Are Genetic Vaccines Game Changers?

Development
- Novel Excipients
- Solubility Enhancement

Manufacturing
- NIR for Downstream PAT
- Raw Material Traceability

Analytics
- Cybersecurity Risk in Labs

Quality/Regulations
- Good Distribution Practices

Outsourcing
- Just-in-Time for Clinical Trials

Peer-Review Research
- QbD for Pediatric Drug Formulation
Stronger together

Luke, Lee and Jessica are part of our growing global team, helping to keep our manufacturing capabilities operating throughout the Americas, Europe and Asia. We are all dedicated to delivering the products you need, when you need them most.

Small details.
Big difference.

Contec is the leading manufacturer of contamination control products for critical cleaning and manufacturing environments worldwide. Our innovative wipes, mops, and disinfectant solutions are used in various industries across the globe.

contecinc.com
IT’S KIND OF A BIG DEAL
Reduce the Risk and Investment with a Solution for Both R&D Studies and Pilot Production

» Robust software for data collection, press control, scale-up, and pilot-scale production.
» Collect key data points to help guide the formulation development process.
» Gather accurate scale-up data during studies with press design that emulates large production press parameters.
» Reduce early-stage R&D formulation usage—from a several kilogram pilot batch to as little as a couple tablets’ weight.

CONTACT NATOLI TODAY! tabletpress@natoli.com

INTRODUCING THE NP-RD30 ROTARY TABLET PRESS WITH NATOLI’S INDUSTRY-LEADING AIM™ SOFTWARE
The New
SMA MicroPortable ICS
Air Sampler

Superior Precision, Superior Control

- Automated Flow Control
- 3 Flow Rates in 1 Unit (1, 2 & 5 CFM)
- Robust, 316L Stainless Steel Construction
- Intuitive Touchscreen
- Automatically Configure Sample Intervals
- Available with the D50 SMA Atrium

www.sterile.com
15 Lee Blvd., Malvern, PA 19355-1234 USA • (610) 644-8335

Veltak Associates, Inc.
Patents: www.sterile.com/patents
PEER-REVIEWED RESEARCH

44 Using Modified QbD to Develop a Novel Pediatric Formulation of Ezogabine

The authors have developed a granular formulation of ezogabine, XEN496, suitable for administration to children, including newborns. This article describes the overall process taken to design and test prototype pediatric formulations of ezogabine, which led to the identification of XEN496.
Who We Are
Chemic Laboratories, Inc. is a full service cGMP/GLP contract analytical chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: Extractables/Leachables analysis, CMC Method Development & Validation, Quality Control analysis, Release testing, Raw Materials analysis, Compendial testing, Organic Synthesis/Formulation Development & ICH Stability testing. Chemic continually strives to exceed the requirements and expectations of our sponsors. We are committed to providing quality services to our clients in support of their product development needs.

Major Markets
Chemic Laboratories, Inc. is located in Canton, Massachusetts and provides cost-effective outsourcing solutions to a broad spectrum of global clients in the pharmaceutical, medical device and biopharmaceutical industries. We are committed to developing long term strategic alliances with our clients. Chemic offers the ideal blend of expertise and experience that is critical to our clients’ success.

480 Neponset Street,
Building 7, Canton, MA 02021
Tel. 781-821-5600
Fax 781-821-5651
www.chemiclabs.com

Services Offered
Chemic Laboratories, Inc. offers a wide array of cGMP/GLP contract testing services including:

• Quality Control Testing of raw materials, API’s and finished products
• Monograph Testing (USP, EP, BP and JP)
• CMC Method Development & Validation
• Degradate Quantitation
• Extractables and Leachables Analysis
• Container Closure Assessment
• ICH Storage and Accelerated Stability Studies
• GMP/GLP Method Development and Validation
• Organic Synthesis and Formulation Development
NEWS & ANALYSIS

FROM THE EDITOR

10 Fighting Through This Slow Season of Change

Bio/pharma works hard today to change the calendar to tomorrow.

REGULATION & COMPLIANCE

REGULATORY WATCH

14 FDA Documents Achievements and Plans for Future

Annual reports showcase FDA’s achievements and activities for 2020, while the agency provides a look at future endeavors.

ASK THE EXPERT

66 Auditing for Good Distribution Practices

Auditing distribution suppliers provides understanding and documentation of the services performed, says Siegfried Schmitt, vice president, Technical at Parexel.
Fighting Through This Slow Season of Change

Rita Peters

Bio/pharma works hard today to change the calendar to tomorrow.

We are now approaching the one-year mark of the year of living distantly, thanks to the public health measures necessitated by the COVID-19 pandemic. In the past 12 months, people have adapted to working from home, buying everything online, and functioning in a bubble.

Like many others, I relate my pandemic experience to the 1993 film Groundhog Day. In the movie, weatherman Phil Connors—the main character—is trapped in time, reliving an unpleasant, monotonous day over and over and over again. In the role, actor Bill Murray plays out Phil’s depression, frustration, and anger until he finds a path from his self-adsorbed existence to one of compassion, collegiality, and personal redemption.

Before the pandemic, the bio/pharma industry had a reputation problem. While the rest of the world lived out pandemic-induced isolation and repetitive days, the bio/pharma industry made remarkable progress by innovating and collaborating with colleagues, partners, and competitors.

Recent reports released by FDA show that despite restrictions posed by the pandemic, 2020 was a very good year for drug development. The Center for Drug Evaluation and Research (CDER) approved 53 new therapies in 2020, the second highest number of annual approvals in the past 10 years, including 21 classified drugs as first in class and 31 approved to treat rare or orphan diseases. The approval rate was impressive; 92% of the drugs were approved without a complete response letter, up from the 85% average of the previous eight years. And 75% of the drugs were approved in the United States first, before other countries (1).

FDA had some missteps in 2020, such as the approval, then revocation, of an Emergency Use Authorization (EUA) of chloroquine and hydroxychloroquine, which raised questions of undue political pressure on a scientific process. And progress has been slow on many pandemic-related drugs in development.

Still, the bio/pharma industry had some notable successes, specifically the emergency approval of two novel vaccines in record time—with other vaccine reviews pending—and the rapid approval of remdesivir to treat patients with COVID-19.

The beginning of … the next phase

When EUAs were issued for the Pfizer-BioNTech and Moderna vaccines in late 2020, it was hailed as the beginning of the end of the pandemic. In reality, it was the beginning of the next phase.

Now, growing concern in public health and medical circles about emerging variants of the SARS-CoV-2 virus and their possible resistance to vaccines and treatments prompted renewed research and regulatory strategies. FDA recently issued a set of guidance documents to address the emergence of variants of SARS-CoV-2, including an update to the October 2020 guidance on EUA for vaccines to prevent COVID-19 and guidance on the impact of the variants on monoclonal antibody (mAb) products and other treatments.

In the cover story for this issue, author Cynthia Challener takes an in-depth look at genetic vaccines, challenges associated with manufacturing and distribution, and the potential for rapid reformulation to tackle virus variants (pages 18–23, 64).

As the pandemic enters its second year, the pressure is still on bio/pharma companies and FDA, as demand for vaccine production intensifies and any delays—from manufacturing issues or bad weather—contribute to growing public impatience.

I finally see signs that we are emerging from this long winter. The snow that fell in my backyard before Groundhog Day 2021 is finally melting. Daffodils are pushing up from the ground. The pace of vaccinations is accelerating.

However, the virus, like the weather, can be tricky. We must maintain vigilance of social distancing and good manufacturing practices. Today will soon be tomorrow.

Reference

Scale up. Without having to power down.

When you put your research in motion, you want it to stay that way. So it’s helpful to have a CDMO partner by your side that can take on late phase/commercial biologic drug substance manufacturing, in the best of times and in the most challenging (for example, when there’s a surge in production demand during a global pandemic).

At Emergent we stand ready — well-equipped with capacity, a finely tuned and rapid tech-transfer process, and proven proficiency in single-use bioreactors — to give your commercial product the attention it deserves to scale up fast.

Start your ascension at emergentCDMO.com/scaleup
Inline High Shear Mixers

Inline high shear mixers from ROSS are available from 1 through 250 HP to accelerate mixing, emulsification, and homogenization in recirculation and continuous modes. The mixer can be used anywhere in a plant because of its mobile skid, eliminating the need for multiple mixers separately dedicated to each vessel or product.

The ROSS Model HSM-410 Inline High Shear Mixer (pictured) has the ability to handle applications with viscosities of up to 20,000 cP. A control panel may be mounted to the cart and wired to the mixer for complete portability. Additionally, 3A-approved sanitary models are available with tri-clamp inlet/outlet connections and a one-piece stator/chamber cover. Ultra-high shear mixer models are also available.

Charles Ross & Son Company
www.mixers.com

Cell Culture Analyzer with Sample Retain Collector

Nova Biomedical added a Sample Retain Collector (SRC) to its FLEX2 cell culture analyzer, which works to measure up to 16 tests including pH, gases, metabolites, osmolality, cell density, and cell viability. Together, the cell culture analyzer and the SRC in combination with Nova's online sampler can provide automated sampling and analysis of key cell culture tests from up to 10 bioreactors, saving time in comparison to manual sampling, analysis, sample storage, and after-hours cell culture monitoring.

The SRC functions by gathering cell culture samples from the FLEX2 online sampler and keeps them in a refrigerated environment to achieve regulatory requirements for long-term sample retains and to allow for additional offline testing. The SRC also permits user-selectable retained sample volumes from 200 uL to 50 mL at a storage temperature of 4 °C.

Nova Biomedical
www.novabiomedical.com

Microbial Air Sampler

Particle Measuring Systems introduced the MiniCapt Mobile Microbial Air Sampler, a monitoring instrument designed to prevent the introduction of bacterial contamination created during monitoring activities. The air sampler comes equipped with antibacterial properties built into the housing and design of the product, an integrated and filtered exhaust to diminish contamination from monitoring activities, and a touchscreen that allows for use with gloves. Additionally, the air sampler’s enclosure can be easily disinfected. Data can be securely transferred to facility management systems or other storage and reporting programs.

Particle Measuring Systems
www.pmeasuring.com

Chromatography Solution for Biologic Drugs

The 3M Polisher ST from 3M Health Care is a single-use anion exchange (AEX) chromatography solution intended to replace the reusable AEX polishing column for biologic drug manufacturing. The new synthetic, fully encapsulated, single-use membrane chromatography solution contains two AEX-functional media: a quaternary ammonium functional nonwoven for the reduction of turbidity, DNA, and endotoxin; and a guanidinium-functional membrane for host-cell protein and virus reduction in a salt-tolerant manner.

Continuous bioprocessing allows facilities to reduce their size and cycle times, the compact product increases biomass production in therapeutic recombinant protein processes in all operating conditions.

3M Health Care
www.3M.com
Adare Pharma Solutions is a global, technology-driven CDMO providing turnkey product development through commercial manufacturing expertise focused on oral dosage forms for the Pharmaceutical, Animal Health and OTC markets. Adare’s specialized technology platforms provide taste masking, ODTs, and customized drug release solutions. With a proven history in drug delivery, Adare has developed and manufactured more than 40 products sold by customers in more than 100 countries globally.

Now you can put Adare’s formulation technologies and manufacturing expertise to work for you.

EMAIL BUSDEV@ADAREPHARMA.COM TO SPEAK WITH ONE OF OUR EXPERTS AND LEARN MORE ABOUT OUR TECHNOLOGIES AT ADAREPHARMASOLUTIONS.COM
Despite critical disruptions and added challenges posed by the coronavirus pandemic in 2020, FDA annual reports on drug regulatory programs and policies confirm successful efforts for meeting review time frames and updating policies and programs. These reviews of FDA initiatives and activities recapitulate efforts to assess and approve new drugs, generic drugs, and biologics, as well as strategies for advancing new initiatives. These efforts appear timely as FDA continues to renegotiate revisions and expansion of user fees paid by manufacturers to support FDA oversight and review activities.

Several reports from the Center for Drug Evaluation and Research (CDER) summarize efforts to ensure drug quality and to maintain a steady pace in new drug review and approvals despite limitations and pressures imposed by the pandemic. A report on new drug approvals in 2020 documents the 53 novel drugs and biotech therapies approved in 2020, describing a range of innovative oversight strategies to evaluate product safety and efficacy. In addition, CDER activities for protecting public health during the pandemic are outlined in an annual drug safety report that describes efforts to ensure appropriate tracking and reporting of safety issues, some related to broader uses of the agency’s Sentinel System.

Separately, an annual report from CDER’s Office of Product Quality (OPQ) highlights the use of alternative tools for on-site facility inspections to support the timely approval of new drugs, an effort that avoided the need for 153 site visits. OPQ notes its role in advancing CDER’s emerging technology program and efforts to bolster continuous and semi-continuous manufacturing and continued development of its knowledge-aided assessment and structured applications (KASA) program for evaluating new drugs, starting with solid oral dosage forms. Another main goal is to move forward with a new framework for assessing and identifying mature quality management systems by manufacturers.

OPQ also cites its efforts to support the approval of 942 generic drugs in 2020, including more first generics, complex generic therapies, and biosimilars. This involves coordination with CDER’s Office of Generic Drugs (OGD) in bringing new generics to market quickly and efficiently, especially to offset shortages in medicines critical to treating patients infected by COVID-19, as is outlined in the OGD annual report. The report discusses efforts to update the Orange Book, publish guidance documents on specific product development standards, advance the science on complex generics, and collaborate with foreign regulatory authorities to support wider global access to generic drugs. OGD is poised for a major reorganization beginning this year, which aims to update operations to better handle a steady rise in abbreviated new drug applications.

Advancing oncology and biologics
The challenges in continuing to speed new oncology therapies to patients are presented in an annual report from FDA’s Oncology Center for Excellence (OCE), which enumerates its achievements in overseeing the approval of multiple new indications and market approval of cancer treatments, including several new formulations. OCE Director Richard Pazdur emphasizes the importance of addressing the needs...
Oradel®
Oral Delivery Innovation

Your Coating Place for 45 years

ML Multilayer Coating  XR Extended Release
DR Delayed Release  EC Enteric Coating  DN Ion Resin

Coating Place, Inc., 200 Paoli St. • PO Box 930310, Verona, Wisconsin 53593 U.S.A.
+1 (608) 845-9521 • www.coatingplace.com • info@coatingplace.com
of cancer patients during the pandemic with initiatives to permit more flexible clinical trials and remote communications. OCE also is continuing its Project Orbis collaborative review of new cancer therapies with other regulatory authorities to speed access to cancer treatments around the world.

Similarly, the annual report from the Center for Biologics Evaluation and Research (CBER) outlines how it met milestones for reviewing new therapies and for ensuring product safety (7). CBER Director Peter Marks highlights the Center’s involvement in the development and evaluation of vaccines against COVID-19. In addition, CBER approved several novel biologics and blood reagents, provided advice to sponsors through virtual meetings, and continued to support pilot programs to advance modern manufacturing and regenerative medicine. Separately, Marks issued CBER’s list of new guidance documents slated for release in 2021 (8). This relatively short list of only 14 planned advisories reflects the considerable progress made in 2020 in issuing more than 20 guidance documents, including several related to development and emergency use of new COVID-19 vaccines and therapies.

In January, CDER also published a much longer list of more than 100 planned guidance documents for 2021, including 42 new items (9). The largest categories involve clinical studies, generic drugs, and agency procedures, and new categories were added for biosimilars, compounding, pharmacology/toxicology, and the animal rule. New guidance documents on the list involve the use of real-world data, developing antisense drug products, and demonstrating efficacy in a single trial. FDA may gain some added resources for its evaluation of new treatments to combat COVID-19 from a Congressional proposal to make an extra $500 million available to the agency this year, on top of its budget for 2021. The funding boost recognizes the considerable added work that FDA has taken on to support the development and oversight of new vaccines, therapeutics, and medical products, as multiple applications for emergency use authorizations and product approvals have overloaded the agency.

References
8. FDA, Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2021 (CDER, accessed Feb. 19, 2021).
Is Your Company Ready for a Remote Audit or Inspection?

Join PDA on 8 April for a one-day interactive Workshop to gain the tools and practical solutions you need to successfully overcome challenges in preparing for and hosting remote audits and inspections.

Through presentations and case studies drawing on industry experiences, this Workshop will explore important topics, including:

- What to consider before your audit begins
- Best practices during COVID
- Applying a risk-assessment approach during audits and inspections
- Anticipating perils and pitfalls: Effective communication across cultures, languages, and time zones
- Technology dos and don’ts

Find out what your company needs to do before and during your remote audit or inspection to ensure success!

For more information and to register, visit pda.org/2021remoteaudits

8 APRIL 2021
LIVE INTERACTIVE ONLINE
Genetic Vaccine Platforms Demonstrate Their Potential

Cynthia A. Challener

In a pandemic, genetic vaccines offer several advantages over traditional approaches.

Traditional vaccines and viral subunit/proteins directly elicit an immune response without the need for cellular transcription and/or translation of genetic material. Genetic vaccines use part of the virus’ own genetic code (either mRNA or DNA) to instruct cells to make a viral antigen that will stimulate an immune response. Viral-vector vaccines allow selection of a non-disease causing, and in some cases, a replication-deficient virus to be used to carry and deliver the antigen of interest to the vaccine and offer a mixture of advantages and disadvantages of live and non-live vaccines.

Challenges with traditional vaccines

Traditional vaccines have a long track record of safety and efficacy. They have been shown, according to Charles Christy, head of commercial solutions for the Ibex Dedicate at Lonza, to effectively treat global diseases and eradicate disease burden, or even eliminate diseases (polio, smallpox).

The immune response is triggered immediately with this type of vaccination; however, the body also has to fight the full viral or antigen load, which may facilitate adverse effects (e.g., feeling under the weather following the flu vaccine), notes Thomas Becker, site quality director for Recipharm.

The potential exists for adverse effects because live viral vaccines are attenuated by genetic mutation of the wild-type, disease-causing virus, either by passaging the virus through cells, eggs, or animals or purposeful deletion of sections of the viral genome, explains Kelly Lyn Warfield, vice president of vaccines research and development within Emergent BioSolutions’ Vaccines Business Unit. “For selection and use of live, attenuated viral vaccines, caution must be applied due to potential safety issues in immunocompromised individuals (i.e., primary immunodeficiencies, patients on immunosuppressant treatment, HIV-infected people, and sometimes the very young or old), since this type of vaccine has the potential to replicate in an uncontrolled manner, spread to other individuals due to shedding of the vaccine, or revert to a virulent (disease-causing) form,” she says. “Care must be taken, therefore, to select a candidate that has an appropriately balanced replication profile to maintain an acceptable safety profile but that can also induce a potent immune response,” Warfield adds.

To modulate the immune response and to increase the duration of the immunization, Becker says that the entire vaccination program may have to be applied in several doses, which can be inconvenient for patients. Live viral vaccines may also be challenged with stability issues and require frozen temperatures to remain viable and potent.
TruCLEAN SPONGE MOP

Sterilized by gamma radiation and validated sterile to AAMI guidelines, ideal for high-grade cleanroom use.

CLEAN & DISINFECT floors, walls, and ceilings.

Product INFO: Dimensions: 16" x 5"  Weight: 1 lb.  Material: Polyurethane Foam

Compatible with gamma, ethylene oxide, and autoclave sterilization - up to 250 °F for 30 minutes.

- Now Available -
TruCLEAN - STERILE

The Original Cleanroom Sponge: #22-34  
Hydrosorb Sponge Mop: #22-24  
Sponge Mop w/Fused-Cover: #22-34F

perfex@perfex.com  
32 Case Street, Poland, NY  
Phone: 1-800-848-8483
Similarly, a viral vector-based vaccine can cause an immune response to the viral vector itself in addition to the antigen of interest for which it is delivering the nucleic acid, according to Gregory Bleck, vice president of research and development at Catalent Biologics. “This issue can make repeated dosing difficult, since with additional dosing, the patient’s immune system may clear the viral vector before it has an opportunity to insert the nucleic acid into a cell for antigen production,” he observes.

There are a multitude of approaches for non-live viral vaccines that can be based on whole, killed organisms; purified or recombinant proteins; VLPs; or genetic vaccines, notes Warfield. “In contrast to live vaccines,” she comments, “non-live vaccines pose no risk to immunocompromised individuals and cannot spread or potentially cause disease.” Development of purified or recombinant proteins, VLPs, and genetic vaccines, however, requires knowledge of the protective antigens, including their identities and possibly structures, to ensure proper and robust immune responses, she adds. In addition, some protein-, VLP-, and killed virus-based non-live vaccines require addition of an adjuvant to improve their immunogenicity due to their non-replicating nature.

Spotlight on genetic vaccines

Genetic vaccines are different because they contain only a small part of the virus’ genome and cause cells to produce the desired antigen(s). Typically, the RNA or DNA sequence that instructs the human cell to produce the viral antigen(s) intended to trigger an immune response is formulated in a lipid nanoparticle that can enter the human cell after vaccination, according to Becker. He adds that because the human cell produces the antigen itself in order to produce the immune response, a smaller dose of vaccinating agent is required for genetic vaccines when compared with traditional vaccines.

Some people consider viral-vector vaccines, in addition to those based on DNA and RNA, to also be genetic vaccines, because the genome fragment is embedded within a virus that usually cannot multiply itself in the human body, but once inside the cell directs the cell to produce the viral antigen.

In the case of DNA-based vaccines—either plasmid/naked DNA- or viral-vector-based—explains Bleck, the cell that takes up the DNA will transcribe the DNA into mRNA, and then the mRNA will be translated into the protein-of-interest, which will be an antigen from the virus. In the case of mRNA vaccines, the transcription step is already completed, so the cells that take up the mRNA only need to transcribe the mRNA sequence into the protein-of-interest. Viral vector-based vaccines utilize the engineered virus to insert the nucleic acid encoding the viral antigen into the cell, where that molecule is then subsequently transcribed to mRNA and translated into the protein-of-interest.

DNA- and RNA-based genetic vaccines have been impeded by the ability to appropriately deliver the nucleic acids intact and to the correct site within the body or a particular cell type, according to Warfield, but this issue has more recently been overcome with the development of novel, improved delivery formulations such as more effective lipid nanoparticles.

Importantly, although they are considered genetic vaccines, the DNA of the human cell is not impacted by the vaccine, and Becker notes that antigen production only continues for a short duration before the RNA or viral vector are eliminated from the body. As a consequence, though, the immune reaction (and potential adverse effects) occurs in a more modulated and delayed manner, Becker asserts. “As a result, to achieve complete immune protection and to increase duration, a prime boost dosing regimen in two consecutive vaccinations with the same or a different vaccine may be applied, which is what we’re seeing in the mRNA COVID-19 vaccines,” he says.

Indeed, while genetic vaccines hold much promise, they have not yet been widely commercialized. This situation has started to change with FDA granting Emergency Use Authorizations to the mRNA vaccines from Pfizer-BioNTech and Moderna for COVID-19 in late 2020 and approval for the viral-vector vaccine for Ebola from Janssen (Ad26.ZEBOV) followed by a second dose of MVA-BN-Filo from Bavarian Nordic, also in 2020.

Development and manufacturing advantages for genetic vaccines

What makes genetic vaccines so attractive is the potential to establish platform solutions that allow the rapid development of a range of vaccines against emerging infectious diseases based on a scalable novel core technology platform. “The process to develop and produce genetic vaccines is highly similar from one to the next, so we have already a lot of information from other vaccine projects that have used the same platform. This saves valuable time and energy when starting the development of a vaccine against a new disease,” explains a company spokesperson from Janssen Infectious Diseases & Vaccines.

The design and development of traditional vaccines is fairly complex. Most importantly, the best way to propagate the virus or its antigen needs to be newly developed in each and every case, Becker stresses. For killed or attenuated viruses, a mechanism must be explored and established that kills or lowers the infectious potential of the virus, without destroying it, so that the ability to generate the immune response remains. If this is not achievable, the traditional vaccine route is blocked for these viruses. For conjugated or VLP vaccines, the appropriate carrier substance or partner molecules also need to be explored and then combined with the antigen in the formulation process.

“While historical knowledge can be applied in the attenuation or formulation process, each case requires developmental activities to some extent. The more similar the new virus is to existing organisms, the easier it will
be to use existing processes, reducing the amount of development time required. This is particularly true when creating vaccines for new mutations of known and treatable viruses such as flu,” Becker remarks.

“Traditional vaccines can take years to develop because they rely on the actual virus or viral proteins grown within eggs or cells,” Bleck agrees. “Viral proteins are developed and manufactured in cell-based expression systems, and they require time to generate a clonal cell line expressing the protein-of-interest and then optimize the manufacturing process so that it can be reliably scaled-up to clinical and commercial scale.” Traditional vaccines based on cell culture are also manufactured using large stainless-steel equipment, which is slower to scale up and requires longer construction timelines, Christy adds.

In addition, traditional vaccines are usually ranked as requiring an elevated biosafety level, and manufacturing facilities therefore need to comply with a higher level of biosafety requirements. “Such capacities may be limited worldwide, especially in pandemic situations, and facilities that are usually used for the manufacturing of ‘normal’ drug products cannot be used. Moreover, the virus propagation or the production of the antigens are biochemical processes that need to be run under controlled conditions and that may take a long time (weeks to months),” Becker observes.

Genetic vaccines, on the other hand, can be designed more rapidly and deployed as soon as the genetic sequence has been identified. The DNA product can be quickly expressed and scaled-up to clinical or commercial scale, Bleck adds. In the case of mRNA vaccines, the DNA precursor can then be transcribed in an in-vitro process that does not require the same long development timelines; for viral vector-based vaccines, the base systems are already established and the gene that encodes the antigen of interest only needs to be substituted into the vector backbones to start the process. Subsequent engineered viral production is performed using well-established manufacturing techniques.

As an example, Christy notes that Moderna went from sequence selection to shipping the first manufactured batch of the clinical drug product in 42 days. In addition, Lonza was able to scale up, build, and commercialize the Moderna vaccine in its Visp, Switzerland facility in only eight months, compared to the two to three years (or more) usually required to build a new cell-culture facility. This speed was also made possible by Lonza’s pre-investment Ibex Dedicate in a manufacturing complex and supporting infrastructure that was pre-primed and ready for fit-out, according to Christy.

“Part of the reason for this speed is that no cell bank or viral seed bank needs to be developed; this time-consuming task is often required for traditional vaccines,” says Christy. “Secondly,” he continues, “the dose for genetic vaccines is very low compared to traditional vaccines; an mRNA dose of 30–100 µg is being utilized. Such low doses require smaller facilities, which can be equipped with single-use (SU) technology, resulting in a faster scale-up and facility implementation.” Similarly, viral vaccines can be produced in small SU bioreactors, with 1000-L vessels sufficient for producing millions of doses.

“Theoretically,” adds Richard W. Welch, vice president of development services for Emergent BioSolutions’ CDMO Business Unit, “once a process and testing have been developed for a genetic or platform-based vaccine, that same process and the majority of the release assays can be used for any

### FDA adds and updates guidance for COVID-19

As the rollout of vaccines to combat COVID-19 expanded globally in early 2021, bio/pharma companies refocused R&D efforts on assessing the effectiveness of initial vaccines and treatments against emerging variants of the SARS-CoV-2 virus and modify existing formulations to combat new strains.

In support of these research efforts, FDA announced on Feb. 22, 2021 a suite of guidance documents to address the industry response to the variants, including an update to the October 2020 guidance on Emergency Use Authorization (EUA) for vaccines to prevent COVID-19, and guidance on the impact of the variants on monoclonal antibody (mAb) products and other treatments.

The updated guidance, Emergency Use Authorization for Vaccines to Prevent COVID-19, offers recommendations to vaccine developers regarding virus variants, including developers who already received an EUA for a vaccine. FDA expects that manufacturing information for an authorized vaccine and a modified vaccine candidate from the same manufacturer will be generally the same. The effectiveness of a modified vaccine candidate should be assessed by data from clinical immunogenicity studies, comparing a recipient’s immune response to virus variants induced by the modified vaccine against the immune response to the authorized vaccine; and the modified vaccine should be studied in both non-vaccinated and previously vaccinated individuals (1).

FDA also issued a new guidance document for developers of mAb-based therapies that recommends approaches to the generation of non-clinical, clinical, and chemistry, manufacturing, and controls data to support an EUA for an mAb product effective against variants (2).

For other drugs and biological products that address COVID-19, FDA revised a May 2020 guidance document that provides recommendations regarding Phase II and Phase III clinical trials for drugs and biologics to treat or prevent COVID-19 to include the new virus variants and authorized COVID-19 vaccines (3).

**References**

3. FDA, COVID-19: Developing Drugs and Biological Products for Treatment or Prevention, Guidance for Industry (February 2021).

—The editors of Pharmaceutical Technology
The majority of these vaccines may vector or antigen. For more traditional vaccines, each process and set of release assays must be developed separately.”

More specifically, the level of development effort required for platform-based vaccines is often substantially less than for more traditional vaccines from a chemistry, manufacturing, and controls perspective, Welch explains. “This decreased level of process and method development results in a substantial reduction in cost, and more importantly during a pandemic, the time from determination of identity and sequence of the target antigen or antigens sequence to clinical production and release of clinical trial material.”

Moreover, the biosafety level category for genetic vaccines usually is lower than for traditional vaccines. “The majority of these vaccines may not even require biosafety measures during production at all, merely the same techniques as those used for other biopharmaceutical products,” notes Becker. As such, facilities that produce “normal” biopharmaceutical drug products can be used also for the manufacturing of these vaccines.

In addition, Welch observes that a genetic- or platform-based approach can also avoid other potential delays for clinical production. “If a site has already manufactured, tested, and released that type of genetic or platform vaccine, then the equipment is in place and qualified for any vaccine that platform can support. Materials and suppliers are already qualified, and materials specifications are already developed and set. Often, long lead-time items with long expiry dates can also be held in stock, decreasing the time necessary to order, release, and supply material to the manufacturing or QC [quality control] suites,” he says.

However, Becker points out, genetic vaccines are a much younger class of drug product compared with traditional vaccine techniques. “The knowledge level for some of the required production techniques, such as the formulation of lipid nanoparticles, is still limited within the pharmaceutical industry. We can expect to accrue even more valuable knowledge over time to further enhance the effectiveness and efficiency of these vaccines,” he states.

**Easy to modify in response to virus mutations**

Viruses naturally mutate, and the longer they are in circulation and the more transmission that occurs, the more opportunities they have to develop mutations that enable resistance to established antigens. Depending on the mutations, the impact can range from minimal to substantial for traditional vaccines, according to Welch. Traditional flu vaccines offer an existing case where the seasonal variation has minimal to no impact on the production process. However, substantial mutations or changes in strains with increased potential for infection can result in substantial changes.

**Genetic vaccines, as with other biologic drugs, face production challenges.**

“If the mutation or shift in strains cannot be produced using the existing process, such as an avian flu not being able to be produced in eggs, then inactivated and attenuated vaccines could potentially require completely new starting strains or production platforms, which would essentially require anything from substantial to complete redevelopment and validation of the manufacturing process for the new strains,” he says. The same could hold true for protein-based or recombinant protein-based.

Because genetic vaccines trigger their immune response via a fragment of the virus genome, they will continue to provide an effective immunization route as long as the gene sequences in those particular fragments remain unchanged or display minimal mutations, according to Becker.

If the mutation is more significant, genetic vaccines also have the advantage of being extremely easy to modify. “That is the beauty of genetic vaccines; they represent a platform approach with a central technology (adenovirus, liposome particle mRNA, or other) that can be readily modified by inserting a new genetic sequence for rapidly response to virus mutations or even novel viruses (e.g., other coronaviruses),” Christy asserts.

The DNA template just needs to be modified to encode the new variants, and manufacturing of the updated vaccine can typically continue with very few, or no modifications to the process, Bleck notes. The existing body of knowledge about related virus strains facilitates the location and isolation of the relevant gene sequence, Becker says. Bleck adds, however, that the new vaccines still need to be evaluated in detailed clinical studies to confirm that the new mutated epitopes do not elicit unwanted immune responses in patients.

**Still scaling challenges**

Like with traditional vaccines, developers of genetic vaccines must ensure sufficient process and product understanding to meet FDA, European Medicines Agency (EMA), and other regulatory guidelines, and they face scalability issues moving from early clinical phase to late clinical phase and commercial. “One key difference for genetic vaccines,” asserts Welch, “is that if the technology is a true platform approach, these issues only have to be worked out once for multiple indications.”

Companies, however, still need to define how much volume should be manufactured in order to meet demand and ensure that they—or their manufacturing partners—have the capacity to scale-up operations to meet the necessary peak volume. Genetic vaccines, while faster to develop than proteins, are still biologic products that require cell culture and sophisticated technology for development and manufacturing at both clinical and commercial scale, according to Bleck.
In a pandemic, adds Christy, the key challenge is manufacturing at risk during ongoing clinical trials. Further, the production scale-up to deliver hundreds of millions (if not billions) of doses places an enormous strain on the supply chain. Becker points out that currently there is only limited global capacity for biopharma production, some of which is required for existing drug and vaccine products. In addition, both traditional and genetic vaccines require filling under aseptic conditions, further reducing global capacity.

**Stability and delivery hurdles, too**

Genetic vaccine approaches have been contemplated for nearly 30 years, but until recently, Warfield says, they had been challenged by the need for large doses to induce mild to moderate immune responses, the instability of the nucleic acids (particularly with RNA candidates), and the inability to efficiently deliver the nucleic acids to targeted tissues or cells.

The recent success of the Pfizer-BioNTech and Moderna mRNA vaccines demonstrates that these issues have been overcome at least to some degree, but Warfield believes further improvements will need to be made for continued and future success of this class of vaccines. She highlights a need for the reduction of costs for raw materials and manufacturing processes and improvements in stability to reduce the need for storage at low or extremely low temperatures, which can create supply-chain challenges.

“Every lower stability of genetic vaccines is definitely the major challenge when it comes to widespread adoption of this new technique,” Becker agrees. Formulation of the lipid nanoparticles required to protection of mRNA vaccines from degradation can be challenging, however; the correct ratio of lipids, proteins and nucleic acids is needed to form the nanoparticle, in addition to any additional excipients, adjuvants, etc., according to Bleck.

In addition, genetic vaccines may only undergo a limited number of freeze-thaw cycles, and thus the bulk vaccine should be filled into vials immediately after the formulation process is completed. In addition, he notes that the filling process should be followed immediately by visual inspection and label and pack operations. “With this in mind, the size of a batch, which is processed in one run, may be limited in order to shorten the exposure of the vaccine to room temperature,” he comments.

Because genetic vaccines are so new, there is also a need for careful short- and long-term monitoring and understanding of side effects to assist in the development of next-generation candidates that are potentially safer with less untoward effects, Warfield adds. “Achieving understanding and approval of the safety and efficacy profile of genetic vaccines by the general public, and especially amongst those with existing vaccine hesitancy, will be required for efficient and broad acceptance of genetic vaccines in the future for a larger set of pathogens outside the current COVID-19 pandemic,” she continues.

Overall, Christy observes that as with any new technology, genetic vaccines will progress through a maturation curve. Equipment and production processes must be optimized and standardized so processes can be made robust and scalable and global supply can be achieved at acceptable costs. He also stresses that the human capital factor must not be neglected. “The availability of trained, regulatory-compliant GMP manufacturing staff and quality control and quality assurance personnel is a critical success factor,” he says. Much investment in facilities will be needed as well, which during the COVID-19 pandemic has been supported by numerous government and private partnerships.

**Additional genetic analysis requirements**

A similar challenge common to all vaccines is the delivery of a safe and efficacious dose to patients. “Full focus on SISPQ (safety, identity, strength, purity, and potency) is common to all medicines. However, for genetic vaccines, this means developing a whole new battery of analytical methods, especially around purity and potency,” Christy states. “Methods exist, but these generally are research-based techniques (such as sequencing, infectivity, transfection assays), and they need to be fully developed to be robust, valuable, GMP-compliant, and able to be routinely implemented across multiple sites (globally for both drug substance and drug product),” he says.

Methods for genetic sequencing and product release, adds Bleck, require specialized expertise and equipment not required for traditional vaccines. In addition, he notes that for mRNA-based vaccines, their instability relative to most proteins will typically expand the scope of stability studies required.

The shortened timelines for manufacturing of genetic vaccines, Becker comments, also means that with currently accepted analytical methods, analysis results for intermediate production materials, such as formulated bulk product or product in filled but unlabeled vials, are not available at the time of processing. “This situation results in an increased risk that non-conforming product may undergo further value-adding manufacturing steps before being identified and discarded,” he says.

**Potential for formulation improvement**

Because genetic vaccines are still a relatively new class of treatments, there is significant potential for further development. Primary opportunities revolve around the selection of more appropriate excipients, observes Welch. Work is ongoing to improve the target product profiles of genetic vaccines to improve their stability, Christy adds. “Formulation development with a range of stabilizers offers the potential to improve both the temperature stability and the shelf life of such vaccines,” he states.

In some cases, Welch believes that the use of existing or novel drying technologies will improve the stability of genetic vaccines. Becker agrees that

---

Contin. on page 64
Novel Excipients Needed More Than Ever Before

Cynthia A. Challener

Without an independent approval pathway for novel excipients, true pharmaceutical innovation could be stymied.

Excipients are essential to the formulation of drug products because they enable the effective delivery of drug substances and can account for as much as 80–90% of the drug product formulation. Despite the exposure that excipients pose to patients, currently there is no independent pathway for approval or assessment of novel excipients.

Other materials, which have higher levels of exposure, have established approval procedures. For example, food additives—including flavorants and colorants—can be approved via a petition to FDA or through the Flavor and Extract Manufacturers Association generally accepted as safe (GRAS) process. Cosmetic ingredients undergo the Personal Care Products Council’s well-accepted Cosmetic Ingredient Review process.

Many excipients used in approved drugs are listed in FDA’s Inactive Ingredient Database (IID); however, most have been used for decades and few were initially developed specifically for use as pharmaceutical ingredients. Novel excipients are those compounds not listed in the IID or compounds listed in the IID, but intended to be used for a new route of administration, at a higher dosage level or modified in some way, such as co-processed excipients that have been combined and enhanced in a physical manner through particle engineering.

New challenges require new tools

The lack of an independent approval pathway for all of these types of novel excipients is creating significant challenges for drug formulators. “In recent years, there have been astonishing advances in the fundamental understanding of disease biology leading to remarkable treatments for once deadly diseases. Many drug candidates for these transformative and breakthrough treatments suffer from very poor physical and/or chemical properties,” observes Eric A. Schmitt, senior director of pharmaceutics at AbbVie and co-leader of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) Working Group on novel excipients.

For oral drug candidates, excipients that can mitigate challenges associated with poor aqueous solubility and/or permeability can enable drug development for these otherwise potentially undevelopable candidates, Schmitt notes. For parenteral delivery, driven by the growth of macromolecules, there are significant needs for excipients that can improve solubility and chemical and physical stability, and reduce viscosity, he says.

“Similarly, tolerability (e.g., pain on injection for parenteral medicines), acceptability (e.g., taste for pediatric patients), and manufacturability challenges can all hinder the development of innovative medicines,” Schmitt says. “These challenges occur across therapeutic modalities, routes of administration, and dosage form types. Novel excipients, or expanded use scenarios of existing excipients, can provide formulation scientists much needed tools to address these challenges,” he concludes.

Novel dosage forms in use and under development today also have unique needs. “The industry as a whole is evolving to different methods for dosage and delivery—transdermal, mucoadhesive, and targeted immunotherapies for instance—that require unique solutions that in many cases cannot be provided by IID-listed options and will only be possible through the introduction and acceptance of novel excipients,” says Meera Raghuram, director of regulatory and sustainability with Lubrizol Life Science.
As one single provider, Marken seamlessly drives your program from clinical to commercialization every step of the way. With our experience, we have mastered clinical drug storage and distribution in an era of advanced therapies and decentralized trials. Our unique suite of end-to-end offerings will help you move your trial forward.

Connect with a Marken expert at info@marken.com
The bottom line, according to David R. Schoneker, president/owner/consultant with Black Diamond Regulatory Consulting, is that drugs today present different formulation challenges, and the numerous excipients used for 100 years no longer resolve these issues, nor do they enable optimization of new manufacturing methods such as continuous processing and 3D printing.

“It is important,” stresses Nigel Langley, global technology director for pharma solutions at BASF, “to think about novel excipients as offering a means for designing functionality to address specific problems given the challenges that drug developers currently face. Without fit-for-purpose excipients, many unmet needs will simply remain unmet,” he states.

**Strong perceived risk prevents use of novel excipients**

Novel excipient approvals, however, are tied to new drug approvals, which adds risk to an already high-risk endeavor. It is natural that adding additional risk with an unapproved excipient will be avoided and only pursued as a very last resort, according to Schmitt. “Tying a new drug product approval to a novel excipient approval essentially doubles the risk of regulatory approval and significantly increases the cost of development. Even worse, if either one fails, the investment in both is lost,” he says.

There have also been examples in the past, notes Priscilla Zawislak, global regulatory affairs advocacy manager at IFF and immediate past-chair of the International Pharmaceutical Excipients Council (IPEC)-Americas, of drug developers being told by FDA that they really should use only excipients listed in the IID. “Hearing such comments can be very discouraging for pharmaceutical companies that have invested time and effort with novel excipients,” she says.

It is also frustrating for companies producing novel excipients, adds Langley. “Drug developers may want to use novel excipients in formulations that can be developed without them to provide improved quality or performance. Without an independent approval process, however, they rarely do so unless the potential reward outweighs the higher risk. Excipient manufacturers therefore don’t have any incentive to develop new products that may not bring a return for 15–20 years,” he asserts.

Some of the risk is perceived, because most novel excipients have more supporting toxicity data than the older approved excipients ever had, according to Schoneker. “It is the uncertainty that results from the lack of an established pathway that is the problem,” he states.

**Developing a new drug is a complex endeavor; using an unapproved excipient can increase development risk and costs.**

There is real risk, though, asserts Raghuram, due to FDA’s silence on the issue, the lack of any specific policy, and the chance that an application containing a novel excipient might land in the hands of a new drug application reviewer that doesn’t really understand how to do this type of assessment. “The awareness of issues related to safety of novel excipients is limited, and this is not surprising as there is no guidance available. It also cannot be expected that considerations related to innovation or an assessment of the positive impact of a novel excipient on the drug landscape will be part of a drug regulatory review process. An independent safety review process is, therefore, very important for novel excipients.”

**Negative consequences already occurring**

A 2020 US Pharmacopeia (USP) survey of 264 respondents who formulated or supervised the formulation of generics, branded medicines, biologics, or biosimilars during the past five years revealed the extent to which drug developers find the lack of access to novel excipients a problem (1). Eighty-four percent said that currently used excipients have imposed limitations on drug development. Seventy-seven percent experienced challenges using novel excipients in advancing formulations through drug development for the US market, with regulatory acceptance, approvals, and other requirements the most common challenges. Forty percent felt compelled to reformulate a drug product for the US market because of an excipient’s limitations, while 28% experienced a discontinuation of drug development as a result of excipient limitations.

The internal structure of pharmaceutical companies that says risk must be managed has led to limited use of novel excipients, even if it means lower performing formulations are pursued, according to Langley. Today, Schmitt agrees, there is a high barrier to using novel excipients in drug development, which can stifle drug product design and potentially lead to suboptimal products with respect to pill burden, injection volume, stability, etc., as well as less efficient and/or robust manufacturing processes.

“What we have today is product development by IID and acceptance of ‘good enough’, rather than quality by design,” Schoneker asserts. In some cases, development projects have actually been halted because to move forward would require the use of novel excipients, meaning patients have therefore not had access to medications that could help them, he adds. In many cases, novel excipients have been available and shown to solve the specific issues, but the drug developers could not justify the perceived risk of using them.

While there is no lack of ideas or energy around the concept of novel excipients, given the hesitancy on the part of drug developers to use them and the lack of a path to market, the business model for excipient suppliers has be-
Robertsite® Bag Access Valves (BAV)

Designed to be integrated by press fit or heat sealing into fluid delivery bags

- Eliminates the use of needles and spikes
- Compatible with all standard male luers
- Eliminates leaking and dripping when disconnected
- Incorporates proven split septum valve technology
- Available in polycarbonate and polypropylene

sales@halkeyroberts.com
727.471.4200
www.halkeyroberts.com

Visit our website to view our comprehensive line of needlefree swabable valves
come impractical, according to Raghuram. “Very few excipient companies are willing to invest resources in innovation and development,” she observes.

“At a time when we have never needed novel excipients more, there is too much uncertainty about using them and thus little reason for anyone to actually develop them. Due to the lack of an appropriate pathway for bringing products forward, very few companies are making decisions to get involved in real novel excipients any more. The only advances we are seeing are minor modifications to existing excipients, and in a few cases, co-processed excipients,” comments Schoneker.

**Independent approval pathway could address uncertainty**

If an independent approval or qualification pathway for novel excipients was established, then the requirements would be defined and everyone would know what must be done, says Zawislak. “FDA expectations would be clearer and more interest would be created in using novel excipients,” she says. For excipients that have FDA opinions generated and made public, drug developers would also know that there is safety data to support their use, at least for certain intended levels, Schoneker adds.

“Not only would an independent approval pathway encourage pharmaceutical companies to evaluate novel excipients, it would also give excipient suppliers a path to market that does not involve waiting 15–20 years,” observes Langley. Indeed, once an excipient receives a favorable review, suppliers can present that product to pharmaceutical companies and show that it has already been reviewed and therefore represents a higher likelihood of success, according to Zawislak.

Langley also believes such a pathway would act as a catalyst to stimulate innovation and collaboration between pharmaceutical companies and excipient suppliers. “An independent approval or qualification pathway for novel excipients could facilitate development, not only potentially reducing the attrition rate, but would also allow for a more cost-effective development process,” he states.

Access to more patient-friendly delivery solutions could also improve patient compliance, adds Katherine Ulman, principal consultant at KLU Consulting. Meanwhile, a new pathway may also lead to an update of the FDA guidance related to excipient safety, which was issued more than 15 years ago. In fact, IPEC is currently working on the revision of the 1996 Safety Guide for Pharmaceutical Excipients to incorporate current thinking related to safety evaluation techniques. IPEC hopes to publish this revised guide later in 2021.

**An independent approval pathway for excipients would act as a catalyst to stimulate pharma innovation.**

**True for both branded and generic drugs**

For branded drugs, novel excipients could be used to optimize drug product performance and presentation, and possibly develop candidates that were deemed undevelopable, leading to transformative medicines with optimized patient presentations, according to Schmitt.

For generic drugs, novel excipients based on new chemical entities may not be appropriate for use; they would be best suited for use with innovator drugs that must go through clinical studies rather than bioequivalence studies. But other types of excipients including co-processed excipients and existing excipients used at higher levels or via different routes of administration, as well as food ingredients used for the first time as excipients, should be suitable for generic drugs. Because these materials have much less safety risk associated with them, the level of safety data required for assessment is typically lower.

“Novel excipients based on new chemical entities should go through a more drug-like approval process, while those based on existing excipients should have a less rigorous approval process that would enable their use by the generic-drug industry,” Schoneker asserts. If this approach was taken, generic-drug developers could make better quality products more efficiently and leverage advances in manufacturing techniques. Co-processed excipients or excipients used at higher levels, for example, might allow more cost-effective manufacture or improve patient compliance while still ensuring bioequivalence of generic formulations.

**FDA proposed pilot program promising start**

In early December 2019, FDA published a Federal Register Notice requesting comments on a proposed pilot program for reviewing the toxicology studies of a limited number of novel excipients via and process independent of the investigational new drug, new drug application, and biologics license application processes (2). Any novel excipient found to be safe under the proposed Novel Excipient Qualification Pilot Program would be listed in the IID with acceptable use levels. In the Federal Register Notice, the agency sought input on seven topics, including what criteria should be evaluated for novel excipients and whether such a program would help overcome the hesitancy of pharmaceutical companies to use them.

By the time the docket closed in early February 2020, 26 respondents had provided overwhelming support for the program (3). There has since, however, been no official public announcements from the agency regarding next steps. “We know FDA is working on the program, but we don’t know what they are going to do or when,” observes Schoneker.
Industry eager to move forward

The pharmaceutical industry’s perspective, according to Schmitt, is that in the past 20 years, tremendous advances have been made with respect to both small- and large-molecule drug substances, but formulators are still limited to the same excipients that were available two decades earlier with very few new excipients approved. “We believe this situation is a direct consequence of the historical approval process for novel excipients and are excited to partner with FDA in this pilot program. We are very encouraged and hope to capitalize on this momentum by seeing the program implemented and novel excipients enter the assessment process in 2021. We also urge readers to encourage their organizations to consider novel excipients when they can make a difference and take advantage of the pilot program if/once it is implemented,” Schmitt states.

The proposed FDA pilot program is the first solid development following many years of effort on the part of excipient suppliers, pharmaceutical companies, IPEC-Americas, the IQ Consortium, and USP to reach out to and educate the agency on this important issue. “For the first time, we are seeing the possibility of a path forward that will encourage excipient innovation and in turn drug product innovation in ways that haven’t been possible before,” Schoneker asserts.

“That is tremendously exciting, and we are eager to work together with FDA to bring the program to fruition,” adds Langley. IPEC-Americas is also willing to provide suggestions for possible candidates for the pilot program that could serve as a means for seeing how the process might work. “We would love to have that kind of discussion with the agency once the decision is made to take the next steps,” Schoneker says. In addition, IPEC also has a team of toxicologists from around the world developing a new safety guide with information FDA might find useful for the proposed assessment process, according to Ulman.

Longer term, there is hope that ultimately some level of global consistency can be achieved regarding the approval of novel excipients. Doing so will be critical to realize the benefits of the US pilot program for patients, according to Schmitt. “The biopharmaceutical industry develops treatments for patients across the globe and a harmonized approach will be required,” he explains. One possible solution would be to have the topic addressed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

References
Reviewing Recent Bioavailability Research

Felicity Thomas

Various strategies to improve bioavailability are being continuously evaluated, affording greater commercial prospects for the future.

Oral solids remain the most widely used dosage forms for pharmaceuticals to date, namely as a result of the convenience the form offers developers, manufacturers, and patients. Despite significant industry growth being witnessed in the area of large-molecule drugs, the oral solid dosage (OSD) pharmaceutical formulation market is anticipated to be worth more than US $926.1 billion by the end of 2027 (1).

However, it is also extensively reported that a sizable proportion of drug candidates in development are poorly water-soluble, an aspect that can contribute to higher attrition rates and is directly related to poor oral bioavailability. Low bioavailability is a frequent cause of failure in drug development (2) and is known to lead to high variability and poor control of therapeutic effects (3).

Oral bioavailability of a drug product can be affected via several factors, such as poor solubility, gastrointestinal degradation, and high first-pass metabolism rates. Aqueous solubility and membrane permeability have been identified as key influencers of oral bioavailability of drug products (4). Strategies employed to overcome the challenges that result in low oral bioavailability include manipulation of drug properties or methods to interfere with physiological barriers to drug absorption (3).

Research and review

Drug properties can be altered via formulation strategies, manufacturing processes, or by modifying physicochemical properties to improve solubility and hence bioavailability. Many techniques have been well documented and researched over the years, providing valuable insight into the mechanism of action of various strategies and pathways for potential future advancement.

A review paper, authored by van der Merwe et al. in 2020, provided a comprehensive overview of selected excipients suitable for use to improve oral bioavailability. In their review, the authors noted that despite the variety of approaches available and the indication from several studies that functional excipients can have a beneficial effect on the bioavailability of APIs, there were also some clinical limitations. When evaluating specific excipient groups, such as pH-adjusting excipients, there were limited in-vivo and clinical data available and mostly, the studies only evaluated one poorly soluble API, demonstrating a clear need for further research (4).

However, it is patently clear that excipients are rightfully considered as more than an ‘inert’ vessel in drug delivery. As the complexity of drug development has increased, so too has the requirement for more sophisticated excipients to manipulate the properties of the final product, for example, multifunctional (co-processed) and high functionality excipients, which are able to fulfill multiple roles in performance improvement of a dosage form (4).

Specifically focusing on amorphous solid dispersions (ASDs), there are several specific excipient functionalities that should be considered. These considerations include the solubilizing effect of the excipient, the capability of the excipient to provide a strong molecular interaction with the API, whether the excipient exhibits thermoplastic behavior, and if the excipient displays a broad range of dissolution behaviors. Critically, the API and the polymer systems in ASDs must have a strong affinity for one another, and if the solubilization of the API within the polymer is done properly, it is possible to gain a thermodynamically stable end product (5).
Despite the capability of ASDs to improve solubility and bioavailability of drug products, there are complexities to overcome to ensure commercial success. In seeking to provide a greater understanding of the mechanisms underlying how ASDs improve bioavailability, Schittny, Huwyler, and Puchkov performed a literature review of all available research in 2019. Reflecting on both theoretical considerations and experimental data, the authors’ literature review led them to the conclusion that dissolution of an ASD can be attributed to three main mechanisms—carrier controlled, dissolution controlled, and drug controlled—and that dissolution is influenced by drug load, homogeneity of the solid ASD, interactions between the polymer and the drug, and surfactants (6).

A sizable proportion of drug candidates in development are poorly water-soluble, which can contribute to higher attrition rates.

Other key findings from the research included the fact that the dissolved states of ASDs are in a dynamic equilibrium; the higher drug absorption of ASDs can be mainly credited to the increased concentrations of molecularly dissolved API and is aided by diffusion by drug-rich particles. Additionally, it was found that, although polymers have the capacity to stabilize supersaturated solutions, they can also lower the amorphous solubility, and surfactants, although useful for enhancing dissolution properties, can not only stabilize but also destabilize supersaturated solutions. Furthermore, translational studies, moving from in-vitro to in-vivo performance, are limited (6).

An investigation by Wilson et al. in 2020 was aimed at evaluating the in-vivo absorption performance following oral dosage of a high-drug load formulation. The researchers evaluated enzalutamide in particular, as it is a lipophilic compound, Biopharmaceutics Classification System class II, that has low drug loading in its current commercially available formulation. As a result of low drug loading, the pill burden for patients is high, and, therefore, there is a desire to increase the drug loading without compromising absorption of the API (7).

Choosing two newly synthesized cellulose derivatives for ASD formulation, Wilson et al. determined that it is important for the polymer used in ASD formulations to have the correct balance of hydrophilic and hydrophobic substituent groups to be effective. Ultimately, after performing both in-vitro and in-vivo tests, the authors discerned that ASD formulation with the cellulose derivative, CPHPC-106, provided a five-fold improvement in enzalutamide absorption relative to crystalline control. Conversely, the polymer that was more effective an inhibiting crystallization yielded minimal improvements in oral absorption, highlighting the fact that ASD performance is a “complex interplay of drug and polymer properties” (7).

Another research paper on ASDs, published in 2020, detailed the possibility of reducing tablet mass using novel architecture. Compared with a typical ASD formulation, in which the dispersion polymer allows for physical stability of the solid-state and the maintenance of dissolution rate in the gastrointestinal tract, the novel high loaded dosage form (HLDF) architecture combines two different polymers to achieve physical stability and dissolution. The drug product evaluated was erlotinib, which is a rapidly crystallizing drug with a low glass transition temperature, formulated as an ASD with Eudragit L100 as the dispersion polymer and hydroxypropyl methyl cellulose acetate succinate as the concentration-sustaining polymer. The authors found that by using the novel HLDF architecture comprising two different polymers—one inside the ASD and the other outside—it was possible to achieve equivalent in-vitro performance as a single dispersion polymer ASD with a reduced dosage form size by 40% (8).

This brief review of some of the recent work being performed to assess various strategies to improve bioavailability demonstrates significant advances in mechanistic understanding and developments to approaches. Furthermore, thanks to research being undertaken in this area, commercial opportunities to improve dosage forms for patient convenience and reduce development attrition rates of poorly-water soluble compounds are coming to the fore.

References
Near Infrared Spectroscopy as a Versatile PAT Tool for Continuous Downstream Bioprocessing

Garima Thakur and Anurag S. Rathore

The need for real-time monitoring and control has spurred the development of new analytical tools.

Process analytical technology (PAT) is an increasingly important aspect of biopharmaceutical manufacturing processes. FDA in 2004 described a regulatory framework for PAT and has been urging the industry to voluntarily develop innovative tools and techniques for quality control and assurance in biopharmaceutical manufacturing unit operations (1). The quality-by-design (QbD) framework encourages the use of PAT tools to “build quality into the process” rather than “testing quality into the product” (2). The importance of PAT tools is amplified in the case of continuous manufacturing processes, where individual batches are not well-defined and critical quality attributes (CQAs) of the therapeutic must be consistently maintained, monitored, and controlled over months of operation, rather than simply tested at the end of each unit operation or each batch (3–4). The need for real-time monitoring and control of CQAs and critical process parameters (CPPs) in continuous manufacturing has led to the adaptation of traditional end-of-batch quality testing techniques, such as analytical high-performance liquid chromatography (HPLC) and ultraviolet-280 (UV-280) spectroscopy, into in-line at-line modalities with periodic sampling from continuous unit operations (5–7). It has also spurred development of new analytical tools that provide information in near real-time and can be placed in-line in process flow streams.

In-line spectroscopic sensors using infrared, near-infrared, or Raman spectroscopy are one such new class of tools finding multiple PAT applications in bioprocessing (8). Spectroscopic PAT applications typically consist of in-line sensors combined with statistical or modeling methodology to monitor, control, and/or predict biotechnology processes. The key advantage of spectroscopy is the ability to gain information about the presence and quantity of multiple analytes in the process mixture simultaneously in a few seconds or less, overcoming a major analytical bottleneck and facilitating real-time control decisions (9). Spectroscopic techniques are also non-degradative and provide a wealth of spectral information that can be used in tracking process trajectories and flagging deviations (10,11). Thus, spectroscopic probes and flow cells are well-suited to PAT applications, particularly in tandem with multivariate data analytics (MVDA) tools, which are critical for reducing the dimensionality of large spectral datasets and extracting statistically significant quantitative information (12).

Table I summarizes the recent literature of the past five years on implementing spectroscopy-based analytical tools in downstream bioprocessing (13–29). The use of spectroscopic immersion probes as PAT tools in upstream microbial and mammalian bioreactors has been extensively reported in the recent literature for identification and quantification of proteins, by-products, and substrates (30–32). However, their use in downstream processing is a more recent development. Near infrared spectroscopy (NIRS), in particular, has been demonstrated to have a wide variety of potential applications in different downstream unit operations, including capture chromatography (24), protein PEGylation reactions (25), and tangential flow ultrafiltration (26). These three case studies demonstrate the versatility of NIRS as a PAT tool and showcase the common underlying framework of the different applications, namely the col-
Considering modern developments in the pharmaceutical industries, our Process Division offers Piloting and Production machines to fit the need for creating vaccines, oral medications, topicals, inhalants and more.

IKA equipment offers the capability to produce stable emulsions and suspensions, conduct wet milling of active pharmaceutical ingredients, and create precipitations.

You want to be flexible in your production, work efficiently, but do not want to accept quality losses? Please contact your local IKA representative to discuss our wide range portfolio of machine options, as well as our engineering services for complete turnkey systems.

AN ESSENTIAL STEP IN ANY PRODUCTION

Considering modern developments in the pharmaceutical industries, our Process Division offers Piloting and Production machines to fit the need for creating vaccines, oral medications, topicals, inhalants and more.

IKA equipment offers the capability to produce stable emulsions and suspensions, conduct wet milling of active pharmaceutical ingredients, and create precipitations.

You want to be flexible in your production, work efficiently, but do not want to accept quality losses? Please contact your local IKA representative to discuss our wide range portfolio of machine options, as well as our engineering services for complete turnkey systems.

IKA MACHINES & EQUIPMENT REPRESENTING UP-TO-DATE TECHNOLOGY AND ARE:

- designed based on FDA or EDEHG standards
- scalable on a lab scale all the way to production
- completely drainable
- suitable for CIP and SIP
- made from high-quality material (all parts)
- deliverable in an explosion-safe design

Engineered Solutions Available | Processing, Detailing, Design

IKA Works, Inc.
2635 Northchase Parkway SE Wilmington, NC 28405
Phone: +1 910 452-7059, Fax: +1 910 452-7693
eMail: process@ikausa.com, web: www.ikausa.com
Protein A capture chromatography is typically the first downstream step in upstream material. The product titer is a key performance indicator (KPI) in downstream processes, batch-to-batch variability of the titer affects the dynamic operating isotherm models, which may not be valid after multiple cleaning cycles. The NIRS-based PAT control strategy was tested by inducing a range of linear and non-linear deviations in the load titer in real time. The deviations were designed to closely simulate those which would potentially occur during a perfusion process. The NIRS flow cells provided the advantage of monitoring not only loading but also changes in the column binding capacity in real time, which is useful for providing early warning of resin degradation or column quality issues and facilitating optimal loading without relying on adsorption isotherm models, which may not be valid after multiple cleaning cycles. The system allowed resin utilization to be maximized, lowering consumable costs.

### NIRS as a downstream PAT tool

#### Case study 1: NIRS for controlled loading.
Protein A capture chromatography is typically the first downstream step in manufacturing of monoclonal antibodies (mAbs). One of the key difficulties in continuous Protein A chromatography is handling variability in the titer of the upstream material. The product titer is expected to change over time in the case of upstream perfusion cell culture systems. Even in the case of fed-batch processes, batch-to-batch variability necessitates flexibility in the downstream capture step. An increase or decrease in the protein concentration in the load stream affects the dynamic binding capacity of the Protein A resin, leading to changes in process performance. Over-loading the Protein A column with high-titer feed can lead to the loss of expensive mAb product, while under-loading decreases the resin utilization of the Protein A resin, one of the most expensive consumables that has been reported to contribute to up to 60% of the costs of the downstream processing train.

The NIRS-based PAT strategy shown in Figure 1 has been used to address this challenge of handling potential titer variability in continuous capture chromatography while maintaining resin utilization and preventing both under- and over-loading. NIRS flowthrough cells placed in the load stream and the outlet of the load column were used to collect spectra of the harvest and column flowthrough every three seconds. These spectra were passed to online MVDA models calibrated with reference spectra to determine the concentration of mAb in the harvest and flowthrough to within ±0.05 mg/mL. The real-time concentration data were used to calculate both the total mg of mAb loaded on the column as well as the percentage breakthrough from the column, and these were used to make control decisions to start and pause the loading in a three-column periodic counter current Protein A process on a continuous chromatography system (Cadence BioSMB, Pall). The normal operating range of the control system allowed for concentration variations in the harvest between 3–8 g/L, achieving optimal resin utilization as well as process scheduling within this range.

The NIRS-based PAT control strategy was tested by inducing a range of linear and non-linear deviations in the load titer in real time. The deviations were designed to closely simulate those which would potentially occur during a perfusion process. The NIRS flow cells provided the advantage of monitoring not only loading but also changes in the column binding capacity in real time, which is useful for providing early warning of resin degradation or column quality issues and facilitating optimal loading without relying on adsorption isotherm models, which may not be valid after multiple cleaning cycles. The system allowed resin utilization to be maximized, lowering consumable costs.

### Table I. Summary of spectroscopy-based downstream process analytical technology (PAT) applications in recent literature.

<table>
<thead>
<tr>
<th>Type of spectroscopy</th>
<th>PAT monitoring/control application</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multi-wavelength ultraviolet spectroscopy</strong></td>
<td>Chromatography pooling decisions for separation of protein size, charge, and type variants</td>
<td>Brestrich et al., 2015 (13) Hansen et al., 2017 (14)</td>
</tr>
<tr>
<td></td>
<td>Loading of capture chromatography</td>
<td>Rudt et al., 2017 (15)</td>
</tr>
<tr>
<td></td>
<td>Column failure detection in capture chromatography</td>
<td>Brestrich et al., 2016 (16)</td>
</tr>
<tr>
<td></td>
<td>Monitoring of ultrafiltration and diafiltration</td>
<td>Ghodbane et al., 2019 (17) Rolinger et al., 2020 (18)</td>
</tr>
<tr>
<td><strong>Fourier transform infrared spectroscopy (FTIRS)</strong></td>
<td>Chromatography pooling decisions for separation of protein size, charge, and type variants</td>
<td>Grobphans et al., 2018 (19) Sanden et al., 2019 (20) Sauer et al., 2019 (21)</td>
</tr>
<tr>
<td></td>
<td>Monitoring of protein refolding</td>
<td>Walther et al., 2014 (22)</td>
</tr>
<tr>
<td><strong>Mid-infrared spectroscopy (MIRS)</strong></td>
<td>Chromatography pooling decisions for separation of protein size, charge, and type variants</td>
<td>Walch et al., 2019 (23)</td>
</tr>
<tr>
<td></td>
<td>Loading of capture chromatography</td>
<td>Thakur et al., 2019 (24)</td>
</tr>
<tr>
<td></td>
<td>Monitoring and control of PEGylation reactions</td>
<td>Hebbl et al., 2020 (25)</td>
</tr>
<tr>
<td></td>
<td>Control of ultrafiltration and diafiltration</td>
<td>Thakur et al., 2020 (26)</td>
</tr>
<tr>
<td><strong>Near-infrared spectroscopy (NIRS)</strong></td>
<td>Chromatography pooling decisions for separation of protein size, charge, and type variants</td>
<td>Feidl et al., 2019 (27)</td>
</tr>
<tr>
<td></td>
<td>Loading of capture chromatography</td>
<td>Feidl et al., 2019 (27)</td>
</tr>
<tr>
<td></td>
<td>Chromatography pooling decisions for separation of protein size, charge, and type variants</td>
<td>Goldrick et al., 2020 (28)</td>
</tr>
<tr>
<td></td>
<td>Titer estimation post perfusion processes for downstream process adjustment</td>
<td>Yilmaz et al., 2019 (29)</td>
</tr>
</tbody>
</table>
Utilizing the GPEx® suite of technologies for cell line development and biomanufacturing of difficult-to-express proteins

Event Overview

Biopharmaceutical products in development continue to increase in complexity, which poses a challenge for pharmaceutical companies looking to improve speed and efficiency of biologic development. Cell line development is a critical step in the development process that impacts protein quality, manufacturing scalability/efficiency, and timelines. The GPEx® suite of cell line development technologies has been utilized to develop hundreds of proteins, including difficult-to-express proteins, in a variety of mammalian cell lines. The GPEx platform is particularly beneficial for complex proteins, such as multi-specific antibodies, unique protein fusions, bioconjugates (including ADCs), proteins requiring cleavage, and proteins requiring other post-translational modification not typically performed by CHO cells.

Key Learning Objectives

• Learn about new cell line development methodologies that are enabling these complex programs to be performed more efficiently
• Hear multiple case studies taking complex biopharmaceuticals through the development process
• Understand a new approach to generate stable pooled cell lines, enabling shortened development timelines

Who Should Attend

• Chief scientific officer
• Process development scientist
• CMC engineer
• Bioprocessing engineer
• Upstream development scientist
• CEO
• VP of biologic development
• Consultant
• VP of bioprocessing
• VP of process development
• VP of biomanufacturing
• Director of biologic development
• Director of bioprocessing
• Director of process development
• Director of biomanufacturing
• VP of bioproduction
• Director of bioproduction
• Director of biologics
costs by ensuring that the total protein processed per mg of resin was consistently maintained. The NIRS flow cells enabled online measurement of concentration and facilitated real-time control decisions for increased efficiency, flexibility, and agility of the continuous chromatography process in the face of unexpected deviations.

Case study 2: NIRS for monitoring/control. Protein modification with biocompatible polymers, such as polyethylene glycol (PEG), is often used to improve the pharmacological properties and stability of biotherapeutics (37). Manufacturing of PEGylated drugs requires a PEG conjugation reaction to be carried out on the purified drug substance at the end of the downstream train (38). Proper control of the PEGylation reaction is critical to maximize PEGylation efficiency while minimizing the presence of over-PEGylated variants. Various critical process parameters affect PEGylation quality, including pH, reaction time, and the concentration and order of addition of the reactants (39). In the present case study, the PEGylation reaction of recombinant human granulocyte colony stimulating factor (rh-GCSF) was considered. The challenge was to monitor the PEGylation process trajectory and reaction kinetics to flag potential deviations in real time, as well as to control the reaction quenching to optimize the production of the desired monoPEGylated variant before its further conversion into undesired diPEGylated and multiPEGylated forms.

A few different PAT tools have been explored in the literature for monitoring and control of PEGylation. Some researchers used at-line size exclusion chromatography to monitor the progress of the PEGylation reaction, though this was not suited for real-time control due to the long method run times of >30 minutes for an overall reaction time of one to two hours (40). Other researchers used at-line matrix assisted laser desorption ionization–time of flight (MALDI–TOF) mass spectrometry for tracking the kinetics of PEGylation, though the time scale of analysis was again too long at over one hour (41). The use of NIRS as a PAT tool in the present case study overcame the bottleneck of analysis time and was able to track the conversion of rhGCSF into its monoPEGylated and multiPEGylated forms on a time scale of a few seconds (25). The NIRS spectra were acquired every three seconds and compared against a calibrated MVDA regression model, built using control runs of the reaction with orthogonal HPLC-based quantification of the PEGylated variants. The spectra acquired during the control runs were also used to develop a multivariate batch evolution model of the ideal reaction trajectory. A flow chart of the NIRS-based PAT tool is shown in Figure 2.

The PAT tool was demonstrated in various control and deviated reaction runs in which online spectra were acquired by the NIRS immersion probe and used not only for quantification of the PEGylated variant, but also for comparison against the ideal reaction trajectory. This allowed process deviations to be identified and flagged in case a statistically significant difference was found between the trajectories of the current process versus the ideal one. A range of deviations were found to be identifiable by the PAT tool, including incorrect concentration of chemical additives, incorrect ratio of PEG to rhGCSF, incorrect order of addition of the reactants, and incorrect quenching time. The impact of each deviation on CQAs of the PEGylation reaction product was characterized, and each resulted in lower product purity and process yield. The NIRS probe was demonstrated to provide critical real-time information and form the basis of a robust PAT tool for monitoring and control of the PEGylation reaction of rhGCSF. The overall approach is generalizable to other downstream reaction steps, such as enzyme reactions or esterification.

Case study 3: NIRS for control of retentate concentration.
Tangential flow ultrafiltration (UF) is a key unit operation in downstream processing of biotherapeutics, used for concentrating and buffer exchanging the in-process drug substance into the desired target concentration and formulation of the final drug product (42). This is typically the last unit operation prior to fill/finish and packaging. The concentration of
Solid Form Screening and Rational Cocrystal Design

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

Event Overview
Solid-form screening and characterization is a crucial part of drug substance development and pre-formulation. Knowledge of the underlying fundamentals of polymorphism, hydrates/solvates, salts, and cocrystals is essential to establish an understanding of a drug substance and its solid-form throughout the drug development lifecycle.

In this webcast, experts will discuss many aspects of solid-form screening including in-silico screening, which can save time and speed up the solid-form development process. A case study will review in-silico screening of cocrystals of a pharmacophore using hydrogen bond energies and hydrogen bond propensities. A second case study will examine cocrystallization of nutraceuticals and their versatile use as coformers.

Key Learning Objectives
- Understand the importance of solid-form screening and the impact of form selection in pharmaceutical development.
- Learn how solid-form services can accelerate drug development.
- Understand the importance of different in-silico screening methods in solid-form development.

Who Should Attend
- Project managers and leaders in pharmaceutical development
- Chemistry, manufacturing, and control (CMC) managers
- Scientists wanting to improve their knowledge of solid-form development
- Decision makers looking to outsource solid-form screening or preformulation services

Presenters
Michael Grass
Head, Solid Form Services
Lonza
Abhijeet Sinha
Senior Scientist
Lonza
Rita Peters
Editorial Director
Pharmaceutical Technology

For questions email kbarry@mjhlifesciences.com
the biotherapeutic in the final drug product is a CQA determined solely by this unit operation, necessitating robust control. In batch mode, concentration is achieved by recirculating the drug substance held in a large tank through the UF membrane until the desired volume reduction is achieved (43). However, batch-mode recirculation is not possible in the case of constantly incoming flow streams in continuous processing. The solution is to use single-pass UF in which the membrane module has a larger area and a long flow path, facilitating volume reduction of the feed stream in a single pass without the need for recirculation (44).

There are several operational challenges that must be overcome, however, to ensure that the retentate stream emerges from the single-pass tangential flow filtration (SPTFF) module consistently at the fixed target concentration. Reversible and irreversible membrane fouling as well as deviations in the concentration of the incoming flow stream from prior unit operations, such as polishing chromatography, lead to changes in the concentration factor achieved in a single pass (45,46). Therefore, a PAT strategy is needed to monitor the concentration of the incoming feed stream and control the flux across the membrane, to ensure that the retentate concentration does not vary over the course of the process. Researchers demonstrated a strategy leveraging in-line NIRS flow cells in the feed and retentate streams of an SPTFF module to make flux-based control decisions and ensure consistency in the retentate concentration, as shown in the schematic in Figure 3 (26).

The NIRS flow cells were able to measure the concentration of mAb in the range of 0.5–200 g/L, a significant improvement over UV-based quantification methods, using suitably calibrated spectral libraries. The control decisions were made on the basis of the real-time NIRS data as well as a pre-characterized design space for the limits of maximum flowrates and concentration factors achievable for a given feed concentration and flow rate within the
Event Overview

For drug developers, being ready to develop and mass produce drugs for a pandemic situation is an essential part of their risk management strategy. But what about the packaging suppliers that create containers, stoppers, plungers, and seals to protect and deliver these vital drugs?

This webinar will discuss work that has been done to develop, manufacture, and distribute parenteral packaging components for the on-going COVID-19 pandemic, while also touching on the critical aspects to consider to prepare for a future pandemic or natural disaster scenario.

Topics discussed will include:
- An introduction to packaging components for vaccine applications
- An overview of common challenges that packaging suppliers face with manufacturing and distributing vaccines and how to overcome them
- Strategies for ensuring business continuity during disaster scenarios

Key Learning Objectives

- Understand the risks that the pharma industry faces when it comes to packaging vaccines in emergency scenarios and which actions to take to mitigate these risks
- Learn steps to take to overcome manufacturing and distribution challenges for vaccine components
- Learn from case studies and best practices about how to ensure business continuity during disaster scenarios

Who Should Watch

- Quality/regulatory personnel in parenteral drug delivery
- Formulation scientists and packaging engineers
- Device development engineers and managers
- Technical functions surrounding drug delivery systems
- Extractable and leachable experts
- Procurement professionals
pressure limits of the membrane module. The NIRS data were analyzed, and closed-loop control established with a permeate pump and retentate valve, allowing flux control on the time scale of <1 second. Control and scheduling decisions were made for integrating the SPTFF step with the rest of the continuous downstream train and for ensuring timely cleaning. The overall PAT strategy was demonstrated over two 12-hour case studies. The NIRS monitoring sensors enabled the development of a robust PAT control strategy to ensure that retenate concentration targets were consistently met over long continuous campaigns.

**Summary**

The need for rapid, non-degenerative, and robust analytical tools will continue to grow as the biotherapeutic industry embraces the PAT and QbD paradigms. Spectroscopic sensors are uniquely suited to fulfill this need as spectral information can be collected in a few seconds and analyzed in milliseconds using multivariate techniques. The spectra can yield a wealth of information about the in-process sample, including quantification of multiple analytes and the overall health of the process compared to an ideal trajectory. Spectroscopic applications in upstream microbial and mammalian cell cultures have grown exponentially in the past 10 years, and this can be expected to happen in the case of downstream unit operations in the near future. The rapidly growing interest in continuous downstream processes in both academia and industry will amplify this effect due to the unique real-time PAT control challenges that arise when batch-mode product quality testing is no longer an option. To truly bring spectroscopic applications into a manufacturing setting, however, the industry needs to gain confidence in the use of multivariate calibration models, which can only be done by having robust guidelines and frameworks for spectroscopic model validation, calibration, and periodic checking to account for shifts in spectroscopic sensor data over months or years. More fundamental studies are also needed to draw clear relationships between biotherapeutic CQAs and their effect on spectral features, as has been done in the case of generic pharmaceuticals. Finally, the ability of spectroscopic sensors to collect time-stamped spectral process signatures at high frequency over months or years is also a potential advantage that can be leveraged to create large-scale manufacturing datasets providing deep process history information, which can be of use to regulatory bodies.

**References**

Top Pitfalls to Avoid When Deploying a Quality and Compliance Management Solution

ON-DEMAND WEBCAST
Aired: Tuesday, February 23, 2021

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

Event Overview
Pharmaceutical manufacturers, both large and small, are trying to realize the full potential of process automation, digital, analytics, and big data. The goal is to create a digitally transformed company that connects people, processes, data, technology, and partner organizations together in a connected ecosystem. However, getting to this point is often fraught with obstacles.

This webcast is a practical and interactive session that explores:

• Why it is critical to address quality and compliance projects not only from a technical perspective, but also a business perspective that evaluates an organization's business needs and assumptions.
• The common mistakes pharmaceutical companies must avoid when automating quality and compliance processes.
• How new technologies can deliver a speedy and cost effective quality management system (QMS) deployment.

Learn how pioneering pharma companies are approaching digital transformations differently and hear how they are taking a holistic approach that hyper-scales the power of data and analytics to quickly automate and streamline processes.

Key Learning Objectives
• Learn how to approach QMS deployments in a phased approach and how to build strategy that is future-ready.
• Review questions to ask vendors to choose the right technology partner.
• Understand how to perform a gap assessment of QMS solutions and learn when to use ready-to-use solutions.
• Hear how to map risks and embark on a benefit driven, risk-based approach for QMS deployment.
• Hear how to avoid improper budget planning by effectively outlining and estimating costs.

Who Should Attend
• Pharma/BioPharma Manufacturing Executives, Quality Professionals, Clinical Research, Compliance, IT, Project Management, QA/QC, R&D, Regulatory Affairs, Technology Transfer Professionals
Digital Tools Enhance Raw Material Traceability

Jennifer Markarian

Integrated, paperless data systems can improve efficiency and quality.

Traceability of the raw materials used in pharmaceutical and biopharmaceutical manufacturing is a crucial part of quality management. Digital tools offer time savings, better compliance, and greater efficiency for all aspects of raw materials qualification and handling.

Supplier and material qualification

Raw material quality begins with raw material suppliers, and supplier and material qualification are crucial steps for any drug manufacturing process. Quality management systems (QMS) can be useful here, says Patrick Nieuwenhuizen, senior manager and consultant at PharmaLex.

PharmaLex introduced a digital tool in November 2020 to help companies perform risk assessments of excipient interactions in the final drug product, which are required by Europe’s EudraLex Volume 4, Part III guidelines (1). “The SmartRisk tool prompts the user with a series of questions to help organize the assessment,” explains Nieuwenhuizen. He notes that the commercially available, cloud-based system complies with US Code of Federal Regulations (CFR) 21 Part 11 (2) and EudraLex Annex 11 (3), including data integrity protection.

“Having a robust quality management system with procedures and processes for raw material traceability and management supports consistency and reliability throughout the supply chain,” adds Jessica Cansler, senior quality management specialist for Nutrition & Health, North America, at BASF. “Adhering to appropriate quality standards, as well as establishing a program based on risk and application will help ensure the appropriate level of review of raw materials.”

BASF’s Virtual Pharma Assistants, introduced in 2019, are digital tools for pharmaceutical development. “Zoom-Lab allows formulators to predict their next starting formulation for a pharmaceutical product; RegXcellence untangles the complexity of the compliance process via instant access to regulatory and quality documentation; and MyProductWorld helps customers find the optimal excipient or API solution for their next formulation challenge,” says Valerie Van Hulle, global strategic marketing manager, Pharma Solutions, at BASF. The company continues to update the online tools, she reports.

Quality systems should not be separated in “silos” from other operations, suggests Matt Lowe, chief product officer at MasterControl, which released a new version of its life sciences QMS software on Feb. 3, 2020. “Gaining greater visibility is the first step toward ensuring traceability. Connecting your QMS with other systems and stakeholders helps provide the necessary visibility and transparency to extend a culture of quality not only across your organization, but also your supplier network. With the technology that we have today, any company should be considering a digital QMS and connecting systems in a paperless environment.”

Electronic records

Digitalization for raw materials handling can take many forms—from online certificates of analysis (CoAs) to electronic batch records (EBR). While the trend is toward digitalization, companies in the pharma industry are at various stages in the process, with some completely manual, others completely automated and paperless, and others in between.

Automated systems for raw materials records remove the double verification required in manual paperwork. “The system virtually does the verification for you as it can act as a ‘pass or fail’ whereby the system is working for you instead of you working for the system, which is a time savings and results in better compliance,” adds Nieuwenhuizen.

“It does take effort and time to implement digital systems,” Nieuwenhui-
zen cautions. He notes one example in which a company implemented a complex vendor management system that required a dedicated project team. The result, however, was the ability to link materials management and ordering with EBR, which also helped manage stock levels. Nieuwenhuizen notes that when implementing digital systems, it can be challenging and potentially counterproductive to translate manual workflows directly into digital workflows. “It may be better to embrace a new way of working and look first at how the digital tools are designed to be used,” he suggests. “The software suppliers have the knowledge about the benefits of the tool, and they can be a resource.”

**Integrating digital systems**

Integrating digitalized systems within a company eliminates data silos, in which data are stored in separate, unconnected digital systems. An integrated platform makes all the data in an organization accessible so that data can be analyzed to identify trends and make data-based business decisions, notes Lowe. For example, he says, if raw materials supplier data were integrated with other quality and manufacturing data, a manufacturer would have another tool to help better identify the root cause of a deviation.

Integrating QMS and laboratory inventory management systems (LIMS) is beneficial, adds Nieuwenhuizen. “Inventory control systems help with QMS. Quality control of materials can be linked to LIMS for intake, quarantine of problem batches, and release or rejection of material. An important aspect is that it gives you full traceability by batch number,” says Nieuwenhuizen. LIMS can then be interfaced to inventory control systems and to vendor management.

Inventory management and supply-chain visibility software can help with managing complex supply chains. “There are more platforms seen in the industry to alert when there is a possible supply disruption in an area due to natural disasters and other issues in the region or sourcing company,” notes Cansler.

Although data interfaces between raw materials suppliers and drug manufacturers are not yet widespread, there is a move toward sharing information so that parties can make informed decisions more quickly. Data security and confidentiality, however, are important. “Use of password protection and user vetting helps maintain confidentiality,” says Cansler. “Confidentiality can be further addressed by allowing visibility only one level up and down; [users would need to] request authorization to further review the transparency beyond their one level capability.”

Connecting supply chain management systems and QMS also improves efficiency of the supplier audit process, adds Lowe. “Manufacturing organizations need to be able to securely track and store supplier audit information, reports, deviations, supplier corrective action requests (SCARs), and more while making it easy to find suppliers that meet audit requirements.” He notes that digital audit tools within quality systems connected to supplier information allowed remote audits to take place during the COVID-19 pandemic’s travel restrictions. “A digital system can even allow you to invite suppliers to participate in tasks relevant to them, providing a secure, online collaboration space and restricted access to suppliers for collaboration and concurrent engineering efforts. For many companies, having this technology has impacted their business continuity. If there is something good that comes from COVID-19, it’s that it has illustrated the need for digitization to maintain business operations and has spurred companies to make the digital transition.”

While more companies are now embracing these well-established digital tools and systems, new data analysis tools are also being increasingly used. “Machine learning (ML) and artificial intelligence (AI) are tools that some companies are already taking advantage of, and I would expect this will be the big trend in the coming years,” suggests Lowe. “Integrating [supplier, quality, and manufacturing] systems to share information and using AI/ML and natural language processing to analyze that data will be a game-changer for companies.”

**References**

2. CFR Title 21, Part 11.
The authors have developed a granular formulation of ezogabine, XEN496 (1–6), suitable for administration to children, including newborns. They used a modified quality-by-design (QbD) approach, as well as a risk-based matrix, to guide development of various prototypes of this Biopharmaceutical Classification System (BCS) Class 2 drug. First, they established excipient compatibility for ezogabine through an accelerated-condition stability study of binary mixtures of ezogabine and excipients at 40 °C and 75% relative humidity. Lead blends within the compatibility space were then designed and their in-vitro dissolution profiles determined. Blends with the most promising dissolution profiles were then dry granulated and re-tested for dissolution prior to stability assessment.

The authors also assessed the impact of drug loading on dissolution performance, along with the potential for non-specific binding to occur with common plastics, such as those used in feeding bottles and nasogastric (NG) feeding tubes. Rat pharmacokinetic (PK) studies were then performed in order to confirm the candidate formulation’s biopharmaceutical performance in vivo, after which it was evaluated for taste/mouth feel and placed on long-term stability studies.

This article describes the overall process taken to design and test prototype pediatric formulations of ezogabine, which led to the identification of XEN496. Data so far suggest that granules containing ezogabine show rapid dissolution, good polymer compatibility and stability, suitable particle size distribution, and ease of dosing on a body weight basis, without requiring extemporaneous compounding. In addition, the final product shows a neutral taste profile, which could potentially enhance both patient and caregiver convenience and patient compliance.

**Materials and methods**

Ezogabine was synthesized by a qualified good manufacturing practice (GMP) facility and re-crystallized to a chemical purity of 99.88% a/a. The crystalline form was determined...
to be Form A (i.e., the same form that had previously been used in the manufacture of Potiga) (7). A number of excipients were then selected for evaluation: Hydroxypropyl methylcellulose (Dow, Midland, MI); Starch 1500 (Col orcon, Stoughton, WI); Butylated hydroxytoluene (BHT) (Spectrum Labs, New Brunswick, NJ); Microcrystalline cellulose (FMC, Philadelphia, PA); and Copovidone (Ashland, Mill Creek, WA). To determine the bioequivalence (BE) of the new formulation, male Sprague-Dawley rats were used for pharmacokinetic (PK) evaluation of XEN496 and Potiga.

High-pressure liquid chromatography (HPLC) chemical purity. Analysis was performed using an HPLC device (Shimadzu LC-20ADXR) equipped with an auto-sampler and a 150 x 4.6-mm, 2.7-µm column (Advanced Materials Technology Halo C18). The sample was analyzed using a gradient method with 0.1% H₃PO₄ in water v/v as mobile phase A and acetonitrile as mobile phase B. The run time was 28 minutes, and the column temperature was 30 °C with an injection volume of 10 µL per sample and a 1 mL/min flow rate.

Analyte detection was carried out by UV analysis at 254 nm with a bandwidth of 4 nm. This method was developed and fully validated for use with ezogabine and its formulated products. Using this method, the parent peak for ezogabine was well resolved. However, the dimers, although observed, were not fully resolved and were (along with certain other impurities) deemed to be related substances for this product.

Excipient compatibility. The excipient compatibility screening was performed with samples consisting of ezogabine mechanically admixed with excipients in proportions typically employed in solid oral dosage products. Samples were stored at 40 °C and 75% relative humidity for four weeks before being analyzed by HPLC for changes in total related substances (TRS).

Formulation development. The excipient compatibility data were used to design a series of prototype formulations prepared via dry granulation to create immediate release (IR) dosage forms. Each of these prototypes consisted of a combination of ezogabine, binders, fillers, antioxidants, and disintegrants in ratios that aimed to promote an optimal release profile of ezogabine along with a minimum degree of degradation caused by interactions with the excipients.

Dissolution. Dissolution testing was performed using a dissolution testing system (Agilent 708-DS) with 0.1 M HCl as the dissolution medium as n=6 samples at 37 °C ± 0.5 °C. The dissolution equipment was set up as per United States Pharmacopeia (USP) <711> as Apparatus 2 (paddles) with a paddle speed of 50 rpm and sampling points at 5, 10, 15, 30, 45, and 60 minutes, after which time the paddle speed was increased to 200 rpm.

The last sampling time point was taken at 75 min. At each time point, 1 mL of the media was sampled, filtered using a 0.45-µm polypropylene filter and analyzed by HPLC using a HPLC (Shimadzu LC-20ADXR) equipped with an auto-sampler and a 150 x 4.6 mm, 2.7-µm column (Advanced Materials Technology Halo C18). The sample analysis was performed using a gradient method with 0.1% formic acid in water v/v as mobile phase A and 0.1% formic acid in acetonitrile v/v as mobile phase B. The run time was 28 minutes and the column temperature was 37 °C with an injection volume of 10 µL per sample and a 1 mL/min flow rate. Ezogabine detection was carried out by UV analysis at 254 nm with a 4 nm bandwidth.

Bioequivalence (BE) study. Male Sprague-Dawley rats (7–8 weeks old, N = 6/group) were used for BE evaluation. Rats were dosed at 10 mg/kg via oral gavage; blood samples were collected via jugular vein at specific time points: 0.25, 0.5, 1, 2, 4, 8, and 24 hours, and processed to plasma by centrifugation at ~4 °C and 3200 g for 10 min within 30 min of collection, and kept frozen at -70 °C – 10 °C. The samples were then analyzed for ezogabine levels using a validated method combining liquid chromatography with tandem mass spectrometry. Plasma concentration-time data were analyzed via a non-compartmental model using Phoenix WinNonlin 6.3 software (Pharsight Corporation).

Taste testing. A taste test was performed on the lead prototype formulation (Blend B or XEN496) of the granulated material. Two healthy adult human subjects each took a sub-therapeutic dose of XEN496 in a taste test designed to ensure that the formulation had a neutral character and to determine its mouth feel.

Non-specific binding. Ezogabine non-specific binding to glass, along with three of the most common materials used in feeding bottles and NG tubes (polyethylenesulfone, polyethylenesulfone and polypropylene), was tested by preparing a stock solution of the API in purified water at a concentration of 0.025 mg/mL and transferring aliquots to feeding bottles made of the different materials. The bottles were hand shaken for one minute before 1-mL aliquots were tested by HPLC and the amount of material recovered calculated.

Granulation. Samples were blended using a blender (Nan-Tong Beite Pharmaceutical Machinery Co., Ltd. HTD-200), then processed in a roller compactor (Alexanderwerk WP 120), after which granulate was sieved using a vibratory sieve shaker (Fritsch Spartan).

Results

Excipient compatibility. Pediatric formulation development of ezogabine began by testing the stability of the API in the presence of a range of excipients. The goal was a formula-
tion with minimal degradation (i.e., no inherent instability due to unfavorable interactions with inactive ingredients). Excipient compatibility screen results are presented in Table I. This screen was performed with samples consisting of the API mechanically admixed with excipients in proportions typically employed in solid oral dosage products. Many of the samples showed limited or no change in total related substances (TRS) readings after storage at 40 °C and 75% relative humidity for four weeks compared to Day 1. A number of excipients were determined to be potentially suitable for use in the formulation development with ezogabine.

**Formulation development.** The main prototype formulations prepared for ezogabine at different drug loads are presented in Table II. Based on the projected clinical dosing regimen for various pediatric age ranges, a relatively wide range of drug loads (ranging from 5% to 20% w/w ezogabine) was evaluated by dry granulation to create immediate-release (IR) dosage form prototypes. Each of these prototypes consisted of a combination of the API, binders, fillers, antioxidants, and disintegrants in ratios that aimed to afford an optimal release profile of ezogabine along with a minimum degree of degradation caused by interactions with the excipients (Table II).

**Dissolution.** To compare formulations based on ezogabine release under simulated gastric conditions, dissolution tests were performed as described. The resulting dissolution profiles are presented in Figure 1, with target criteria being a repeatable dissolution profile with Not Less Than Q+5 (Q=75%) at T=15 minutes for the blend. The optimum blends were designated as the lead (Blend B, XEN496) and back-up (Blend I) formulations for subsequent development. The lead formulation showed in-vitro dissolution profiles (both pre- and post-granulation) consistent with an IR product (e.g., 91.2 ± 1.2% released after 10 minutes, 99.1 ± 1.0% released after 45 minutes).

Analysis of the formulations between 10–60 minutes in the dissolution profile gave no clear impression of function/property relationships for the excipient types used. For ex-

---

**Table I.** Excipient compatibility screen as binary mixtures with ezogabine. TRS is total related substances.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Appearance</th>
<th>Change in TRS</th>
<th>Excipient</th>
<th>Appearance</th>
<th>Change in TRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezogabine</td>
<td>White powder</td>
<td>0.03%</td>
<td>Butylated hydroxytoluene (BHT)</td>
<td>White powder</td>
<td>0.07%</td>
</tr>
<tr>
<td>Microcrystalline cellulose (MCC)</td>
<td>White powder</td>
<td>0.25%</td>
<td>Croscarmellose sodium (CCNa)</td>
<td>White powder</td>
<td>0.07%</td>
</tr>
<tr>
<td>Erythritol</td>
<td>White powder</td>
<td>0.60%</td>
<td>Polylasdone</td>
<td>White powder</td>
<td>0.03%</td>
</tr>
<tr>
<td>Hypromellose (HPMC)</td>
<td>White powder</td>
<td>0.08%</td>
<td>Colloidal silicon dioxide</td>
<td>Pink powder</td>
<td>2.51%</td>
</tr>
<tr>
<td>Starch 1500</td>
<td>White powder</td>
<td>0.07%</td>
<td>Cellulose, powdered</td>
<td>White powder</td>
<td>-0.01%</td>
</tr>
<tr>
<td>Ethylcellulose</td>
<td>White powder</td>
<td>0.07%</td>
<td>Sodium starch glycolate</td>
<td>White powder</td>
<td>0.08%</td>
</tr>
<tr>
<td>Talc</td>
<td>White powder</td>
<td>0.20%</td>
<td>StarCap1500</td>
<td>White powder</td>
<td>0.06%</td>
</tr>
<tr>
<td>Sodium Stearyl fumarate</td>
<td>White powder</td>
<td>-0.01%</td>
<td>Leucine</td>
<td>White powder</td>
<td>-0.06%</td>
</tr>
<tr>
<td>Silicon dioxide</td>
<td>White powder</td>
<td>1.84%</td>
<td>Calcium phosphate tribasic</td>
<td>Yellow powder</td>
<td>0.36%</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>White powder</td>
<td>-0.04%</td>
<td>Methylcellulose</td>
<td>White powder</td>
<td>-0.03%</td>
</tr>
</tbody>
</table>

**Table II.** Formulation design. HPMC is Hypromellose or hydroxypropyl methylcellulose; MCC is microcrystalline cellulose; BHT is butylated hydroxytoluene.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>API (%)</th>
<th>Excipient 1</th>
<th>Excipient 2</th>
<th>Excipient 3</th>
<th>Excipient 4</th>
<th>Excipient 5</th>
<th>Excipient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blend A</td>
<td>5</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 42.49%</td>
<td>MCC 42.5%</td>
<td>CCNa 5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend B</td>
<td>20</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 19.99%</td>
<td>MCC 45%</td>
<td>Polylasdone XL 10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend C</td>
<td>5</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 24.99%</td>
<td>MCC 25%</td>
<td>Lactose 40%</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend D</td>
<td>5</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 59.99%</td>
<td>MCC 30%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend E</td>
<td>6.98</td>
<td>HPMC 6.98%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 79.05%</td>
<td>CCNa 6.98%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend F</td>
<td>10</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 29.99%</td>
<td>MCC 45%</td>
<td>Polylasdone XL 10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend G</td>
<td>10</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 29.99%</td>
<td>MCC 45%</td>
<td>Polylasdone Ultra 10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend H</td>
<td>10</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 42.49%</td>
<td>MCC 45%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend I</td>
<td>20</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 37.49%</td>
<td>MCC 37.5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend J</td>
<td>10</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 19.99%</td>
<td>MCC 40%</td>
<td>Lactose 20%</td>
<td>CCNa 5%</td>
</tr>
<tr>
<td>Blend K</td>
<td>5</td>
<td>HPMC 5%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 44.99%</td>
<td>MCC 45%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blend L</td>
<td>5</td>
<td>HPMC 20%</td>
<td>BHT 0.01%</td>
<td>Starch 1500 37.49%</td>
<td>MCC 37.5%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A: Not applicable
ample, Starch 1500 is used in these formulations as a binder between 19.99–79.05%. While the formulation with the optimum dissolution rate gave the lowest binder level, other formulations with the same percentage of binder had only moderate dissolution rates, approximating those of formulations with the highest level of binder.

What did seem to have a significant effect was the level of API in the formulation. Typically, formulations with the poorest dissolution have low levels of the API (5%) and the optimum formulations for dissolution have the highest percentage of API (20%). It can therefore be postulated that ezogabine in these granules acts as a disintegrant or dissolution enhancer. At this point, no research has been performed to explain how this mechanism might work. Future studies are planned to elucidate the mechanism underlying this observation.

**Stability of selected formulations.** The formulations selected for advancement on the basis of their dissolution profiles (Blends B and I) were re-prepared and placed on stability under nitrogen in a potential clinical presentation (i.e., 2 g of XEN496 in 80 x 80-mm sachets made from a polyethylene terephthalate/aluminum/polyethylene [PET/Al/PE] compound film designed for pharmaceutical packaging). The samples were placed under International Council for Harmonization (ICH) accelerated conditions (40 °C / 75% relative humidity) for 36 weeks, with appearance and HPLC purity/related substances evaluated at the time points described in Table III. Ongoing stability assessments have shown that ezogabine is stable in both the lead and back up formulations under ICH accelerated conditions.

**Bioequivalence studies.** Because the molecule had been previously marketed, it is desirable to show there was no significant change in oral bioavailability and PK profile between the IR Potiga tablet and the current XEN496 granule formulation. To mimic the reported off-label use for pediatric patients, Potiga tablets were crushed before administration, and these crushed tablets were compared head-to-head with the XEN496 granules in a rat PK study.

The crushed Potiga tablets and the XEN496 granules were dosed (10 mg/kg) orally in a rat cross-over PK study. Both formulations were dosed as a suspension at a concentration of 1 mg/mL in 0.02% w/v aqueous carboxymethyl cellulose (CMC); the CMC concentration was selected to match the viscosity of infant formula.

The plasma-concentration curves of the crushed Potiga tablets and XEN496 (Figure 2) are virtually superimposed, indicating that the granule formulation was equivalent to Potiga in terms of biopharmaceutical performance. This was confirmed through PK analysis, which showed that the geometric mean ratio and its 95% confidence intervals of the PK

---

**Figure 1.** Dissolution profiles of formulations A-L.

**Figure 2.** Plasma concentrations of ezogabine after oral administration of XEN496 granules and crushed Potiga® tablets in rats.
Taste testing. Taste is a key parameter in the development of medicines for pediatric populations, particularly infants, who have functioning taste buds on their tongue, tonsils, and at the back of their throats. This makes them more sensitive to bitter and sweet tastes than adults, and they have a strong preference for slightly sweeter flavors (8). Because infants cannot understand or comment on flavors they find unpleasant, they will reject any food which tastes bitter, which, in the case of medicines, may cause an under-dose due to incomplete intake of the administered dose. Pediatric formulations, therefore, must be specifically designed to be neutral or slightly sweet so that they would be accepted by the infants taking the medication.

An informal taste test performed on XEN496 (Blend B), showed it to be slightly sweet with a slightly grainy texture; however, this test used the granulated material, which would be either completely or partially dissolved in the dosing matrices, hence eliminating or mitigating any potential disagreeable mouth feel. It is therefore expected that this product will be accepted by infants when mixed with food.

Particle size. The dissolution profiles indicate that XEN496 will dissolve in 0.1 M HCl; however, the dissolution profile in baby formula could not be determined, because this medium caused interferences in the UV spectra. Because this could, in principle, affect the ability to dose patients effectively and accurately, the particle size distribution of the granules was carefully controlled so that they could pass through the nipple of an infant feeding bottle.

Laser light scattering was used to determine the particle size distribution of the XEN496 granules. It indicated that they would be small enough to pass through the nipple of a standard baby bottle or pediatric NG tube (i.e., with a d10 of 13.4 ± 0.4 µm, a d50 of 41.6 ± 1.6 µm, and a d90 of 153 ± 31 µm). By comparison, typical baby bottle nipple apertures are >500 µm, and size 4 Fr pediatric NG tubes have a 1330-µm inner diameter. XEN496 is therefore considered compatible with pediatric dosing, including common feeding devices without risking blockages, which may impair administration.

Non-specific binding. The effect of polymer binding on drugs is well-known (9) and can be extremely beneficial when designing a drug delivery system; however, it can also cause undesired effects when polymers trap or adsorb to the API so that it cannot be effectively and/or efficiently absorbed. Because XEN496 is designed to be added to foods, including baby formula, it is important that there be limited polymer binding such that the full API dose can be readily available for absorption in the body.

Glass and three of the most common materials used in feeding bottles and NG tubes (polyether sulfone, polyphenyl sulfone, and polypropylene) were tested for non-specific binding with ezogabine. Analysis of the samples showed 100% recovery from the glass vessel and minimal binding to each of the polymers, with recoveries of 96.9% for polyether sulfone; 96.7% for polyphenyl sulfone; and 96.5% for polypropylene: 96.5%. However, these levels are not expected to affect patient dosing.

Discussion
The challenges inherent in this project were threefold: to develop a stable pediatric formulation of ezogabine; to ensure that the formulation has adequate PK characteristics and preferably is bioequivalent to Potiga; and to make sure that parameters were within the BE range of 80–125% (Table IV).

![Table III. Stability study on select formulations. TRS is total related substances.](image)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Appearance</th>
<th>Purity%</th>
<th>TRS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T=0</td>
<td>White granules</td>
<td>99.79</td>
<td>0.21</td>
</tr>
<tr>
<td>T=1 week</td>
<td>White granules</td>
<td>99.82</td>
<td>0.18</td>
</tr>
<tr>
<td>T=2 weeks</td>
<td>White granules</td>
<td>99.80</td>
<td>0.20</td>
</tr>
<tr>
<td>T=4 weeks</td>
<td>White granules</td>
<td>99.82</td>
<td>0.18</td>
</tr>
<tr>
<td>T=8 weeks</td>
<td>White granules</td>
<td>99.81</td>
<td>0.19</td>
</tr>
<tr>
<td>T=12 weeks</td>
<td>White granules</td>
<td>99.79</td>
<td>0.21</td>
</tr>
<tr>
<td>T=24 weeks</td>
<td>White granules</td>
<td>99.82</td>
<td>0.18</td>
</tr>
<tr>
<td>T=36 weeks</td>
<td>White granules</td>
<td>99.80</td>
<td>0.20</td>
</tr>
<tr>
<td>Total change in TRS after 36 weeks:</td>
<td>-0.01%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Table IV. Plasma concentrations for XEN496. CI is confidence interval; AUC is area under the curve, related to drug exposure and clearance from the body; and C_max is maximum plasma concentration.](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>C_max</th>
<th>AUC0-last</th>
<th>AUC0-∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower bound 95% CI</td>
<td>105.4</td>
<td>94.9</td>
<td>94.9</td>
</tr>
<tr>
<td>Point estimate of geometric mean ratio</td>
<td>115.1</td>
<td>108.0</td>
<td>108.0</td>
</tr>
<tr>
<td>Upper bound 95% CI</td>
<td>125.7</td>
<td>122.9</td>
<td>122.9</td>
</tr>
</tbody>
</table>
the formulation would meet the stringent requirements of pediatric dosing, yet still facilitate preparation and accurate dosing of the patients without having an unpleasant taste or mouth feel.

The approach used for this work was initially to develop a formulation that would allow the API to be dosed in a manner suitable for the patient population, in a formulation that was stable under accelerated conditions. Once a suitable formulation was prepared, its properties were controlled through particle engineering activities such as micronization and encapsulation of specific strengths, which can be combined to allow for effective and accurate dosing based on each patient’s weight. The approach used in the development of the formulation has proven to meet all design characteristics established in the initial project plan.

Conclusion

A novel pediatric formulation of ezogabine (XEN496) was successfully developed for use in the pediatric population (through dispersal in breast milk, infant formula, or soft foods) as granules packaged in a way that would allow for highly accurate body weight-based dosing. XEN496 has shown suitable physiochemical properties such as dissolution rate and stability. The rat cross-over PK study with XEN496 and Potiga showed that these formulations of ezogabine were bioequivalent, which makes XEN496 suitable for further clinical development and, potentially, for use in pediatric clinical trials in patients with KCNQ2-DEE. XEN496 has since been manufactured under GMP conditions for Phase I/III clinical studies.

References

8. G.K. Beauchamp and J.A. Mennella, Digestion, Mar; 83(Suppl 1), 1-6 (2011).

Matthew D. Tandy, PhD,* mtandy@xenon-pharma.com, is associate director of chemistry, manufacturing, and control; Jay A. Cadieux, PhD, is vice-president of product development & operations; and Rostam Namdari, PhD, is senior director of translational drug development, all with Xenon Pharmaceuticals Inc., 200-3650 Gilmore Way, Burnaby, BC, Canada.

*To whom all correspondence should be addressed.
Precision Particle Fabrication™

Enabling precise control over particle structure

In pharma delivery, size matters. So, too, do the intricacies of dosage format, active ingredient compatibility, and effective delivery to patients—whatever their needs or preferences may be.

Yet standard dosage forms haven’t always provided companies the options, flexibility, or performance to bring all those puzzle pieces together during therapeutic development.

So it’s a relief to know that things are changing. Advances like Precision Particle Fabrication™ technology, for example, produce uniform microspheres and microcapsules with narrow size distribution and precise control over particle structure, making the platform versatile enough to accommodate a range of active ingredients and delivery formats.

We spoke with Nathan H. Dormer, PhD, Director of Drug Product Development at Adare Pharma Solutions, to learn how this new technology platform is expanding the frontiers of therapeutic delivery and improving patients’ experience in the process.

PHARMTECH: Please tell us about Adare Pharma Solutions and your role in the organization.

DORMER: Adare Pharma Solutions is a contract development and manufacturing organization (CDMO) focused on providing specialized formulation solutions and manufacturing expertise to the pharmaceutical and OTC and animal health markets.

At Adare, I’m a Director of Drug Product Development, so I oversee non-GMP formulation development activities at our Kansas City location. The formulations we develop in Kansas City then go on to be tech transferred and scaled up at one of our other GMP sites, either in the United States or in Italy. Many great things are happening across all our locations, and Kansas City is where a lot of the R&D action has been taking place.

PHARMTECH: How does Adare solve formulation and manufacturing challenges that other CDMOs can’t solve?

DORMER: What Adare is really proud of is our proprietary microencapsulation technologies, by which I mean that these aren’t standard tableting or liquid technologies that are freely available. They’re patented, and Adare retains the institutional knowledge and know-how for operating these technologies and formulating with them.
For example, Adare has Microcaps®, which is a coacervation technology that can directly coat drug particles for taste masking or modified release. And the acquisition of Orbis added other proprietary technologies, like Optimun® and Stratum™, which are processes that create very uniform microparticulates that can be used in many different types of solid oral dosage forms.

PHARMTECH: Could you describe Orbis's platform technologies and how those fit into Adare's portfolio?

DORMER: Adare was traditionally one of the leading CDMOs in the microparticulate space, particularly in the solid oral space. The company has a handful of proprietary technologies that microencapsulate drugs and provide taste masking or modified release at a size that would be in the millimeter range down to fractions of a millimeter. When Adare acquired Orbis, what we were able to add is the ability to go even further down in particle size than before, and with greater uniformity, which translates into being able to include those particle sizes in different types of dosage forms.

For example, Orbis's technology Optimun® is a melt-spray-congeal technology meant for solid oral-dosage forms that can create very uniform microspheres and microcapsules a quarter of a millimeter in size or even smaller in a single step—which was a range that no other technology could get to, and that's certainly a range that Adare is now excited to offer.

With the acquisition, Adare also added Orbis's Stratum™ platform, which is geared mainly toward long-lasting injectable microspheres. Prior to the acquisition, Adare wasn’t active in the long-acting sterile-injectable space, but now they have that capability and the institutional knowledge behind it.

PHARMTECH: Describe a specific case or application for each of Orbis's platform technologies.

DORMER: For Optimun, Orbis's solid oral platform, we’ve been able to do multiple applications, including taste masking, extended release, and delayed release. One of the best things that Optimun can do is provide extended release in addition to taste masking.

If you look at the market, many of the extended-release pills that are available are 12-hour pills that last all day. And as an analog to that, you’d want to find dosage forms that are acceptable for little kids to take, or for people with swallowing difficulties. Traditionally, that’s meant moving toward a liquid. The problem is that long-lasting, 12-hour liquids just aren't freely available. It takes complex technology to make them, and the technologies that exist aren’t able to serve every molecule.

So with the Optimun platform, we’ve been able to take a 12-hour OTC pill and turn it into a 12-hour microparticulate suspension. That’s one of the better things about Optimun—it gives you that format flexibility while still maintaining performance.

For Stratum, our injectable technology, one of the most impactful avenues we’re exploring now has involved partnering with a women’s health company to develop a long-acting contraceptive.

If you look at contraceptive options available for women today, you have the daily pill, then you have a three-month Depo-Provera injection, and then you have implants that start at three years and extend longer. There’s really no option between three months and three years for patients.

So with Stratum, we’re working on developing a long-acting injectable contraceptive that can be used over six months or one year, which makes family planning a little bit easier for those who are looking for intermediate coverage in their contraception.

PHARMTECH: What is your perspective on the market for drug delivery technologies and how is Adare suited to address them?

DORMER: The trends we see in the industry include many pharma companies and therapeutics focused on chronic illnesses and diseases that affect a large number of patients, and then on diseases that affect a small number of patients, but in a very bad way.

What we have to remember is that when therapeutics are developed, companies focus on making sure that they have the safety and efficacy to address the problem so that patients can take them reliably while getting the outcomes they want. But sometimes a side effect of that is that these therapeutics may not taste very good or be very easy to administer, or that the regimens needed to administer the drug are less than optimal.

With Adare’s proprietary technologies around taste masking and modified release, we are well positioned to address many of the solid oral-dosage form problems that are present in the industry today. With the addition of Stratum, we’ll now be able to provide a different play on long-acting injectables to help our pharmaceutical customers even more.
Determining cybersecurity risks as a result of the ongoing pandemic is necessary for pharmaceutical laboratories complying with lab data integrity practices. Pharmaceutical Technology spoke with Bob Voelkner, vice-president of Sales and Marketing at LabVantage Solutions; Matt Grulke, vice president of Research and Development, also at LabVantage Solutions; Dennis Curran, BIOVIA portfolio technical director at Dassault Systèmes; and Paul Smith, strategic compliance specialist, and Humera Khaja, software compliance program manager, both at Agilent Technologies, about the best practices for maintaining lab data integrity during the COVID-19 pandemic while combating cybersecurity risks.

Precautions for security

PharmTech: What precautions need to be taken to protect lab data integrity and security during the pandemic?

Voelkner (LabVantage): As organizations deploy enterprise lab information management systems (LIMS) in their laboratories to digitize their operations, data integrity features and capabilities are vital in ensuring compliance. Documenting and protecting data maintained in online systems during the pandemic is a key solution to keeping the lab working and its data safe.

Grulke (LabVantage): Organizations also need to continue to elevate the importance and visibility of cybersecurity. Many organizations will deploy a comprehensive cybersecurity program that includes routine training of staff on common techniques, ongoing patching of systems to address known vulnerabilities, and the continued use of tools and frameworks to prevent, detect, and minimize cyber threats.

Curran (Dassault Systèmes): With many employees working remotely during the pandemic, biopharma organizations are under increased pressure to maintain the highest standards of data integrity, security, and quality. On the one hand, they are engaged in often multi-organizational, collaborative R&D initiatives to bring safe and efficacious therapeutics and vaccines to patients faster than ever. On the other hand, working remotely comes with many challenges related to accessing and sharing data securely. Increasingly, mobile teleworkers can inadvertently open the doors to bad actors who can access critical data and disrupt supply chains. As a result, organizations need to beef up their virtual private networks (VPNs) with robust system access logging. Who was in? When were they in and why? Were the activities approved, and by whom? Most importantly, organizations need to take precautions to ensure that project teams are sharing data securely. In this new, remote sharing ecosystem, is critical project data available to more people beyond just the involved project team?

Smith (Agilent): The pandemic resulted in all labs requiring the implementation of social distancing measures, as well as performing risk assessments associated with the potential impact and management of COVID-19 transmission within the lab. This constrained operations considerably, therefore, additional precautions were required to ensure that labs could continue, and to be compliant operationally with fewer lab personnel, and potentially reduced direct supervision.

Travel restrictions also limited external personnel such as service engineers from visiting labs to perform repairs, planned maintenance, and operational qualifications on analytical instruments. As a result,
GLOBAL CAPABILITIES

- Vials
- Pre-filled Syringe Assembly
- Safety Device Assembly
- Auto-Injector Assembly – Multiple Platforms
- Precise Labeling
- Dividella Top Load Cartoning
- Side Load Cartoning
- Cold Storage
- Phase 1 Sterile Clinical Manufacturing

THE PCI WAY

With over 22 years of experience in the packaging of biologic products, we deliver a consistently outstanding performance every time.
lab personnel may have had to perform these tasks while being remotely supervised, for example, via video link to the instrument manufacturer. With restricted service visits, it may have been necessary to utilize lab instruments outside of their scheduled maintenance or qualification tolerances, potentially impacting instrument performance and possibly data quality. Many non-essential lab staff, not able to enter their labs, were required to access lab systems remotely, which required closer attention to information technology (IT) infrastructure to ensure business continuity as well as data integrity.

Although all above mentioned actions were most likely supported by additional regulatory guidance and instructions related to the pandemic, labs may still have been exposed to unforeseen data integrity risks. To safeguard, it was essential that all deviations from standard working practices, and all controlled non-compliance with company policies, were well documented and subject to rigorous risk assessment to identify additional risks and implement additional safeguards to reduce the impact of these risks.

Areas of non-compliance

PharmTech: Since FDA has reduced inspections, what are you seeing as the top areas of non-compliance regarding lab data integrity during the pandemic?

Curran (Dassault Systèmes): To protect R&D data and avoid non-compliance with regulatory requirements during the pandemic, biopharma organizations need to pay close attention to lab procedures. Having procedures in place and following procedures can both be significant lab challenges in today’s new work environment. Organizations should assess standard operating procedures in the light of current working conditions to ensure that electronic reviews/approvals are properly structured and appropriate. This is especially important whenever paper-based organizations need to implement electronic workflows due to the pandemic. This can create a high-risk situation for regulatory violations by creating uncertainty around data.

Smith (Agilent): In response to the pandemic and travel restrictions, regulators issued communications confirming the halting of on-site inspections. This initially applied only to overseas inspections but was then extended to domestic on-site inspections due to potential risks to inspectors. This triggered a move to remote and office-based inspections using secure video links. One positive to this approach has been closer pre-audit sharing of data and information prior to the virtual audit. One not so positive consequence of remote audits was reduced capacity of the auditor to apply critical thinking skills to what they found during the ‘walk-through’ of the labs. The pandemic also drove regulators to be more reliant on risk-assessments associated with a lab’s historical regulatory footprint to prioritize virtual audits.

Voelkner (LabVantage): FDA has been transparent in documenting cases of data integrity problems. When labs come to us, they either want to avoid compliance-encountering issues or need to remediate known problems. The pandemic has amplified this need as labs accelerate their digital transformation plans.

Significant vulnerabilities

PharmTech: What have been the greatest vulnerabilities that companies face regarding lab data integrity during the pandemic?

Khaja (Agilent): During the pandemic and ensuing lockdown, virtually all labs were forced to embrace remote working conditions. Vulnerabilities labs have faced during this time have been to the maintenance of data quality and data security, which are the essential subsets of data integrity. Organizations’ data governance programs have had to re-evaluate their IT security, data quality, and data management policies and procedures, to mitigate these vulnerabilities. Though regulatory audits were significantly reduced in 2020 due to the pandemic, regulators still expected that laboratories’ electronic data and computerized systems should remain compliant.

The pandemic also exposed that labs changed the way their employees accessed, viewed, and processed results, and other critical eRecords. Lack of trust in the results, or outputs of data analysis, could be of concern. If the data is to be considered trustworthy and of high-quality, it must adhere to the principles of data quality.

Voelkner (LabVantage): Dealing with fully online and digital processes as compared to paper or spreadsheets requires the lab to adapt to commercial solutions and the rigor that compliance requires. Without a purpose-built LIMS solution that meets the current and future compliance needs of the regulated laboratory, labs face higher risk of non-compliance of data integrity guidelines.

Curran (Dassault Systèmes): Increased electronic workflows and remote access during the pandemic gives malicious actors more opportunities to penetrate networks and compromise critical data, whether it is testing data for a batch of new vaccine or a Raw Material Certificate of Analysis documenting the material make-up of a product. With this in mind, biopharma organizations need to ensure that they are operating with robust VPNs and data backups. Biopharma organizations have already expanded their IT footprint to support home workers and hybrid workflows (e.g., lab staff onsite and supervisors, reviewers, and quality assurance [QA] offsite). They should continue to review their hardware, contingency plans, and any new, extended networks for vulnerabilities, especially if further shutdowns occur. In addition, organizations storing data in the cloud should ensure that their hosting company is following appropriate security protocols and that there is adequate redundancy built into the system. Finally, organizations should monitor their supply chains closely, as well as machines and equipment that generate data to ensure that the data is accurate and trustworthy.
Enabling Streamlined Formulation Development of Amorphous Solid Dispersion Drug Products

Event Overview
Amorphous solid dispersions (ASDs) are an important technology for improving oral absorption of poorly water-soluble drugs. To achieve robust ASD drug products, pharmaceutical scientists must design ASD formulations to attain several key attributes including in-vivo performance, stability, and manufacturability while minimizing dosage form size. Combining knowledge of key drug, polymer, and gastrointestinal properties together with an in-vitro and in-silico toolkit is critical for achieving key attributes while reducing development timelines and drug substance requirements.

This webinar highlights best practices for streamlined development of ASD drug products using traditional and novel formulation architectures.

Key Learning Objectives
- Learn how custom and off-the-shelf in-vitro and in-silico tools can be combined to streamline ASD formulation development
- Gain knowledge about how drug and polymer properties, drug loading and dosage form architecture can influence ASD in-vitro and in-vivo performance
- Learn how to maximize drug loading in ASD dosage forms while still achieving good performance, stability, and manufacturability

Who Should Attend
- Industrial and academic pharmaceutical scientists and engineers, and consultants

For questions email kbarry@mjlifesciences.com
Migration to Prefabricated Cleanrooms

Prefabricated solutions can facilitate speed to market and drive down costs in biopharmaceutical manufacturing.

In the biopharmaceutical industry, there has been a shift away from on-site construction to prefabricated solutions. Peter Makowenskyj, Director of Sales Engineering at G-CON Manufacturing Inc., recently told Pharmaceutical Technology that speed to market and lower total cost of ownership for facilities has accelerated this movement in the biopharma sector. He also discussed the strain that the COVID-19 pandemic has placed on operations across the industry and how the situation is creating a need for additional capacity.

PHARMACEUTICAL TECHNOLOGY: What is one benefit of prefabricated construction that businesses might not know about or might not expect?

MAKOWENSKYJ: When people think of prefabricated construction, they often associate it with speed to market and risk mitigation. What sometimes gets overlooked is that prefabricated solutions can provide significant financial benefits. They are considered to be a piece of equipment, and this allows for accelerated depreciation over typical onsite or modular construction that has been more of the historical pathway in our industry. Traditional fixed installed infrastructures are depreciated for 30–40 years because they are considered to be part of the facility for tax purposes. Prefabricated, modular and mobile cleanroom units are depreciated as equipment during a period of 7–8 years (1). Also, there are advantages for people looking to preserve cash flow because this equipment can be leased.

PHARMACEUTICAL TECHNOLOGY: What are some growing practices in prefabricated construction for cleanrooms and facility design in general?

MAKOWENSKYJ: About 5–10 years ago, only a few key players specialized in prefabricated cleanrooms. More recently, we’ve seen multiple companies enter this space. This shift is being driven by demand in our industry to move to prefabricated solutions. We’re also seeing interest in adaptation to standardized and pre-engineered solutions, which typically facilitate speed to market and can drive down costs. This follows some general trends we saw years ago on the equipment side where people were looking to avoid the complexities involved in custom bioreactor and custom crossflow projects and moved toward standardized solutions. That’s definitely becoming more prominent in our space.
PHARMACEUTICAL TECHNOLOGY: What about the opposite end of the spectrum? What do you think is an outdated practice in construction?

MAKOWENSKYJ: Historically, cleanrooms have been viewed as a commodity item, but this situation has been changing because of technological advancements in our space and the market drivers associated with that. It’s not just about minimizing upfront cost per square foot, specifically on the cleanroom side, so we are seeing a dramatic shift in how cleanrooms are being designed and supported. In addition, some outdated practices are still in use today. There are still many projects where the actual work is being farmed out to multiple subcontractors that specialize in their space. But it is difficult to maintain oversight over these skilled labor forces, especially those that are not specialized in the biopharmaceutical space. This practice negatively impacts project schedules and project budgets.

PHARMACEUTICAL TECHNOLOGY: What are the most important parts of the company-client relationship that can ensure success?

MAKOWENSKYJ: Communication often gets overlooked as a project progresses. As simple as it sounds, communication, or lack thereof, can turn a project from a success to a disaster. Each client we work with has different process needs and preferences for how they like to interact on a project level. We need to ensure that we can adapt effectively to communicate with them in their preferred methods and means. Communication is critical to ensuring success for a project.

PHARMACEUTICAL TECHNOLOGY: Have you seen an increase in interest from businesses looking to prevent infection because of the pandemic?

MAKOWENSKYJ: Yes, disease prevention is critical and many have seen the risks associated with operating in an uncontrolled environment. Many policies have to be put in place to ensure risk is reduced and infection is mitigated. Unfortunately, this will lend itself to efficiencies being impacted on a project level. Moving to a controlled environment as opposed to on-site construction allows for reducing risk and maximizing operating efficiencies when designing and building a cleanroom environment. This will allow for de-bottlenecking the constraints of on-site construction because you can have now multiple swim lanes that will have little to no overlap as you can work through them. It’s a more effective way to deal with the constraints of personal space and mitigate overlap of workers in the field.

PHARMACEUTICAL TECHNOLOGY: How do you see the market rebounding after the pandemic?

MAKOWENSKYJ: We have seen an increased demand in the cleanroom space to alleviate the constraints around COVID. Sites that weren’t focused on manufacturing vaccines or treatments for COVID now are and they need additional capacity. There is also a pent-up demand for other projects that were put on hold. We anticipate that they will be released slowly and those projects will take hold. As a whole, the cleanroom space—the facility design space—has actually seen some positive impacts.

References
Where, for some, JIT may conjure images of slashing inventories of urgently needed medications, in clinical trial operations, it signals the move to a less wasteful distribution model. Under the old “push” model, an innovator would announce that it was enrolling patients for trials at, say, 100 sites, and supplies would be sent to all of those sites, Jacobs explains. In the end, however, the Pareto principle would usually rule, and 20% of sites would end up enrolling 80% of the patients. “These days, especially with oncology trials and comparator drugs that cost millions of dollars, we can’t have materials sitting in depots or on sites and not being used. These are all key factors that continue to make JIT extremely advantageous,” he says.

With JIT, distribution is based on a “pull” approach. A master document is created in advance, and all packaging and labeling is standardized so that it can be made on demand before being shipped to the clinical site or patient’s home. The economic motivation for JIT is compelling. According to Frost and Sullivan, one third of global clinical trials were disrupted in 2020, affecting some $3 billion in new product revenue (1). Benefits of a “pull” approach include a 75% reduction in overall clinical trial timeframes and reduction in waste and rework, according to Natalie Balanovsky, JIT Solutions Manager at Almac Clinical Services (2). This is especially important in an environment in which each day of delay in a clinical trial costs $37,000 and between $600,000 and $8 million in lost opportunities (3). Research has shown that 85% of all clinical trials experience some kind of delay, 94% of them for a month or more (4). On the logistics side, Marken has been applying pull concepts to maximize the flexibility of its clinical trial sourcing, increasing the number of supply options available to clients, according to Nina Vas, vice-president of clinical distribution for cell and gene therapies, who discussed trends in a February 2021 webcast (5). For direct-to-patient distribution, which has become much

The COVID-19 pandemic is pushing more companies to adopt just-in-time practices, but success demands careful upfront risk assessment and planning. Like many business practices brought to the world by Japan in the 1980s, just in time (JIT) brought agility to many industries. For pharma, however, the term often triggers fear and loathing, given chronic and ongoing shortages of comparator drugs and investigational medicinal products (IMPs).

Since the COVID-19 pandemic began, however, more companies have been embracing JIT for clinical trial supply and distribution operations. Both the unique challenges posed by the pandemic and the European Union’s new Annex VI clinical trial labeling regulations have been driving this change. In the past, labels were only required on secondary packaging; however, the new regulation will require labels on both secondary and primary packaging (i.e., the vials, blisters, and metered dose inhalers containing the therapeutic), explains consultant Steven A. Jacobs, president of Global BioPharm Solutions.

Under the regulations, if new stability test data dictate the need to update a label for primary packaging, patient kits will need to be opened, which would be considered a manufacturing process requiring certification by a qualified person (QP), Jacobs explains. However, pharmaceutical QPs are not at clinical sites, so this impasse could potentially affect product quality and supply.

Meanwhile, pandemic-driven changes in clinical trial design, including greater use of pooled trials and direct-to-patient (DTP) distribution, have piqued interest in JIT. “Companies are shifting to smaller packaging runs and pooling supplies to get supply chains running as efficiently as possible,” Jacobs says.
cGMP Manufacturing. Sterile and Non-sterile.

- Formulation Development for Poorly Soluble Drugs
- cGMP Manufacture for Clinical Materials
- Parenteral, Topical & Oral Solids Dosage Forms

ASCENDIA PHARMA

OUR TECHNOLOGIES

EmulSol
AmorSol
NanoSol

P: 732.640.0058
E: bd@ascendiapharma.com
ascendiapharma.com
more important during the COVID-19 pandemic, the company relies on strategically placed regional and global networks of depots throughout the world.

Despite its benefits, JIT cannot work without early collaboration, communication, and planning. For one thing, Jacobs says, it’s crucial that all packaging to be used in any clinical trial be in the same configuration. He recalls one clinical trial that started with 2-mL vials but then switched to 2-R vials. Even though the two types of vial are similar and R vials offer some improved capabilities, changing midstream added significant complexity because placebo vials had to be manufactured to match the new vials.

“There are so many different configurations for drug delivery that it can be difficult to do JIT without standardizing. We need to get everyone to agree, early on, on what packaging will be used; how we get the new drug to the patient; and how patients will take the treatment once they receive it,” Jacobs says. Once agreement is there, he says, JIT principles can be applied to any operation from filling to labeling and kitting.

Early risk-assessment needed

Risk assessment needs to be conducted as soon as possible in the planning stages, says Jacobs, which is much easier said than done when a company is under pressure to meet the types of clinical targets that have been set during the COVID-19 pandemic. He suggests following the principles outlined in the International Council for Harmonization’s (ICH’s) Q9 guidance on risk-based quality management and assessment (6), and gathering all stakeholder groups together for a brainstorming session to ask: What’s the worst that can happen; how likely is it to happen; and what can we put in place to prevent it from happening, or to mitigate the risk?

For the contract development and manufacturing organization (CDMO), Catalent, risk assessment and mitigation has been crucial to ongoing trial successes, says Stephanie Graham, director of clinical supply management. For ongoing studies, she says, the primary focus has been on whether it is safe for patients to continue to visit sites, especially those who might be at greater risk if they contract COVID-19. She also notes the importance of determining whether the frequency of planned visits is necessary.

Challenges drive innovation

Clearly, it became extremely difficult to conduct clinical trials after the pandemic’s impacts were first felt in the second quarter of 2020. The combination of uncertain patient visit scheduling and transportation disruption forced sponsors and their contract partners to perform a delicate balancing act: preventing supply wastage while ensuring that enough buffer supply was available in case of shipment delays or country lockdowns, says Graham. For trials that were still recruiting patients, enrollment slowed, driving the need for specialized packaging campaigns to extend the shelf-life of IMPs, she says.

In 2020, the number of countries accepting Direct-to-Patient distribution for clinical trials nearly doubled, enabling improvements in safety and efficiency.

Sponsors had to make hard decisions about which studies should continue and which should be delayed or canceled altogether. “For those studies that can progress, we have jointly had to answer how, why, and with what changes. Sometimes it has been necessary to explore alternative strategies, such as using decentralized trial designs to reduce risk and maintain continuity,” Graham says.

Raw material availability also posed problems, resulting in the need to manage shipment delays caused by disruption in raw material production or transportation disruption for normal routes, explains Mathias Dassel, storage and distribution manager for Catalent, based in Germany. “Distribution of pharmaceutical supplies could take longer than expected, and transportation costs may increase for high-risk regions when import/export restrictions are introduced because of the pandemic. In such cases, it has become extremely important to manage supplier and courier relationships effectively,” he says.

At the height of the COVID-19 pandemic in 2020, the number of daily commercial flights—which are used to ship 70% of the medicines used in clinical trials—was reduced to 10–15% of its pre-pandemic levels, says Jacobs. Fulfilling orders required more time, he says, typically two to four weeks, instead of the two-to-four-day pre-COVID norm. Some companies even booked chartered flights at a cost of over $100,000 each time, to ship their medications, Jacobs says. “We’re now at 25–30% of where [commercial] flights were before COVID-19, but gaining global acceptance for DTP was an amazing achievement,” he adds.

Focus on ongoing trials

Sponsors and contract partners first began to see a major increase in delayed patient visits in China, from January through April 2020, says Sylvain Berthelot, global head of IRT (interactive response technology) and electronic data capture (EDC) solutions for Calyx. His company, an e-clinical and regulatory solutions provider, was spun off by Parexel and became an independent firm in January 2021. “In Italy and Spain, for example, we didn’t see the same number of delayed visits in the Spring of 2020, despite lockdowns, because sponsors focused efforts on en-
ON-DEMAND WEBCAST
Aired: Tuesday, March 9, 2021

Presenters

Dr. Eszter Paldy
Product Manager,
Premium Weighing Solutions
Sartorius

Dr. Holger Densow
Product Manager,
Software Solutions Lab Balances
Sartorius

Moderator

Amber Lowry
Senior Editor
Special Projects

Compliance, Data Integrity and Software-based Workflow Guidance in Today's Lab

Event Overview
Correct data is fundamental in a GxP quality system. This webcast will introduce the ALCOA principles and discuss how data integrity can be achieved. Participants will be guided through FDA warning letters about the most frequent and most typical violations and shown how the Cubis II laboratory balance from Sartorius provides the technical features necessary to automate processes and avoid data integrity compliance issues. Software applications, such as Tablet or Vial Checker and Standards Preparation, and how they ensure safe guidance, will also be discussed.

Key Learning Objectives
• How to ensure data integrity and minimize the risk for an organization
• How a laboratory balance can support full pharma compliance without the need for additional software
• How software applications with guided workflows help to achieve trustworthy and compliant results

Who Should Attend
This webinar is most relevant for lab managers, quality managers, staff scientists, lab supervisors, department heads, and research scientists working in pharma, biopharma, biotech, private research institutes, or CRO labs.

For questions email mdevia@mjhlifesciences.com

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

Sponsored by
Presented by
Sartorius

Pharmaceutical Technology
For personal use. Commercial use prohibited.
suring that patients were supplied with medications directly,” Berthelot says.

Changes in trial methodology, in the context of the unfolding COVID-19 pandemic, also had a major impact on clinical trial operations. With some clinical testing being done in parallel, Berthelot says, sponsors were using more master protocols, which allow different compounds to be tested on the same group of patients or vice versa. “These protocols enable more program-level supply management, which reduces drug wastage, but make managing medications more complex, both for sponsors and for IRT systems, [used to manage clinical trial patients and supplies]” he says.

**Increased acceptance for DTP**

In the end, one of the most dramatic changes that occurred in clinical trials supplies and distribution during the pandemic was higher acceptance and demand for DTP shipments. The DTP model eliminates a major problem with clinical trials: getting patients on site consistently, without attrition, says Jacobs.

For years, many in the industry had discussed decentralizing trials, and regulators such as FDA and the European Medicines Agency supported the idea. The model was accepted in the United States, yet the pace of its adoption around the world was slow before the pandemic, says Jacobs. After the COVID-19 pandemic began, however, countries such as Italy and Russia, that were originally very resistant to the DTP concept turned around. Out of 195 countries, the number of those permitting DTP shipments doubled, to over 90 in 2020, he says. “This was amazing to see, and on the clinical operations side, we are all supporting this trend to make sure that we don’t go back to the old ways,” Jacobs adds.

Another achievement was increased acceptance of JIT and on-demand packaging, and more use of planning, forecasting, and simulation tools, says Jacobs. For both sponsors and contract partners, flexibility has become key, as have proactive and clear communication and collaboration, Graham comments. Where possible, she says, DTP services can limit the need for patients to visit drug dispensing sites, allowing DTP and site-to-patient distribution strategies. For new trials, building such supply strategies within the protocol, the randomization and trial supply management, and the IRT design allow flexibility to minimize risk in the future, she says.

However, that flexibility should have some limits, Graham says. “Some sponsors are providing patients’ full treatment supply at the first visit. Although this approach can work, it is not optimal for an investigational product with a limited shelf life, or one that requires temperature monitoring. It is up to CDMOs and clinical supplies managers to work collaboratively with customers to determine the optimal solutions that work best for patients, sites, and the sponsor,” she adds.

Since the start of the pandemic, Graham has seen more sponsors use adaptive designs in clinical trials. In addition, she remarks, many are exploring ways to provide healthcare remotely through DTP or site-to-patient distribution strategies of the clinical trial material/investigational drugs. For biologic drugs, she also sees greater use of autoinjectors for non-COVID-19 therapies, and IRTs built to handle the additional functionality required. In terms of small-scale manufacturing, Graham says, Catalent has developed manufacturing processes that permit switching to different batch sizes using the same manufacturing lines to meet the challenge to scale production up or down quickly.

**Breaking down silos**

For a risk-averse and often siloed industry, Pharma made great progress in removing the barriers that can separate different stakeholders in clinical trials management and operation. In a typical scenario, Jacobs says, clinical operations used to be in one area, and chemistry, manufacturing, and control in another, with the clinical supply chain department functioning as the bridge to success. During the pandemic, says Berthelot, “vendors and sponsors are functioning more as part of a single team.”

That all this change could take place during a time when people didn’t meet face to face is significant, Jacobs says. “Before the pandemic, one could hear ‘weak signals’ of developing problems, just by overhearing snippets of conversation in the hallway or cafeteria. This gave teams more time to plan remediation. You can’t do that on Zoom,” he notes. There is also more acceptance of the concept of clinical operations as a work in progress, and an understanding that procedures may have to change.

“A few years back, sponsors used to wait until they had the perfect protocol before starting a trial. Now they’ll start recruiting for a trial that they know that they will have to change,” Berthelot says.

On the technical side, better integration between IRT and EDC has seen substantial improvement, reducing errors and the need for data reconciliation between the two systems, and enabling more automation, says Berthelot.

In the future, he sees technology playing a more important role. “Real-world data are already becoming incorporated into more clinical trial designs. Use of machine learning will improve patient recruitment and site selection, and, from the supply chain perspective, will help reduce drug wastage and better identify risks that could have an impact on the supply chain,” he says.

**References**

The Importance of Titrations in Pharmaceutical Analysis: From the Basics to the Modern Method

Event Overview

Titration plays an important role in pharmaceutical analysis. Despite the recent attention given to chromatographic methods, several applications are only feasible by titration, making it a fit-for-purpose method for many analytes. For example, distinguishing between carbonate and bicarbonate or monobasic and dibasic phosphate salts can only be accomplished by titration.

Another example for the importance of titration in pharmaceutical analysis is water determination by Karl Fischer (KF) titration. This technique is highly selective for water and sensitive enough to reach the ppm level. While the industry is already utilizing modern KF titration instruments, many USP monographs still refer to the manual visual endpoint titration methods for other applications.

In this session, pharmaceutical and titration experts come together to review the basics of pharmaceutical titration and explain the benefits of converting to a modern, autotitration analysis method. The live event includes time for a live Q&A where you can pose your specific questions to the experts.

Key Learning Objectives

• Understand the difference between manual titration and autotitration for pharmaceutical samples
• Learn how an electrode works and its role in a pharmaceutical titration
• Get your specific questions answered by titration and pharmaceutical experts

Who Should Watch

Please plan to attend if you:

• Use titration on pharmaceutical raw materials or finished products
• Want examples of what pharmaceutical titration procedures look like on an autotitrator
• Want information on how to improve accuracy and reliability of manual titration results

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

ON-DEMAND WEBCAST
Aired: Wednesday, February 24, 2021

Presenters

Dr. Margareth R. C. Marques
Principal Scientific Liaison
USP

Dr. Kerri-Ann Blake
Titration Product Manager
Metrohm USA

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions email kbarry@mjhlifesciences.com
transferring liquid formulations into lyophilized products can potentially improve thermal stability and reduce the need for cold-chain handling. Recipharm’s site in Wasserburg, Germany, for instance, successfully developed and implemented a lyophilization cycle that can freeze-dry a COVID-19 mRNA vaccine. “Initial results indicate that the lyophilized product has a significantly improved thermal stability profile in comparison to the liquid formulation,” Becker says.

The need for formulation improvement, however, creates its own challenges for vaccines being used to treat emerging infectious diseases, especially in the case of pandemics, where speed is of the essence, according to Welch. “Opportunities to increase stability that involve substantial revision of the final formulation may require additional and extensive clinical trials to establish efficacy and safety along with revalidation of the drug product production process.”

Still a place for traditional vaccines
While there are many advantages to genetic vaccines, there are also many reasons why traditional vaccine approaches will continue to be used. “Traditional vaccines have been on the market much longer than genetic vaccines and, in most cases, can currently be made at a significantly lower cost,” Bleck. “Over time,” he adds, “these technologies have evolved to adapt to changes in the viruses that they protect against. In addition, if necessary, multiple antigenic proteins in certain ratios and configurations can be expressed to get the correct epitopes produced for a neutralizing immune response, which is currently difficult to achieve in genetic vaccine formats. Furthermore, getting adjuvants to work effectively with genetic vaccines can also be difficult.”

Traditional approaches might be preferential when preclinical animal studies indicate that an effective vaccine requires the presentation of an antigen or antigens in a complex structure that cannot be engineered or can only be effectively and reproducibly done using the entire infectious agent, a company spokesperson from Janssen Infectious Diseases & Vaccines says. In addition, when the protective antigens are not known for an emerging pathogen, traditional approaches incorporating the entire pathogen (live or killed viral vaccines) may be required until a firm understanding of protective immune responses is established, Warfield notes.

Furthermore, Becker points out that traditional approaches allow the combination of vaccination agents for different diseases, which may not be possible for genetic vaccines for the foreseeable future, as they are less robust. “With this in mind,” he says, “traditional vaccines may be more appropriate not only to address a wider variety of mutations of one virus type in one vaccination, but for routine vaccination programs against different diseases.”

Finally, Warfield notes that killed virus, protein, and VLP vaccines potentially have the advantage of more temperate storage requirements compared to some live virus- and genetic-based vaccines, which can be particularly important in remote areas and developing countries that lack the necessary cold-chain infrastructure.

But genetic vaccines are creating real excitement
The arrival of the new class of genetic vaccines heralds an exciting time in vaccine development, asserts Becker. “This new technology offers a number of promising routes to help us not only enhance infectious disease prevention, but to progress the fight against other serious diseases, such as cancer,” he says. The fact these vaccines can be manufactured in standard multi-product facilities, rather than on specialist sites, will also enhance efficiency for pharmaceutical companies and offers greater scope for maximizing vaccine production capacity in the event of future pandemics.

Process and product regulations for genetic vaccines and viral-vectored vaccines still have to mature, however, as the technologies thus far have only recently produced commercially viable products that have been approved by stringent regulatory agencies like FDA and EMA. “Our expectation is that both technology regulations and platform regulations will evolve over the next several years,” says a company spokesperson from Janssen Infectious Diseases & Vaccines.

As more genetic vaccines become available, Welch envisions a shift to their use not only for pandemics, but also for existing and emerging infectious diseases. “Such as shift could enable companies to decrease time and cost, at least for manufacturing development, from inception to market,” he notes.

New advances in mRNA vaccines and other novel vaccines may indeed mean that we are entering into a new “golden age” for vaccines, according to Christy, but with the caveat that important work remains to be done to ensure global access, adequate capacity, and ease of administration, as well as education to ensure widespread uptake. He also notes that effective vaccines have yet to be developed for many well-known viruses, and more than 80 emerging viruses have been identified since 1980, with two novel viruses appearing every year. “Despite recent successes, much remains to be achieved to protect humanity,” he insists.

In addition to novel genetic vaccine technologies, Christy is excited about mucosal vaccines that aim to boost local immune memory and effector responses at the point of entry of pathogens and mRNA vaccines in development as cancer vaccines, intra-tumoral immune-oncology therapies, and localized regenerative therapies. Other cancer and T-cell vaccine are in development to treat antibody evasive viruses, and existing vaccines are being re-developed to provide better protection and coverage.

“Ongoing global pre-investment by governments, private foundations, and other groups will be needed to drive further advances in technology, manufacturing capacity, and infrastructure that will enable effective response to epidemics/pandemics going forward,” Christy concludes. PT
supply chain scenario. Yes, the applicable GDP regulations differ from one jurisdiction to another and from one country to the next. One goal, however, is common to all, namely the protection of the patient from products that are adulterated, be it from inappropriate storage or transport conditions, or from falsified products entering the supply chain. Your audits need to evaluate if your service providers have everything necessary in place to assure that goal. Their licences will support that assertion but it will be your audit that proves it.

References

1. 21 Code of Federal Regulations 210, 211.
5. CFDA, Good Supply Practice for Pharmaceutical Products (China Food and Drug Administration Decree No. 13) Issued on July 1, 2015.
Q. We have updated our vendor audit program for 2021, and the list includes several companies that perform transport and warehousing services for us. This is a new area for us, and given the continued travel restrictions, we are not certain how best to audit these companies. Can you give us some direction?

A. Good distribution practices (GDPs) are required by regulators in most regions. The United States is different from all other agencies as there are no separate GDP regulations in place. FDA covers violations of storage and distribution under GMP violations (1). The European Union has codified GDP in two directives (i.e., community law, which has been transposed into member states law) (2–4). In China, GDP is the law, they call it Good Supply Practice (5–6).

Service providers for the storage and transport of goods will have to comply with different regulations, based on their location and the specific type of services they provide. Generally, these companies will have to comply with GDPs. This means that it is essential to have a clear and unambiguous understanding and documentation of the precise nature of the services.

Let us look at an example for illustration: company A (headquartered in Germany) performs the road transport of drug substance and drug product from your warehouse in Switzerland to company A’s warehouse in Germany, where the goods are relabeled, picked, and packed for distribution to wholesalers in the European Union. Based on these activities, which include wholesaler activities, such as importation, storage, and transport, company A must hold a respective licence from the German authorities.

If you cannot audit on site, you have the possibility to perform a virtual audit via videoconference instead. Irrespective of the mode of audit, preparation is essential. This includes a detailed audit agenda, which in this case may look something like this:

- Opening Meeting
- Facility and Site Overview
- Virtual Facility Walkthrough
- Documentation Review
  - Quality system and management review
  - Personnel qualification and training program
  - Self-inspection management
  - Deviation management
  - Change control
  - Customer management
  - Subcontractor management including quality agreements
  - Inventory management control system
  - Recall management
  - Complaints management
  - Returns management
  - Shipping route validation, including security and risk management
  - Cold chain and ambient temperature shipping management processes, including vehicle qualification.

The three items in bold letters are those you may wish to focus on particularly, because the vast majority of service providers subcontract all transport. Subcontractors merely performing transport may not even have to comply with the GDP regulations by law. They may not even have a quality system, yet they are transporting your goods. You really want to make sure that company A, with which you have your contract, has a good system of subcontractor oversight. Such oversight may have to include training of the transport company’s staff in aspects of security and documentation (particularly with regards to temperature records).

The best way to understand who performs what activity in a supply chain is to follow it step by step.

In fact, the best way to understand who performs what activity in a supply chain is to follow it step by step. Request supporting documented evidence for each step. This way you will be able to fully understand who is involved, which procedures govern these activities, and how these are documented.

The previous example may not necessarily apply to your situation, but the principles are the same for any other
In drug manufacturing, every day a facility project is delayed can mean that the needed capacity is not available, putting more patients at risk. At G-CON, we reduce the design, build, and delivery time of operational cGMP cleanroom environments from 1-2 years to 3-6 months so that companies can supply life saving medications faster than ever before. Our prefabricated and prequalified turnkey cleanroom systems (PODs), allow for scaling without interruption, minimizing the impact on existing operations and reducing the risk of delays, helping to ensure that drug products are available for the patients that need them.

**Viral Vector POD Key Features & Benefits:**

- Robust containment with localized AHUs
- Utilize local or integrated VHP systems for effective turnover of campaigns
- Add an additional USP/DSP suites without impacting existing manufacturing
- Established platform designs for AAV and Lentivirus
- Scale up or out while reducing risk

Let us help you get therapies to patients faster.

www.gconpods.com | sales@gconbio.com | 979.431.0700
Successful cell & gene therapies are built on innovative cellular science, viral technologies and the art of orchestrating fast and scalable manufacturing processes.

Catalent's proven expertise across multiple cell and viral modalities, development technologies and accelerated scale-up to commercial supply, help turn your science into approved treatments.