer review paper, the authors describe a quality-by-design approach to the development of a fixed-dose combination tablet.

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.

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 Europe.
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Divest and Conquer?

Recent news of GlaxoSmithKline’s (GSK’s) sale of its entire stake in Innoviva (1), its respiratory drug partner, indicates the company’s momentum to split into two by 2022 is on track. This type of divestiture is certainly not uncommon in the bio/pharma world—with recent news including Takeda and Teijin Pharma’s transaction for diabetes products (2), and Lonza’s divestiture of its specialty ingredients business (3)—as streamlining operations allows companies to focus on strategic priorities in a fast-moving industry.

Yet, concerns are being raised around GSK’s future, as the company has struggled in the COVID-19 pandemic landscape and has seen its revenues dip in the first quarter of 2021. Additionally, a floundering pipeline and the arrival of activist investor, Elliott Management, taking a major stake in the company are placing more fuel on the fire that the company is under the cosh. The news isn’t all bad, however, as the European Medicines Agency concluded that sotrovimab—a monoclonal antibody being developed by GSK and Vir Biotechnology—can be used as a treatment for patients with COVID-19 (4). Furthermore, positive clinical trial results have been reported for GSK and Sanofi’s COVID-19 vaccine (5), as well as for Medicago’s COVID-19 vaccine candidate, which has been tested in combination with GSK’s pandemic adjuvant (6). So, a potential Europe-wide use of sotrovimab and COVID-19 vaccine developments further down the line will surely boost the company’s reputation and stock price.

References

Felicity Thomas
Editor of Pharmaceutical Technology Europe
FTom@mjhlifesciences.com
Balancing...
With over seven decades of experience, Mission Pharmacal has mastered the equilibrium of expertise and efficiency. Our mid-sized advantage allows flexibility, responsiveness, and unmatched support in executing your vision while providing a wide range of specialized services for products at any stage of their life cycle. Regardless of the scope and size of your project, we will create a custom program to meet your individual requirements and exceed expectations.

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Double Planetary Mixer

The ROSS Double Planetary Mixer from Charles Ross & Son Company is available with an optional weighing system for precise measurements throughout the batching procedure. The turnkey system (pictured) comes equipped with a mixer, weighing scale, and discharge system on mobile benches, with the ability to attach to one another, and to transfer carts of the same height. V-groove tracks allow easy movement of the Double Planetary Mixer vessel to the weighing station, and on to the discharge press for direct filling of syringes, tubes, or other containers.

Charles Ross & Son Company
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Benchtop Syringe Filling Machine

The TipFil Syringe Filler from TurboFil Packaging Machines is a benchtop syringe filling machine that offers full control of filling parameters in single or dual operation and fills at a rate of up to 12 pieces per minute.

Using a piston instrument that draws the needle back via the plunger, the distance the plunger is pulled back dictates the amount of drug filled, which eliminates the need to clean the metering device and offers repeatable product filling driven by a servo motor. Additionally, the device can perform through-the-tip filling for liquids or viscous products in typical infeed scenarios including hoppers and reservoirs; it offers an optional attachment for the filling of bottles and vials; and features fully disposable, single-use plastic product contact parts.

Fill volumes are electronically adjustable via a human-machine interface, a priming function works to enable air bubble removal, and a draw-filling method provides the device with operator safety, simple changeover, and flexible parameters for a variety of syringe sizes and product types. The syringe filler also has the ability to fit underneath a laminar flow hood for aseptic filling, while its product and fill volumes remain accessible by an optional barcode scanner.

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Semi-Preparative Affinity Column

Tosoh Bioscience introduced the TSKgel FcR-IIIA-SPW HPLC column, a semi-preparative affinity column based on a recombinant FcγRIIIA receptor ligand bonded to porous 10 µm polystyrene particles. The column is the newest addition to the company’s FcRγ affinity chromatography portfolio for antibody drug analysis. With the ability to be loaded with up to 5 mg of monoclonal antibody (mAb), the column allows for an adequate amount of material collection for thorough analysis.

Along with the FcR-IIIA-NPR, a separate column in Tosoh’s FcRγ affinity chromatography portfolio, the column separates antibodies according to the affinity of their Fc region for a particular Fc receptor (FcγRIIIA) into three fractions, which correspond with different mAb glycoforms and their antibody-dependent cellular cytotoxicity activity. The columns represent a tool that link the FcγRIIIA receptor affinity with mAb function and structure. Additionally, characterizing each fraction with orthogonal methods connects FcγRIIIA receptor affinity to structural causes and functional effects.

Tosoh Bioscience
www.tosohbioscience.com

Analyzer for Pure Water Applications

Shimadzu released the TOC-1000e, an analyzer in the eTOC series of on-line TOC analyzers formulated for pure water applications. With a focus on miniaturization, high sensitivity, and a mercury-free oxidation technique, the analyzer has a small, light cabinet that offers high-sensitivity detection for fields that require high-purity water applications.

With an "Active-Path" flow line design, the analyzer uses an excimer lamp rather than a mercury lamp to integrate sample flow channel and the light source. This lessens sample residue in the flow channel and removes intrusive air layers, so high sensitivity is maintained over long-term use.

Additionally, the analyzer can be installed as table-top, wall-mounted, or pole-mounted. It provides high sensitivity with a detection limit of 0.1 µg/L; it contains consumable parts that can be removed and installed without tools; and it is compliant with regulatory requirements through its highly sensitive UV oxidation-conductivity method for ultra-pure water monitoring.

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The emergence of new biotherapeutics has prompted the advancement of innovative technologies that enable or support unique approaches to biotherapeutic drug development, including vaccines. Some of these new technologies include intranasal formulation technology, new cell reprogramming technology, and virus-like particle technology, among others. The progress of drug development technologies will also have implications for the future direction of new biotherapeutic modalities.

**Challenges**

The challenges to creating new biotherapeutic modalities stem 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.”

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 follow 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.”
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 toxicology 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,” 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.

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 paediatric 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,” he states.

“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.”

—Margaret Temple, SGS

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 genetic instability of coronaviruses as a major hurdle to the development of a traditional live attenuated SARS-CoV-2,” he explains.

Live attenuated vaccines are typically manufactured on a cell line with relatively high productivity of doses/liter of capacity, resulting in a significantly lower footprint and cost of goods to manufacture. In addition, the dose of a live attenuated vaccine is typically much lower than all the other non-replicating vaccine types, including genetic (RNA/DNA), viral vectors, protein subunit, inactivated, and virus-like particles (VLPs).

Thus, to meet global supply and demand, Meissa is implementing straightforward, economical, and scalable vaccine manufacturing technologies, Moore says. “Meissa’s vaccine candidates grow well in cell culture to support manufacturing. Furthermore, Meissa’s single, low-dose vaccine candidates allow for a smaller manufacturing footprint and fewer batches to support production.”

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 programme is supported by a US$10-million (€8.2-million) grant from the Bill & Melinda Gates Foundation and US$6.5 million (€5.3 million) from Open Philanthropy, a US-based research and grantmaking foundation (3).

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

Simpson explains that VLP-based vaccines present key parts of the pathogen in a symmetrical and repetitive way, similar to how a virus would present itself. Meanwhile, the immune system 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 with a high potential to effectively block transmission.”

—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. Naturally occurring VLPs have historically induced strong, broad, and durable immunogenicity and protection, Simpson asserts. “However, naturally occurring 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 technology,” he says.

Icosavax’s computationally designed VLP technology is designed to solve the problem of constructing and manufacturing 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-CoV 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.”

However, the translation from lab-scale to commercial-scale production can be challenging if the technology was not designed with large-scale manufacturing 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-assembly of two protein components that can be manufactured using traditional recombinant protein manufacturing techniques. The technology is designed to be highly scalable and distributable,” 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 vaccine candidate] have high manufacturing yield, and all data gathered to date support a competitive cost-of-goods. In 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 immunology, ophthalmology and other disease areas.

“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

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. “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.”

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 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 $10^{9}$ to $10^{10}$ plaque-forming units (PFU)/dose compared with multiple doses of $10^{9}$ to $10^{11}$ 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.

"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."

—Joe Foster, Mogrify

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. 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," states Simpson.

"Furthermore," Simpson 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, Simpson notes. "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," he 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
Assessing Risk and Production of Potent Substances

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. There are, however, 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.

Highly potent does not necessarily mean toxic, notes Hasslacher. “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,” says 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 potent substances and their production processes ultimately defines how those substances will be handled to protect operators and the environment. Waste management also 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, it is possible to calculate the permitted daily exposure. In combination with pharmacokinetic data, an OEL and ultimately appropriate occupational exposure bands can be calculated.

Containment solutions

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 operations. “Once the risk assessment described above is completed, required measures are implemented according to company policy, local...
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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, and necessitates the proper safety culture, which can present a challenge that is essential for companies to overcome before they introduce highly potent processing into their facilities.

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.

In addition, 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 programme,” 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.

Equipment advances

Fortunately, 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 Vers-A-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.

As an example, Bertholjotti points to single-use systems available today that enable the implementation of single-use process concepts for closed manufacturing. “Improved single-use systems facilitate the manufacturing of a small number of batches for clinical supply and represent an important development in the industry,” he remarks.

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. PTE
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.

Felicity Thomas

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 CrystecPharma.

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 programmes 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.”

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.

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 programmes, 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.”

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.

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, emphasises 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 anti-solvent, 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.”

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 behaviour (4).”

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.

“[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
Optimizing Tablet Production through Established Maintenance Methods

Andy Dumelow

“85% of punch and die problems can be traced back to poor handling and aftercare procedures.”

This surprising figure highlights the importance of why correct maintenance procedures are integral to obtaining the maximum tooling life to mass-produce quality tablets quickly and in the most cost-effective way.

Tablet compression tools are often viewed as consumable items. Though they can be easily replaced, they should never be viewed as disposable. The “throw-away” approach is a mistake that will directly affect production.

Correctly maintaining tablet tooling and ensuring everything is in good working condition will not only reduce tablet press downtime, but it will also minimize common compression problems like sticking and picking. Regular maintenance also increases the lifespan of the tooling, thus retaining the value and productivity of each set of punches and dies.

Stepping up Maintenance Procedures

All tablet manufacturers should implement certain tried-and-tested processes as standard operating procedures to ensure productivity per punch can be maximized more effectively to meet high-capacity manufacturing requirements.

A program of professionally planned and consistent maintenance procedures like the I Holland PharmaCare® 7 Steps will help in maintaining and storing punches and dies correctly so tooling is clean, serviceable, and within specification when required for production (see Figure 1).

The first and most critical step is to clean the tooling. Removal of dirt, lubricant, and product contamination not only prevents cross contamination, but it also increases the accuracy of tooling inspection and assessment.

Cleaning should take place after every campaign but, for particularly challenging formulations, tooling may need to be cleaned mid-campaign. This minimizes potential production issues like sticking, which is caused by product adhering to the surface of the punch tip. This step also uncovers any damage to punch tip edges like nicks and bruises, which can cause burrs and occasionally chipping.

An ultrasonic cleaner is the most efficient and effective method to clean both coated and uncoated tooling (Figure 2). It is important to clean all equipment, not just punches and dies. Also, ensure die table segments are cleaned using an efficient and repeatable process like the I Holland Segment Cleaner (Figure 3). Equipped with a specially designed fixture to prevent scratching and damage, it holds the segment safely and securely within the tank and leaves the bores unobstructed to ensure effective cleaning of the entire segment.

The next important step is to assess the tooling, checking its condition and suitability to produce tablets of sufficient quality and to prevent tablet press damage.

Punches and dies should be digitally inspected to establish if the tablet production process is running well. Close-up inspection of the punch tips and cups, die bores, embossing, and land will help to identify defects and wear.

Tooling repair should take place after assessment. This will recondition the surface finish of...
uncoated punches and rectify minor damage to the tooling before further maintenance steps take place.

Minor damage and corrosion can be repaired using a motorized chuck with double-ended polishing motors used in conjunction with abrasive polishing accessories. It is important to remember that repair to punches and dies should only be carried out when only necessary and by trained technicians to ensure that the tooling does not exceed tolerance limits.

Step 4 is to measure the tooling, which is crucial after any repair. Critical tooling dimensions must be maintained within an acceptable range for accuracy and quality throughout the manufacturing process. Even if a repair has not been necessary, measuring should be carried out at regular intervals to check for natural wear during the compaction process.

Polishing is the next step in the process. Frequent and controlled light polishing will ensure the tools are maintained to a smooth finish, helping to maximize tooling life. An automated polishing regimen is preferable due to the controlled and repeatable process.

Next in the process is to lubricate the tooling. Lubrication is important to protect, preserve, and aid the smooth operation of continuous press tooling operations. A non-toxic, FDA-compliant oil or grease that offers machine component protection and lubrication performance with a wide temperature range is recommended to ensure it can be used in all equipment.

The final step is proper storage. Transport and keep tooling in specially designed storage containers to reduce the likelihood of damage. The tooling must be separated to ensure it avoids contact with other punches and prevents deterioration.

**Maintaining Skills**

Application of the PharmaCare 7 Step Process will have a direct impact on the reduction of many common tablet and tooling problems, resulting in a better quality tablet, and can provide a direct cost saving. However, if each step is not performed correctly the processes are inefficient.

Technicians should be proficient in all areas of tablet compaction, including maintenance procedures, to ultimately improve productivity and enhance the end product.

E-learning provides an economical training solution that results in optimized tablet production (Figure 4). Online learning programs can combine comprehensive and flexible courses in a wide variety of disciplines and is an important method for bringing operators in line with the procedures quickly.

By ensuring key training in procedures like tool maintenance is achieved, tablet manufacturers are helping to make processes more effective and proficient, therefore facilitating increased output and efficiency.
Considering Robotics for Drug Compounding

Automation offers benefits for sterile manufacturing in 503B outsourcing facilities.

Jennifer Markarian

Traditionally, compounding facilities—also called 503B outsourcing facilities in the United States in reference to the section of the US regulation under which they are registered (1)—have conducted drug manufacturing operations manually; “on demand” production of a wide range of drugs needed by hospitals and pharmacies as well as drugs on the US Food and Drug Administration (FDA) drug shortages list did not lend itself to automation in the way that longer-run, scheduled production did. Robotic automation technologies available today, however, offer benefits of greater efficiency and higher quality even for small volumes.

Benefits

“Robotics offer several significant advantages for aseptic compounding. Most notable is that the greatest source of contamination, the person, is removed from the process,” says Chris Smalley, an independent compounding pharmacist advisor. “There is a robust traceability to what is performed, including volume, drug barcode scan and more, and it does not matter what hour or day of the week the robot operates,” explains Smalley. He notes that, in some cases, a robot is set up to operate on its own overnight (i.e., “lights-out” manufacturing), and the completed products are unloaded and checked the next day.

“Minimizing risks associated with aseptic processing is crucial when working with compounding systems,” agrees Randy Fraatz, vice-president of North American Operations at Steriline, which produces aseptic manufacturing equipment. “The primary benefit of robotics and automation in general is safety, coming from the reduction of human-related mistakes in the entire process.” Other benefits, says Fraatz, include the accuracy, efficiency, and reliability that result from automation. “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 Kantonsapotheke 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).

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.

“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, including 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
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.”

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.”

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“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 without impacting productivity of the area or overall equipment effectiveness (OEE).”

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 Luis Santos, director of Hovione’s Continuous Tableting Center of Excellence, who suggests that end-users 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.
equipment cleaning.—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
[management 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.

**PAT sensors may require special handling during
equipment cleaning.**

Another best practice 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,”
Santos explains.

**PAT considerations**

Process analytical
technology (PAT) sensors in the
equipment are a crucial part of
continuous manufacturing systems,
but, in some cases, such as near
infrared (NIR) probes, they may
be fragile and require special
handling during assembly and
disassembly, notes Santos. He
adds that it is important to use
the PAT vendor’s procedures for
proper cleaning and maintenance.
“Having additional instruments to
address concurrently with cleaning
of the manufacturing equipment
is logistically quite demanding,
requiring close communication and
planning in order to keep operations
running efficiently. 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 biopharmaceutical process equipment

In biopharmaceutical manufact-
turing, process intensification can
change the way the equipment is
used and thus affects cleaning
methods. “Process intensifica-
tion continues to influence trends,
such as higher-titers in bioreactors,
greater binding capacity in resins,
improvements in upstream clarifica-
tion, and other advances in technol-
ogy 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
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read “Considerations for Cleaning
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Using Quality by Design to Develop Fixed-Dose Combination Tablets

Rajendra Kotadiya, Krunal Jasani, and Gayatri Patel

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. Precompression and post-compression parameters were determined indicating excellent flow properties of granules as well as good tabletting characteristics of the final tablets. Dissolution study showed higher drug release nearly 80% within 30 min for all prepared batches attributed to conversion from crystalline to amorphous form of the drug. ANOVA studies revealed that there was a linear correlation between the predicted, and the observed responses gave higher values of $r^2$, indicating excellent fitting of the model ($P < 0.001$). Thus, the prepared FDC tablet executed a good relationship between selected critical formulation parameters and critical quality attributes. The drug release rate obtained met the selected dissolution criteria.

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 EZE 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),...
Micromeritics is the world's leading supplier of high-performance systems to characterize particles, powders and porous materials with a focus on physical properties, chemical activity and flow properties. Our industry-leading technology portfolio includes: pycnometry, adsorption, dynamic chemisorption, intrusion porosimetry, powder rheology, activity testing of catalysts, and particle size.
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 (QTTP) for orally dissolving tablets was studied in detail. The initial CQAs were defined from QTTPs 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 I. Design matrix table for $2^3$ factorial design.**

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<thead>
<tr>
<th>Batch code</th>
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<tbody>
<tr>
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<tr>
<td>F8</td>
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**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 API</td>
<td></td>
</tr>
<tr>
<td>Drug 2 (EZE)</td>
<td>10 mg API</td>
<td></td>
</tr>
<tr>
<td>Alpha TPGS</td>
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<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>

The prepared granules were collected and weighed.

**Evaluation of prepared granules (pre-compression)**. 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).

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**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 PH 101 and Starch 1500 DC mixture) and the granulating fluid, using double-cone blender. Final mixing was done by adding the remaining amount of Avicel PH 101, 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)**. 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).

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</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 possible angle 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:

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

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.

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

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-081, 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, by using UV-visible double beam spectrophotometer (Shimadzu1800).

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

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1^2 + \beta_4 X_2^2 + \beta_5 X_1 X_2 + \beta_6 X_3 + \beta_7 X_4 + \beta_8 X_1 X_2 X_3 X_4 \]  

[Eq. 5]

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

where \( \beta_0 \) the intercept is the arithmetic average of all quantitative outcomes of nine runs, \( \beta \) to \( \beta_8 \) 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 \( X_1, X_2 \) and \( X_i^2 \) to \( X_i \) 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 from the output files generated 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 Q1AR2, 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 1 a, 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 dimensional uniformity of materials in
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.

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 (Y1) shows the linear correlation plot, 3D-response surface graph, and corresponding contour plot. At the fixed value of X1, it has been found that the increase of X1 to a high level (1 level), along with the increase of X2 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 r² (ranging between 0.964 and 0.977), indicating excellent fitting of the model (P < 0.001).

**Statistical analysis (Y1) at 20 min.** The full model equation was found to be as follows in Equation 7:

\[
Y_1 = 81.51 + 0.53 (X_1) + 2.34 (X_2) + 2.15 (X_3) + 3.81 (X_1X_2) + 1.63 (X_2X_3) + 0.29 (X_3X_1)
\]

[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 (Y2)** shows the linear correlation plot, 3D-response surface plot, and corresponding contour plot. It was found that at the fixed value of X1, increase X3 up to high level along with increase X2 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 r² (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 D1, and predicted value. The factors obtained at the maximum points of Y1 and Y2 (target: 45 % and 85%, respectively) were calculated as X1=3.79, and X2=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 the 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 2³ 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.
References

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 the US Food and Drug Administration (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 9 April 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 cleaning 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 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
may have inherited practices used for years, or the facility overall safety. "At some companies, their importance to patient and pharmaceutical industry, despite disinfection are undervalued in the on the webcast, is that cleaning and promote the buildup of cleaning inhibition microbe-killing mechanisms cleaning chemistries that might interactions between different modes of action should be rotated. Care must also be taken, he said, to avoid practices at individual facilities. Establishing a programme 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, Shepherd 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 programme may rest on one champion supporting it,” Forsyth says.

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

Multiproduct facility challenges

Today, multiproduct facilities, and particularly biopharmaceutical facilities, pose several cleaning validation challenges. "You worry more about bioburden in a biological plant than in a small-molecule facility, but generally if you have an effective cleaning validation programme, you’re fine," he says. However, setting cleaning limits can be tricky because traditional methods fall 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 product 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.

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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.

Felicity Thomas

The market for outsourced pharmaceutical and biotechnology services is expected to experience healthy growth and is forecast to reach US $91.4 billion (£74.6 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 programme.”

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 (ICH), for the release of the product to clinic or market, asserts Amanda Curson, head of Analytical Development, Tredegar, PCI Pharma
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 Mörtberg, 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 labour 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 matrixes. 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 programmes 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 knowledge 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.

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 Mörtberg, who highly recommends opting for a single supplier that is capable of providing all required resources for a project, wherever possible.

**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.**

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 programme, 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**

As biotechs grow in market prominence, the reality is dawning that their pharmacovigilance (PV) obligations are equivalent to those of pharma companies several times their size. For young, ambitious, product-oriented companies, such demands could be a barrier to market success, unless they devise optimum strategies for fulfilling the differing safety demands of respective regulators.

Companies with ambitions for Europe and the United States tend to favour filing in the US first. On top of the US market’s vast size, it benefits from being a single country governed by one main agency—the US Food and Drug Administration (FDA). In Europe, marketing authorization can take much longer because beyond the central European Medicines Agency (EMA) each European Union (EU) member state has its own unique requirements to navigate.

Taking the US and EU as key territories, the diverse PV requirements highlighted in the following give a flavour of just what’s involved and where biotechs are likely to need help.

**Pre-marketing expectations**

Although in the pre-marketing stage of development, most PV requirements are harmonized across the European and US markets, there are some small, noteworthy variations—for instance FDA’s particular requirements around causality assessment, affecting what’s submitted in the two regions.

Even at a central level, EMA submissions have a different look and format to US dossiers, so they require different handling. For instance, the Summary of Product Characteristics (SmPC) and labelling in relation to side effects are not presented in the same way in Europe.

Differences exist too between the risk management approaches—FDA’s Risk Evaluation and Mitigation Strategies (REMS) versus EMA’s Risk Management Plan (RMP)—and one cannot be substituted for the other. Failure to factor in these differences could present an issue at the time of filing. In addition, national EU-specific requirements may be requested in certain countries, on top of the RMP EU requirements, even for centralized procedures.

To successfully and efficiently navigate the differences between regions, biotechs must set out a clear strategy and timeline for how they will file to their target markets, and plan for multiple markets concurrently (it could take a long time to prepare for EMA’s diverse requirements)—and those of each EU country beyond that, plus the United Kingdom, which now sits outside of the EU/EMA.

It isn’t just European information and formatting requirements that differ and are more involved than in the US. Standard operating procedures (SOPs)/process requirements can be more complex in Europe too. Although, during the pandemic, ‘crisis mode’ enabled emergency acceleration of these processes to expedite the marketing authorization of vital products such as the US-originating Moderna vaccine for use in European markets. This approval was ‘conditional’, and such measures are temporary and cannot be expected going forward.

**Post-marketing**

The post-marketing regulatory environment is highly regulated and inspection driven, and it is here that biotechs are likely to find the greatest challenges in managing their PV obligations. In post-marketing, the differences between US and European requirements are starker than for pre-marketing.

Europe overhauled its post-marketing PV requirements a couple of decades ago, making these very clear and prescriptive. For post-marketing safety studies, for instance, it has broken down the requirements for interventional versus non-interventional studies and what needs to be reported—or left...
out—for each. In the US, equivalent post-marketing safety requirements are much older and leave much to interpretation, so companies tend to tread a more cautious path.

Where Europe is content with a final study report, in the US companies still file expedited single case reports; in the EU, expedited reporting is required for Individual Case Safety Reports (ICSRs) for post-marketing safety studies. If studies are used to support a product claim, and the right data have not been collected in the right way for the given market, this could pose problems. So, the different requirements must be well understood and designed into post-marketing and market research studies.

Acquiring the right skillsets
Although biotechs may lead the way with product expertise, this is not typically matched in understanding and expertise in PV requirements and process rigour. To mitigate safety compliance-related risk, they need to establish both the right knowledge and experience, plus skills in writing SOPs and setting up PV systems which, in Europe, must be in place from the time of marketing authorization application (MAA) filing.

Relying on a third-party safety services provider to take on this burden without in-house oversight is not recommended—not least because the marketing authorization holder (MAH) retains ultimate responsibility for PV compliance. Irrespective of the biotech's size and scale, then, it will need to bring in someone experienced who understands PV and can keep a check on vendor quality.

In Europe, a nominated qualified person responsible for PV (QPPV) is personally responsible for the safety of the human pharmaceutical products marketed by that company in the EU. There will need to be a designated person inside each region, too: so, a US company with European marketing authorization must have a named QPPV based in Europe, and potentially also at a country-level (in France and Spain this is a regulatory requirement).

Establishing remits and responsibility
Where biotechs have entered into distribution relationships with other MAHs, there will be additional considerations—such as who will coordinate and be responsible for the PV requirements in a given market and how this will be written in any contracts. The MAH in the local country always is ultimately responsible for meeting PV requirements in that country. There is also the decision of who will be the global PV database holder (usually the company that developed the product and secured approval).

PV capabilities shouldn’t stand still, either. Biotechs will need to keep pace with both changes to regulatory requirements across all markets globally, and evolving channels and technologies when tracking safety signals; companies have an obligation to monitor and filter web/social media forums for potentially important real-world safety information, where digital media is company-sponsored.

Meanwhile, the increase in combination treatments involving drugs and devices could trigger new rules clarifying how responsibility for adverse drug reactions is apportioned, another situation that needs to be tracked. Establishing an appropriate PV budget will be essential for any biotech navigating all of this international complexity.

Analytics
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Statistics and instrumentation
ASTM standards have been focusing on use of statistics, which are important after a cleaning programme 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.

The best way to remove subjectivity from inspections has been to qualify those who must perform those inspections.

“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 programmes 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, 20 April 2021.

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

ICH (www.ICH.org) was founded in 1990 with the mission of bringing together regulatory authorities from around 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).
**Q.** What’s the difference between an IND, NDA, ANDA, and a BLA?

**A.** Companies need to get approval from the US Food and Drug Administration (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 labelling 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. In the centralized procedure, pharmaceutical companies submit their regulatory filing to EMA. The use of the centralized procedure is required for most innovative medicines, including those indicated for rare diseases. Because many of the pharmaceuticals authorized for use in the EU did not receive a marketing authorization at the time of application, they are out of scope for the centralized procedure, so companies gain approval to market their products through the decentralized procedure or 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 labelling 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).

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