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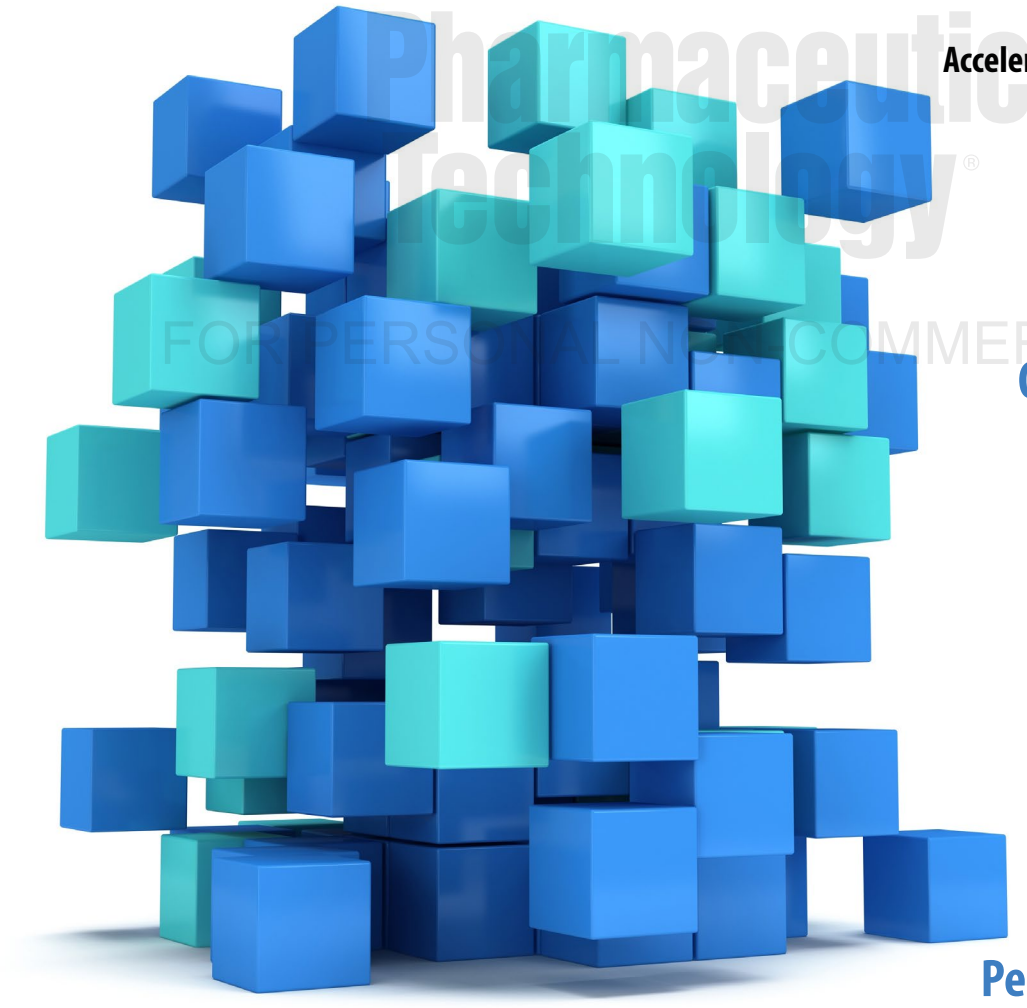

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On the cover

COVER STORY

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FEATURES

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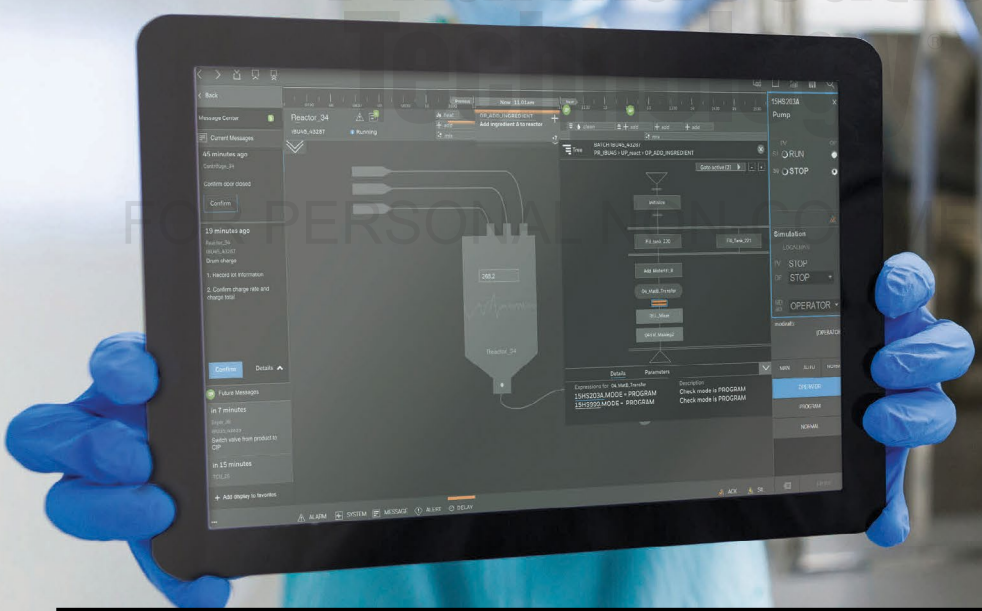
PEER-REVIEW RESEARCH

SUPPLEMENT

Be sure to read this month's Solid Dosage Drug Development and Manufacturing supplement for coverage on OTC drugs, tableting, and more!

PATIENTS ARE WAITING.

Modernizing Technologies in Manufacturing:
Is the Gain Worth the Pain?



Be the First to Know. Sponsored research from Axendia details drivers and adoption of technologies such as AI, machine learning, IoT, and virtual reality for life sciences. The report will tackle questions such as: What forces are supporting facility modernization? Which segments are finding new technologies a better way to go to market? What are executives looking for in new solutions? What factors effect rate of adoption? Results released during INTERPHEX 2020. Visit **www.honeywellprocess.com/lifesciences** after May 4.

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86 Critical Knowledge for Preparing Audits

Addressing data integrity, quality culture, aging facilities, investigations/corrective actions and preventive actions, and risk management is key when conducting audits, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

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PHARMACEUTICAL TECHNOLOGY (Print ISSN: 1543-2521, Digital ISSN: 2150-7376) is published monthly, except two issues in June, by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512. Subscription rates: US and possessions — 1 year (13 issues), $79.80; 2 years (26 issues), $139.65. Canada and Mexico — 1 year, $103.95; 2 years, $158.55. All other countries 1 year, $152.25; 2 years, $276.15. International price includes air-expedited service. Periodicals postage paid at Cranbury, NJ and additional mailing offices. POSTMASTER: Please send address changes to Pharmaceutical Technology, PO Box 457, Cranbury, NJ 08512-0457. PUBLICATIONS MAIL AGREEMENT NO. 40612608, Return Undeliverable Canadian Addresses to: IMEX Global Solutions, P. O. Box 25542, London, ON N6C 6B2, CANADA. Canadian G.S.T. number: R-124213133RT001. Printed in the U.S.A.

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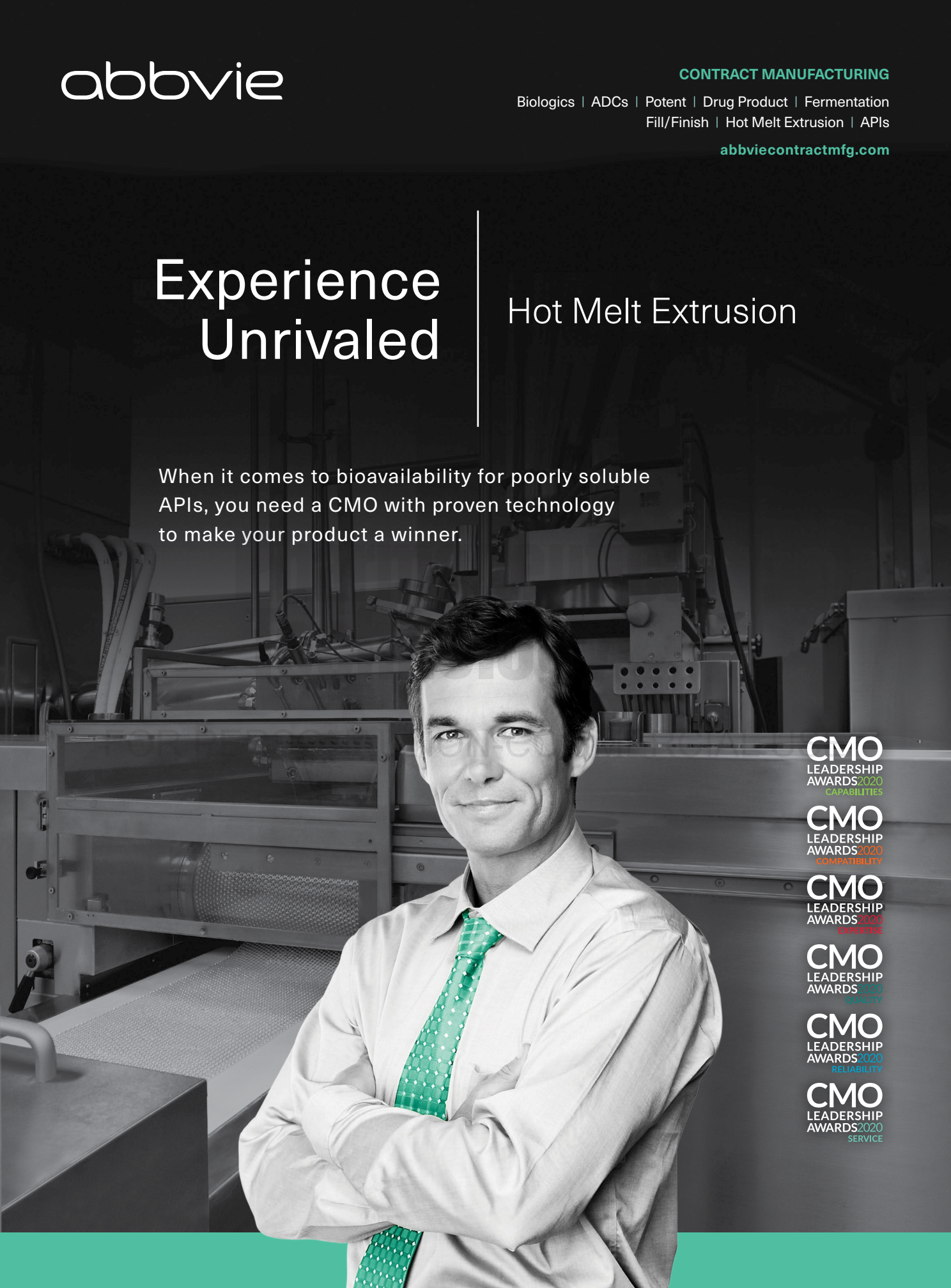

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Pharma's Leadership Role in a Pandemic

Rita Peters

As the coronavirus pandemic unfolds, Pharma must practice science over hype.

The coronavirus pandemic is sweeping around the globe at a rapid pace, forcing governments, regulatory authorities, healthcare systems, and the bio/pharma industry to take novel measures to address the crisis.

Some public health officials and doctors sounded early alarms about the spread of a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—in January 2020; however, many people and governments did not heed the alarms or were slow to respond to the spread of coronavirus disease (COVID-19).

During the past few weeks, public sentiment has ranged from denial (crowded beaches during Spring Break) to panic (hoarding toilet paper). A new term—social distancing—became part of our vocabulary. Everyone was reminded about proper handwashing techniques. And kitchen tables and spare bedrooms became home offices and classrooms as governors ordered major segments of the population to stay home.

As politicians weigh protecting public health versus the impact on the economy, medical professionals beg for adequate supplies of face masks and ventilators. Meanwhile, many drug companies and research organizations have announced R&D efforts to test approved therapies as treatments to minimize the effects of COVID-19. The research focus of drugs in development has been redirected to target coronavirus symptoms. And, groups around the world have accelerated efforts to develop much-needed vaccines.

Following initial criticism for delays in approving diagnostic testing to detect who had the virus, FDA stepped up its activity, issuing more than a dozen guidance documents in March 2020. Actions included issuing emergency authorizations for diagnostic test and ventilators, easing regulations for remote monitoring of patients and clinical trials, allowing the compounding of hydroxychloroquine sulfate under certain conditions, releasing guidance for the preparation of hand sanitizers, and facilitating access to COVID-19 convalescent plasma for use in patients with life-threatening infections (1).

The immediate goal is to "flatten the curve" of new cases of COVID-19 to reduce strain on the healthcare system. Staying home, avoiding crowds, and washing your hands are simple measures we all owe the medical professionals, first responders, grocery store clerks, delivery services, transportation workers, and others on the front lines of maintaining our basic needs to get through this crisis.

Obviously, these non-pharmaceutical measures are only part of a temporary solution; therapies are desperately needed to treat COVID-19 patients, and vaccines ultimately required for long-term control of the virus. Bio/pharma researchers, development and manufacturing professionals, and companies supporting drug development and manufacturing are essential to these efforts.

At the same time, patients still need effective, affordable therapies to treat chronic diseases, cancers, and other conditions. A reliable drug supply is vital to maintain health and alleviate public concerns.

During the past few weeks, we have learned about many drugs and vaccines as potential cures. The world could use a "magic pill" right now. But drug developers know the challenges of working the science and producing the data to ensure that the therapy is safe and efficacious.

One challenge for those in the bio/pharma industry is to avoid using excessive hype about a potential therapy, which can create false hope. Now is the time to lead with the message that science—not hopes or gut feelings—should drive all healthcare decisions.

The *Pharmaceutical Technology* team thanks those working to develop new treatments and vaccines and those maintaining the drug supply; we are here to support those efforts. In addition to our normal coverage of all phases of drug development and manufacturing, we offer added coverage of COVID-19 drug development programs, links to research, industry suppliers, and regulatory updates. Visit *www.PharmTech.com* for the latest news, updates, and access to an archive of previous issues.

Stay safe, stay healthy, and we wish you success in your drug development efforts.

Reference

1. FDA, Coronavirus Disease 2019 (COVID-19), *www.fda.gov*, accessed March 26, 2020. **PT**

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rpeters@mjhlifesciences.com.

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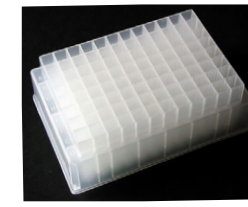

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Biosimilars Poised for Gains in US Market

Jill Wechsler

FDA is encouraging alternative insulins and challenging anticompetitive practices.

The 10th anniversary of the enactment of the Biologics Price Competition & Innovation Act (BPCI) in March 2020 has focused attention on the advances made over the past decade and main challenges ahead. Despite general disappointment over the slow pace of consumers gaining access to less costly biotech therapies, new FDA guidance and clarified policies provide added support for biosimilar development and approval, particularly for diabetes treatments. FDA also has teamed up with the Federal Trade Commission (FTC) to counter anticompetitive practices that thwart development and raise concerns about biosimilar safety and effectiveness.

A positive sign is that the pace of FDA approvals of biosimilars has picked up in recent months, with more than 26 approved products as of early February 2020—10 approved in 2019—and more than a dozen competitors on the market. In addition, the World Health Organization has begun to prequalify biosimilar versions of "essential medicines" to make these treatments more available and affordable in less developed countries.

Insulin competitors

An important FDA initiative aims to encourage manufacturers to prepare the data needed to support applications for follow-on versions of insulins now deemed to be licensed as biologics and thus eligible for competition from biosimilar or interchangeable therapies. In February 2020, FDA issued a final rule defining the new process, as established by the BPCI and revised in legislation to clarify that the deeming process applies to insulin, human growth hormone, and most proteins—specifically any alpha amino acid polymer with the specific, defined sequence greater than 40 amino acids in size (1). The new rule aims to "bring down prices and help patients have access to more choices for these life-saving drugs," said FDA Commissioner Stephen Hahn. FDA also issued explanatory documents for consumers (2) and physicians (3) to clarify that treatments approved under the new program will be just as safe and effective and accessible as brand insulin reference therapies.

Efforts to bring insulin competitors to market builds on FDA guidance issued in November 2019 outlining a streamlined development pathway for these long-established therapies (4). That advisory proposes reduced clinical immunogenicity studies for products that present strong comparative analytical assessments demonstrating high similarity to the reference drug, and no residual uncertainty regarding immunogenicity. In May 2019, FDA provided detailed advice on designing and evaluating such analytical studies and on providing scientific and technical information for the chemistry, manufacturing, and controls (CMC) portions of an application for a biosimilar in draft guidance (5). At that same time, FDA published long-awaited guidance on developing interchangeable biosimilars, again noting the importance of analyzing critical quality attributes and identifying analytical differences between the reference product and the proposed interchangeable (6).

Misinformation crackdown

The FDA–FTC initiative further aims to encourage prescribing and reimbursement for biosimilars by taking aim at "misinformation" campaigns backed by brands to discourage biosimilar uptake. The regulators outline how they will work together to promote competitive markets for biological products that "contribute significantly to drug costs," noted Commissioner Hahn (7).

The two agencies also offered to help biosimilar makers gain ready access to samples of reference products needed to develop and test follow-ons—a difficulty that also has plagued the broader generic-drug industry. And FTC is taking a close look at patent settlement agreements involving biologics and biosimilars to detect any antitrust violations. A joint public workshop held on March 9, 2020 addressed these efforts and other strategies to build a more competitive market for biological products.

In a related move, FDA also published guidance in February 2020 outlining the process for seeking FDA approval of a subset of approved in-

Jill Wechsler is *Pharmaceutical Technology's* Washington editor, jillwechsler7@gmail.com.

dications of a reference product. This approach applies when patent and exclusivity provisions may prevent a newly licensed biosimilar from including all indications of a reference product on the label, a situation that often involves pediatric or orphan disease treatments. But once those limitations expire, FDA encourages the follow-on manufacturer to file a supplemental application with data supporting the expanded uses, as seen in an advisory outlining how data and labeling should be presented to add previously omitted conditions of use (8). FDA says it will review such supplements within six months, much faster than the usual 10-month timeframe set for supplements to biologics license applications (BLAs).

And to ensure that promotional messages related to biosimilars by both brands and competitors are truthful, non-misleading and balanced, FDA draft guidance issued Feb. 3, 2020 instructs brands to avoid implying in its messages that a reference product is safer or more effective than an approved biosimilar, or that the follow-on is "not highly similar" to the reference product, even if the competitor is not licensed for all indications (9). The guidance emphasizes that a biosimilar product is not required to be identical to the brand to be licensed, but just that it be "highly similar" and without "clinically meaningful differences" in terms of safety, purity, and potency. An added proposal is that the FTC take antitrust action against brand manufacturers that make misleading claims to counter competitions.

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Building Better Manufacturing Facilities

Jennifer Markarian

The need for quick build times, flexibility, and production efficiency is driving trends.

In adding manufacturing capacity—whether through new, greenfield sites or by refitting existing spaces—biopharma and pharma companies seek flexible and efficient production. Getting a facility up and running quickly with a tight budget is increasingly important.

Flexibility is crucial in biopharmaceutical manufacturing, because companies increasingly have multiple modalities (e.g., monoclonal antibodies, cell therapies, and gene therapies) in their pipelines. New biopharma facilities often use single-use technology, and modular buildings and systems are becoming more popular.

"The biggest challenge is to map the current need for flexibility in manufacturing processes to the facility," says Stefan Kappeler, technology manager for life sciences at Exyte. He notes that facilities must be prepared for changes in process flow, in scale, and in manufacturing technologies.

Flexibility is important in oral solid dosage drug (OSD) manufacturing, as well. Manufacturers are seeking to "right size" their operations and capacity based on their product portfolios and to upgrade processes, equipment, and technology for improved efficiency and faster product changeovers, notes Dave DiProspero, director of pharmaceutical process technology at CRB. Improving equipment and facilities for product containment and cleaning operations are other active areas in OSD, he adds.

An ongoing drive toward closed processing simplifies facilities and allows lower room air cleanliness classifications, which corresponds to savings in capital and operational costs, adds Eric Bohn, partner at JacobsWyper Architects. Similarly, the smaller equipment associated with continuous processing and the smaller-scale processing associated with advanced therapy medicinal products (ATMP) result in smaller production suites that are easier to support and operate, says Bohn. "Facilities are being more closely tailored to the needs of the process," he notes.

Renovating facilities

In the past year, multiple life-sciences companies have updated or expanded manufacturing capacity by renovating existing facilities. GlaxoSmithKline (GSK), for example, completed a retrofit of its Rockville, MD site in October 2019 that increased capacity for its injectable drug Benlysta (belimumab) and involved demolition of existing suites and installation of new equipment (1). The company also renovated its Upper Merion, PA site and updated laboratory and manufacturing capabilities, including adding single-use bioreactors (2). A nearby, former GSK facility is being transformed into The Discovery Labs biotech campus, which announced in January that it would be the home of The Center for Breakthrough

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Medicines, a new contract development and manufacturing organization for cell and gene therapies (3).

Renovating an existing facility can save time compared to a greenfield site, where approvals can be complex and potentially last a year or more, says Bohn. Although renovations typically have costs for demolition, waste disposal, and the need to bring roof structures up to current building codes, for example, a significant cost savings is often found in site infrastructure, he notes.

"The most common refurbishments we see are from mothballed facilities," says John Noble, vice-president and general manager, life sciences, at Jacobs. "If you can start with a building shell that accommodates your process and meets planning needs, you can save nine-plus months in construction."

Facility refurbishment and renovations represent more than 60% of Fluor's work, adds Dave Watrous, vice-president, advanced technologies and life sciences, Fluor Corporation. Reconfiguring existing life-sciences manufacturing space or using suitable vacant buildings for a box-in-a-box approach can both accelerate speed to market.

ATMP capacity crunch

Speed is crucial in biologics manufacturing, especially in the fast-growing cell therapy and gene therapy industry as products are reaching clinical phase and there is a lack of manufacturing capacity.

"For manufacturing these advanced therapies, CDMOs [contract development and manufacturing organizations], can be scheduling six to 18 months out, and this wait time is disruptive to a company's go-to-market strategy," says Joe Makowiecki, Enterprise Solutions director of business development at GE Healthcare Life Sciences. He says that despite CDMOs adding capacity, many cell and gene therapy companies are deciding to build their own capacity using modular, box-in-box facilities that can be delivered in a year or less.

"In many cases, having a facility up-and-running and licensed may be the critical path to gaining approval for a new product. As such, site startup timing is critical," says Mitch Lower, vice-president of global engineering for AveXis, a Novartis company specializing in gene therapies. The company received an honorable mention in the 2019 International Society for Pharmaceutical Engineering (ISPE) Facility of the Year Awards (FOYA) for being one of the first companies to scale up a gene-therapy manufacturing process and doing so on a short timeline. To build its Libertyville site near Chicago, IL, AveXis used G-CON Manufacturing's prefabricated cleanroom PODS—built off-site in parallel with facility construction—which expedited startup.

AveXis also purchased and refurbished a facility in Longmont, CO in 2019 to add manufacturing capacity. The facility is operational and is undergoing the remaining steps to become licensed, which the company expects to occur in 2021. A facility the company is building in North Carolina is also anticipated to become licensed in 2021.

"There are benefits and challenges to both purchasing an existing facility and building a new facility," says Lower. "Purchasing an existing facility may be more cost effective and have an expedited startup schedule. However, the existing infrastructure and facility layout may drive additional costs to retrofit to accommodate the necessary manufacturing process. When building a completely new facility, the timeline may be longer; however, you will have the flexibility to build the facility to meet the needs of your unique and novel manufacturing processes."

Although AveXis is today mainly using manual processes, it is moving towards automation in its existing and new equipment and facilities, says Lower.

The lack of automation that is currently common in the novel ATMP industry is changing, agrees Noel Maestre, Life Science Core team leader at CRB. "These novel therapies are quickly proving a need for process closure and automation, which in turn is driving equipment vendors to create and test novel equipment solutions," notes Maestre.

Some equipment vendors are employing adaptable and flexible "plug-and-play" automation platforms. "Customers want options around automation," says Makowiecki. "Some may prefer to start small with entry-level automation, but we aim to make flexible and scalable automation platforms that can grow and scale to more centralized and advanced levels."

OSD trends

In OSD manufacturing, facility layout is becoming more important as equipment and processes are moving toward greater integration, says DiProspero. Continuous manufacturing and processes such as direct compression, which are growing in use, are examples of integrated systems, but integrating unit operations is also preferred in more traditional OSD processes. "A typical integrated equipment train will incorporate material handling, high shear granulation, wet milling, fluid bed drying, dry milling, and granulation collection in a linked, semi-continuous contained operation," explains DiProspero. Efficient product flow is crucial. "Good facility design is marked by uninterrupted uni-flow process direction, with appropriate hold and work-in-progress spaces and minimization of cross/backflow. Specifically, modern washing operations make use of a dirty-wash-clean uni-flow arrangement for improved efficiency and compliance."

Modular and prefabricated construction is being used in OSD manufacturing. "This type of construction is well suited for powder processing operations due to good cleanability, visual aesthetics, and the ability for use of glass to bring light into the spaces and provide for a user/operator-friendly working environment," says DiProspero.

Modular approaches

Modular approaches are transforming the way the industry builds facilities. Both modular design methods using standardized templates and modular construction methods for buildings and systems can improve speed to market, says a report by the BioPhorum Group (4).

Modular construction includes factory fabricated utility skids, wall pan-

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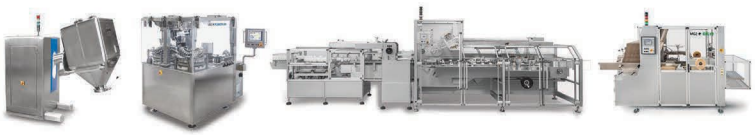

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els, or entire rooms or building sections, which can save time and improve quality and construction safety, explains Bohn. He points out that, although the initial cost of modular construction is typically more than that of field-built alternatives, the savings that comes from a shortened timeline is quantifiable. Factory testing reduces problems in the field and makes commissioning, validation, and start-up faster.

G-CON's PODs, for example, are prefabricated, autonomous, plug-and-play cleanroom environments, which can be installed within an existing facility or as part of new greenfield construction, for any type of bio/pharma manufacturing, including OSD, aseptic filling, and cell and gene therapy, says Dennis Powers, vice-president of business development and sales engineering at G-CON. The mobile facilities provide flexibility because they can be transported anywhere to quickly add or subtract capacity.

Modular construction started out in the bio/pharma industry for building infrastructure in developing countries with a lack of skilled construction capabilities, but now speed is the primary driver. "Modular construction and prefab cleanrooms are often must-have components in any new facility. Even in very mature market locations, these strategies help simplify and accelerate the market delivery strategy for most products," adds Watrous.

"The modular facility concept is a paradigm shift that provides companies with options for establishing rapid and flexible in-house production," says Makowiecki. "With standardized, modular systems, typically 80% of the design work has been completed, which reduces design time and results in faster speed to delivery," explains Makowiecki.

GE Healthcare's FlexFactory is a modular end-to-end biomanufacturing platform, and the company reports that it has sold close to 70 FlexFactories globally to date. Four of these FlexFactories were installed inside of the company's KUbio facility, which is the FlexFactory inside of a modular, prefabricated facility. Pfizer's Biotechnology Center located in Hangzhou, China, for example, is a KUBio facility, and it won an ISPE FOYA 2019 award for project execution.

In 2019, GE Healthcare launched the KUBio Box for viral-vector-based gene therapy manufacturing; in this box-in-box approach, the FlexFactory platform in a modular cleanroom facility is intended to be placed inside a new or repurposed space or shell-building. The KUBio box for viral vectors is a cGMP, biosafety level 2 modular facility solution.

"We're also having discussions around building biomanufacturing campuses and shell facilities to house the modular boxes. A best practice approach here is to build for what you need today but allow for enough space in your facility or facility shell to expand," explains Makowiecki. He expects the KUBio box offering will expand into additional product modalities and biomanufacturing scales.

Standardizing for speed and quality

Standardization of facility modules, equipment, unit operations, automation, and consumables are essential to the speed of deploying modular facilities and

efficient and effective technical transfer. These capabilities support the trend to distributed manufacturing, with the same company manufacturing a drug in multiple regions rather than one centralized location, notes Makowiecki.

"Standardized, closed systems provide optimal aseptic processes that support very high drug product quality," adds Chris Procyshyn, CEO and co-founder of Vanrx Pharmasystems. He notes that other industries rely on standardization for reliability and safety, and he says that the pharma industry needs to move to this model. "If the process from one site can be repeated on the same machine at another site, that's a positive change in our industry," suggests Procyshyn. Vanrx designs closed robotic workcells with "purpose-built robotics and a standard method of handling all types of containers to achieve repeatability," he explains. These systems remove human involvement to make the aseptic process more robust, which benefits drug quality.

Standardized equipment improves speed to market. For example, WuXi Biologics moved from purchase order of the Vanrx workcell to their first GMP batch release in only 15 months, says Procyshyn.

Placing standardized filling machines inside a modular cleanroom further increases speed and gives companies the ability to implement a fully prequalified facility within months, says Procyshyn.

The Microcell POD is an integrated solution from Vanrx and G-CON that meets the "increasing industry need for rapidly deployable turnkey aseptic filling capability for small batch therapies, specifically in the cell and gene therapy space," adds Powers. Standardization lends itself to "scaling out" rather than "scaling up." The standard POD design can be replicated to rapidly increase manufacturing capacity, he notes.

Collaborating on integration is key

Although standardizing improves quality and speed, integration of the equipment into the facility building is still important. For example, in building the Bayer facility in California in 2019 using GE's FlexFactory, Fluor's team helped design the optimal people, product, and material flows around the established FlexFactory set-up, and then integrated these flows in the building envelope and associated utilities and infrastructure. This collaborative process with an integrated end result reflects the future of the industry, says Watrous.

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Can Vaccine Development Be Safely Accelerated?

Cynthia A. Challener

Biopharma companies responding to the COVID-19 outbreak think accelerating the development of vaccines is safe.

Human coronaviruses (HCoVs) in the past were considered to cause nothing more than the common cold in healthy people. That changed with the advent of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in the past decade. The latest coronavirus disease—named by the World Health Organization as COVID-19—emerged in December 2019 in Wuhan, China. As of late February 2020, it had sickened tens of thousands and killed nearly 3000 people.

Four of these large, enveloped, positive-strand RNA viruses are endemic globally and thought to cause 10–30% of upper respiratory tract infections in adults (1). They possess a surface spike (S) glycoprotein that binds to host cell receptors, and the nature of this protein is believed to determine the main properties of each coronavirus. SARS-CoV was the first coronavirus to jump from animals to humans; MERS-CoV and COVID-19 have as well.

The genetic sequence for COVID-19 was released to public databases on Jan. 10, 2020 by the Shanghai Public Health Clinical Center & School of Public Health (1). The three-dimensional (3-D) structure of the spike protein suggests that it binds more tightly to human cell surface receptors than SARS-CoV, a possible reason that this coronavirus exhibits greater infectivity (2).

Platform diagnostic methods have been rapidly adapted to include COVID-19 for early identification of cases. Several academic and industrial researchers have also focused on applying novel vaccine development and manufacturing platforms to the accelerated development of a COVID-19 vaccine.

In terms of vaccine development and protection against dangerous viral pathogens, there is nothing particularly unique about coronaviruses, according to Eric von Hofe, chief scientific officer of NuGenerex Immuno-Oncology. "All of the recent potentially pandemic viruses, including SARS and MERS and two flu viruses (avian and swine flu), have the common feature that they simply had never been seen before by the human immune system. That said, we now know a lot about how the human immune system protects against viral infections and can rapidly identify the critical parts of a new virus to target for vaccine development," he says.

Platform technologies are ideal

Traditional vaccines, like the seasonal flu vaccine, are made by growing up large quantities of the virus and in some way killing or inactivating it so that it can be used safely as a vaccine. This approach is an old technology from the middle of the past century, according to von Hofe. "The main problem here is the time it takes to produce the vaccine, which is at least a year and can be several. Ideally, we'd have a platform technology that could be used to produce a vaccine in a few months," he observes.

Such technology platforms should be flexible enough to respond to any new viral threat. "We would like to have a simple 'plug-and-play' setup where the critical components of a new virus required to make the vaccine can be determined by rapid computer analysis and plugged into the platform to generate a vaccine," von Hofe notes. "Getting all of the critical components produced and structured in a way that perfectly models the vaccine is the big challenge," he adds.

A reductionist approach is best

The best way, von Hofe says, is to follow a reductionist strategy to identify key

Cynthia A. Challener, PhD, is a contributing editor to *Pharmaceutical Technology*.

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Just 42 days after sequence selection, Moderna shipped the first batch of mRNA-1273 to NIAID for use in a planned Phase I clinical study in the United States.

viral components that alone produce complete protection in a safe vaccine that can be manufactured rapidly and in a cost-effective manner. "Clearly this is a tall order, but we're making good progress in that direction," he asserts.

As an example, he points to the development of subunit vaccines that rely on recombinant DNA to encode a critical subunit of the vaccine that generates a response. There are additional challenges to this approach, however. "While responses can be produced, the protection may be short-lived, as there is no guarantee that immunological memory will be generated as is possible with a whole virus vaccine," von Hofe comments.

The DNA approach against COVID-19

San Diego-based Inovio Pharmaceuticals is one company developing a DNA-based vaccine against COVID-19. The biotech was the first to advance a vaccine (INO-4700) against MERS-CoV into human testing and is currently preparing to initiate a Phase II trial for INO-4700 in the Middle East. This vaccine, however, cannot be used against COVID-19 because the two coronaviruses are too different.

To develop a new vaccine, Inovio first converts the virus' RNA into DNA and identifies short sections that will, according to computer simulations, generate the greatest immune response. The plasmids are then produced in large quantities using bacteria. The overall development and approval timeline is thereby significantly reduced.

Inovio began animal testing of INO-4800, its COVID-19 vaccine candidate, in February 2020 and is aiming to begin human safety testing in early summer 2020. The company will conduct tests in both the United States and China, the latter in collaboration with Beijing Advaccine Biotechnology Co. (3). Work in the US is supported by a $9-million grant from the Coalition for Epidemic Preparedness Innovations (CEPI). The collaboration with Beijing Advaccine is anticipated to accelerate developed on INO-4800 in China by providing access to not only its vaccine expertise, but also its relationship and experience with Chinese regulatory authorities and clinical trial management in the country.

Prophylactic Messenger RNA Vaccines

Two companies, both also supported by grants from CEPI, have developed platform technologies based on messenger RNA (mRNA). Cambridge, MA-based Moderna—which has developed numerous prophylactic mRNA vaccines with positive Phase I clinical readouts and also has a fully integrated clinical-material manufacturing site—is progressing its COVID-19 vaccine candidate (mRNA-1273) into the clinic (4,5). The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), collaborated with Moderna to design the vaccine. NIAID will conduct investigational new drug-enabling studies and a Phase I clinical study in the US.

Moderna's mRNA vaccines can contain multiple mRNAs coding for different proteins and mimic natural infection, thus stimulating a more potent response, according to the company. Only the coding region of the mRNA must be changed for each new vaccine. The rapid discovery approach and the manufacturing agility of mRNA vaccine design and production also make it an effective platform technology.

Just 42 days after sequence selection, Moderna shipped the first batch of mRNA-1273 to NIAID for use in a planned Phase I clinical study in the US. The mRNA vaccine encodes for a pre-fusion stabilized form of the COVID-19 S protein.

German biotech CureVac also has an mRNA platform technology for vaccine development and manufacturing suited for rapid response to viral outbreaks, it says (6). Using an extensive in-house nucleotide sequence library, CureVac is able to identify optimum sequences for any given vaccine target and eliminate the need for chemical modification, shrinking the development timeline.

The company has also developed specific carrier molecules for its mRNA products, including lipid nanoparticles (LNPs), developed in partnership with Acuitas Therapeutics and Arcturus Therapeutics). It is developing The RNA Printer, a mobile, automated production unit for rapid supply of LNP-formulated mRNA vaccine candidates.

Stabilizing the pre-fusion virus form

A fourth group receiving funding from CEPI for application of a vaccine platform technology to accelerated development and manufacture of a COVID-19 vaccine is located at Australia's University of Queensland (UQ) School of Chemistry and Molecular Biosciences (7). Its rapid response technology relies on molecular clamp technology, an approach developed by UQ researchers and patented by UniQuest.

The molecular clamp technology is used to create subunit vaccines against class I and III enveloped viruses by stabilizing the pre-fusion form of viral fusion proteins, thus mimicking the protein conformation found on live virus and generating a strong immune response. A polypeptide is used to maintain the pre-fusion structure and prevent the protein from folding after entry into the cell.

The platform technology, which does not require prior knowledge of a protein's quaternary structure, therefore facilitates

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the expression of recombinant viral glycoproteins without loss of native antigenicity (8). It has previously been used to produce chimeric polypeptides that mimic the pre-fusion conformations of several enveloped viruses. The goal is to complete preclinical development within 16 weeks and then progress directly to Phase I clinical trials, with completion of that step in 10 weeks, followed by large-scale production of more than 200,000 doses in eight weeks.

For its COVID-19 vaccine, the UQ researchers created a first candidate in the laboratory in just three weeks (9). This work confirmed that the engineered vaccine candidate is readily recognized by the immune system and triggers a protective immune response. Plans for preclinical testing were underway as of late February, and the researchers hope to begin clinical testing by mid-2020.

Leveraging computer technology

NuGenerex Immuno-Oncology is focusing on what von Hofe refers to as the smallest and simplest fragments of the virus needed to produce an immune response. These short fragments of proteins are identified by a computer algorithm and can be made rapidly by entirely synthetic means. They are modified to ensure that they activate immune cells that are key in producing immunological memory. "While these virus fragments may not produce as complete a response as whole inactivated viruses, they basically produce a 'memory', so when a person treated with our vaccine does encounter the virus, he or she is more prepared to mount an effective response," von Hofe explains. The technology is also a platform approach because it can be applied to virtually any virus that may emerge as a threat.

Big Pharma has programs too

While these smaller biotechs have generated attention for their accelerated development platforms, Big Pharma companies have also been actively working on COVID-19 vaccine candidates. Both Johnson & Johnson and Sanofi are collaborating with the US Department of Health & Human Services (HHS).

Johnson & Johnson's Janssen Pharmaceutical Companies unit is collaborating with the HHS' Biomedical Advanced Research and Development Authority (BARDA) to rapidly advance the initial stages of Janssen's COVID-19 vaccine development program, which is based on its AdVac and PER.C6 platform technologies (10). BARDA is funding accelerated development of a candidate into Phase I clinical trials, while Janssen is upscaling its manufacturing capacities.

Sanofi Pasteur, the vaccines global business unit of Sanofi, is also collaborating with BARDA, using its established recombinant DNA technology platform to accelerate the development of a potential COVID-19 vaccine (11). This technology produces an exact genetic match to proteins found on the surface of the virus, which are then expressed using Sanofi's insect (baculovirus) expression platform. The technology is used for Sanofi's licensed recombinant influenza vaccine and a SARS vaccine that has been shown in non-clinical studies to be immunogenic and afford partial protection in animal challenge models.

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Delivering the Goods

Felicity Thomas

The new molecules entering the development pipeline are bringing forth exciting challenges in drug delivery.

As drug pipelines have expanded to include a wide range of novel, and sometimes difficult-to-handle molecules, so too has the number of methods available to deliver these innovative therapies and drugs. Not only do developers need to consider the route of administration, but it is also necessary to consider solubility, bioavailability, the precise target of the active ingredient, patient convenience and safety, and reducing toxicity, among other factors.

"It is now more common for formulators to be presented with 'non-druglike' molecules and yet be tasked with formulating them to achieve high oral bioavailability, good pharmacokinetic properties with minimal toxicity, and good stability," emphasizes William Wei-Lim Chin, manager, Global Scientific Affairs, Catalent. "The key challenges of these molecules can be attributed to their poor aqueous solubility, poor permeability, or in worst cases both."

Challenging aspects

These challenging attributes of molecules entering the development pipeline are largely associated with the increasing complexity of molecules, agrees Srini Shanmugam, technical director, Phama Product Development and Manufacturing, Avomeen. "Formulators must balance targeted release profiles for therapeutic efficacy with patient safety and convenience of use," he says. "Furthermore, every drug delivery system has unique characteristics that come with specific formulation challenges."

Developing the optimal drug delivery strategy for molecules that are classified as poorly soluble according to the biopharmaceutical classification system (BCS)—that is those molecules in class II and class IV—is a major challenge for industry, notes Archana Akalkotkar, PhD, research scientist II, Charles River. "To come up with alternative approaches that are appropriate for the drugs' physicochemical properties, as well as the limitations of choice of excipients, which are safe-to-use in the intended species dosed during the preclinical and clinical testing, has been a challenging task," she states.

For Rich Shook, director, Drug Product Technical Services and Business Integration, Cambrex, there are two main obstacles facing developers in ensuring the optimal level of drug substance is available with a targeted window of transit in the gastrointestinal tract (GI). "One of the main obstacles is the pH dependent solubility and/or degradation of the API, which can decrease the overall absorption of the drug substance and result in a negative impact to the intended therapeutic response," he says. "The other obstacle is *in-vivo* delivery of a specific therapeutic dose at a targeted therapeutic site in the GI tract based on the mechanism of action. Some drug substances have a topical mechanism of action on a disease making it important to ensure the release of a high dose of drug substance to that targeted area."

"In terms of inhalation delivery, the main challenge is the diversity of molecules coming through the pipeline into development," adds Sandy Munro, vice-president, Pharmaceutical Development, Vectura. "Historically, the inhalation space was dominated by small-molecule therapies for moderate asthma and chronic obstructive pulmonary disease treatments. These days, the interest is much broader both in terms of the diseases that the developers are interested in, and also the range of molecule types."

Available approaches

There are several approaches available that are in use by developers to help overcome the challenges associated with drug delivery. Approaches such as pH adjustment, co-solvent complexation, solid-dispersion, micellar formulations, among others, help to improve solubility, confirms Akalkotkar.

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"A tremendous amount of knowledge has been accumulated in modern pharmaceutics so that now there are several sets of *in-silico* guidelines correlating the influence of an API's physiochemical properties on oral absorption," adds Chin. "Today, formulators use data to make decisions about their formulation strategy because there is a range of solubilization techniques to choose from. However, sometimes it is easy to get lost in the choice, as data are only as valuable as the insights you can draw from them."

By way of example, Chin explains that by combining the developability classification system (DCS) along with physiologically-based pharmacokinetics (PBPK) modeling, it is possible to gain insights into a molecule's developability and the route for selection of the most appropriate solubilization technology. "If a compound is classified as a DCS IIa, it means that the *in-vivo* absorption of the compound is limited by its dissolution rate, and technologies such as particle size reduction, salt or co-crystal formation approaches can be employed to develop simple formulations that improve dissolution rate," he says. "For a DCS IIb compound that is limited by its intrinsic solubility, the preferred technology would include lipid formulation or amorphous dispersion via spray drying or hot-melt extrusion."

For those compounds with permeability issues (classified as DCS III or DCS IV) it is a little more complicated. "As there are several causes of low permeability, a formulator will need to identify a strategy to either stabilize the API from degradation in gastric acid, stimulate lymphatic transport, inhibit P-glycoprotein (P-gp), prevent drug metabolism in the gut, or to alter the permeability of the membrane in the GI tract itself," Chin continues.

According to Shook, high molecular weight polymer matrices or hydrogels, which use high molecular weight polymers to blend to the drug substance, can create a slow eroding matrix to enable API passage through the GI tract. "These matrices can be combined with enteric components to resist release of the drug substance until it reaches a targeted region of the GI tract," he says.

Additionally, Shook notes that enteric coated tablets or multi-particulates can be used to overcome pH dependent solubility issues. "The ratio of types of co-polymers in the coatings can be modulated for a specific pH release profile using *in-vitro* models to target an *in-vivo* release of the drug substance in the GI tract," he confirms. "This ensures that the optimal level of drug substance is presented to the targeted therapeutic region and absorbed."

An emerging route of oral delivery is in the form of oral thin films (OTFs), adds Shanmugam. "OTFs are polymeric films intended to deliver therapeutic moieties either locally or systemically in the oral cavity or through gastrointestinal absorption," he notes. "OTFs are an attractive novel drug delivery option and come in two major categories—oromucosal and orodispersible. Oromucosal films are 'mucoadhesives', designed to stick to the inside of the oral cavity and release drugs slowly across the mucous membrane, and are fast-acting with high bioavailability. Orodispersible films are non-mucoadhesive and are designed to break down immediately upon contact with saliva."

This mode of drug delivery is relatively new and so there are limited options currently commercially available, none of which are generic, Shanmugam continues. Yet, the available OTFs do treat a wide range of diseases and disorders and studies have shown that poorly soluble drugs can be incorporated into films (1–4). "However, as this is a streamlined drug delivery system relying on polymers to increase drug solubility, formulators must explore new particle engineering techniques and find innovative ways to solubilize OTFs and incorporate a wide variety of water-insoluble drugs," he adds.

Within the field of inhalation delivery, there has been some evolution, explains Munro, but the traditional platforms, pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and nebulizers, are still the mainstay. "Even within these long-established routes of delivery are technology evolutions," he asserts. "For example, breath activated pMDIs that overcome the issues associated with the coordination of actuation and inhalation, high-dose DPIs that are better able to cope with the demanding new molecules in development, and smart jet nebulizers and smart mesh nebulizers that guide the patient inhalation maneuver to maximize lung delivery."

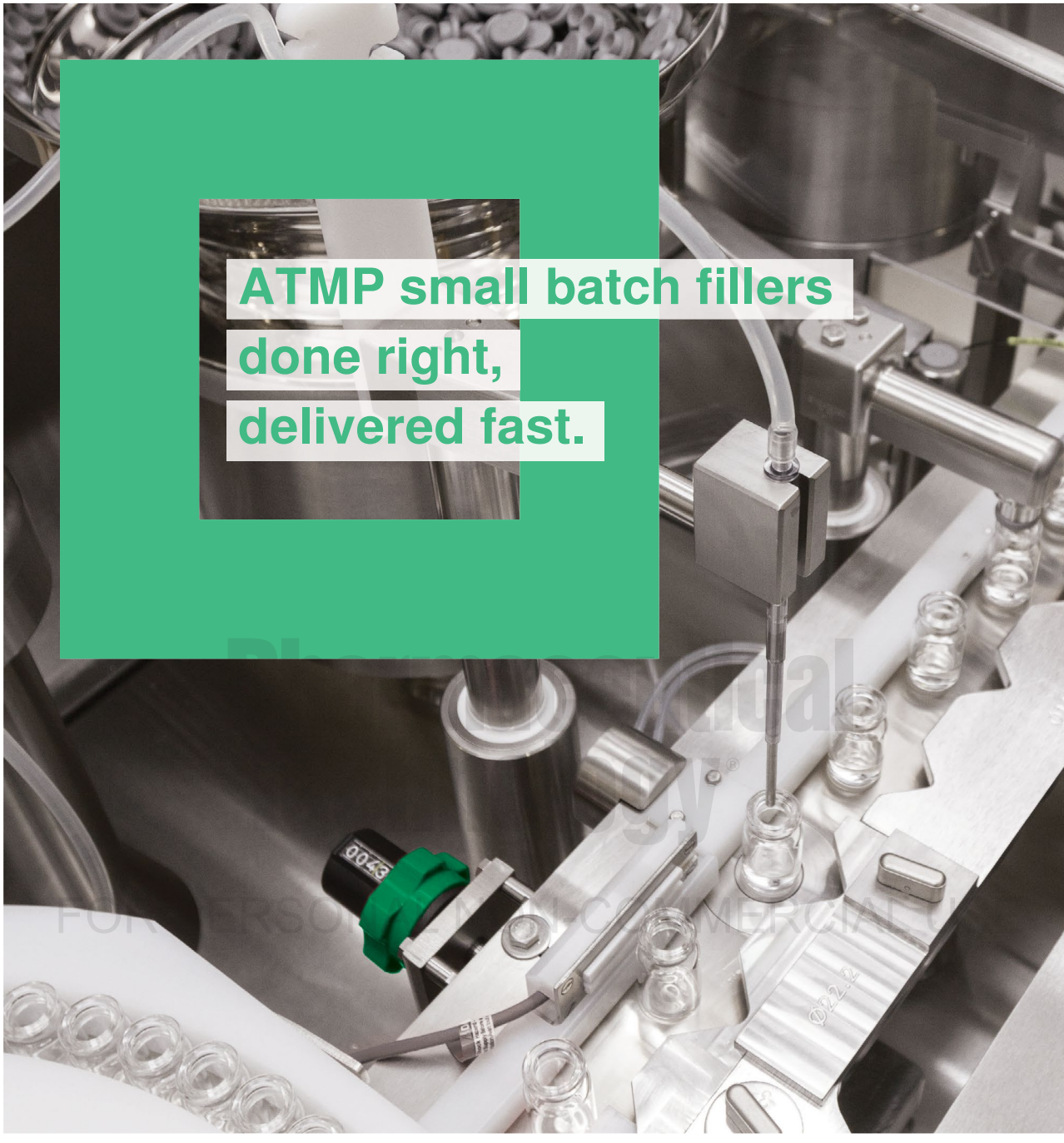
Specific considerations

Patient adherence to a therapeutic regimen can be particularly tricky if the route of administration has not been considered appropriately. "When targeting pediatric and geriatric dosing, taste and difficulty in swallowing can hinder patient compliance," confirms Shook.

Difficulties with swallowing tablets is now thought to affect 37% of the population, states Shanmugam (5). "Children, the elderly, and those experiencing dysphagia or nausea often struggle to swallow tablets and capsules, and, therefore, stand to benefit significantly from drugs delivered without swallowing," he says. "OTFs have potential in these populations. In fact, the growing size of the elderly population is predicted to drive the growth of the OTF market. Because the elderly population is more prone to chronic illness, the demand for safe and hassle-free drug delivery methods will only increase."

"A multi-particulate approach can be used in a form of a sachet 'sprinkle' formulation with taste-enhancing ingredients," asserts Shook. "This dose would be added to water or juice which the patient would then drink." It is also possible to manufacture multi-particulates as a powder for oral suspension (POS) formula, where water is added to the bottles at the pharmacy and given to the patient as a ready-to-dose suspension, he continues. "These methods of drug delivery help address patient compliance while maintaining the target drug substance *in-vivo* absorption profile," Shook says.

"In pediatric drug development, many published studies have reported the acceptability and preference of certain dosage forms based on evidence gathered in clinical trials involving chil-



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Avoiding Negative Drug–Device Interactions

When ensuring effective drug delivery, developers must not consider the drug and the delivery vehicle completely separately. Formulation ingredients have the potential to interact with the delivery device, such as an autoinjector, and potentially negatively impact the ability for the device to deliver the required dose as expected.

To learn more about the potential issues that may arise from interactions between drug formulation ingredients and delivery devices, *Pharmaceutical Technology* spoke with Fran DeGrazio, chief scientific officer, Strategy & Science Integration, West Pharmaceutical Services.

Potential impact

Pharm Tech: How can drug components, excipients, and/or combinations of these ingredients impact delivery systems?

DeGrazio (West): Over the past several years, there have been multiple cases of challenges with autoinjector function over time. An example of one of these challenges is extrusion variability, which can lead to increasing delivery times. Extrusion is the force required to maintain plunger movement once it starts down the syringe barrel. The regulatory expectation of understanding essential performance requirements (EPRs), such as delivery time and delivery volume, means that EPRs must be evaluated during the development process. This expectation has led multiple pharmaceutical companies to identify problems with function that can occur with certain combinations of drug formulations and drug solutions. The issues arise due to the prefilled syringe system in the autoinjector, not the autoinjector itself. The autoinjector is consistent in applied force to move the plunger down the glass barrel of the syringe; it cannot adapt to variability in the barrel of any kind. The need for consistency means that the function of the syringe cannot vary. The drug–device combination product must deliver consistently over shelf life to assure safe and effective patient use.

Understanding is key

Pharm Tech: Why should formulators and developers take these potential interactions into consideration? What sort of complications may arise from these interactions further along the development cycle and ultimately for the end users, for example?

DeGrazio (West): It is expected that drug formulators ensure the chemical and physical stability of a drug product. It is also expected that the EPRs of the drug–device combination product are met. This means developing a product that performs as required for the drug/patient application. If drug formulators do not understand the final delivery format and develop a drug product only with consideration of its efficacy, they may find variability with EPRs as they move to later stages of development. If a complication is not identified until the Phase III stability program, this delay could force the drug formulator to conduct a root cause investigation, which, in turn, may require reformulation of the drug product or switching to another prefilled syringe system/autoinjector combination product. This type of complication being discovered late in development would extend the development timeline substantially.

Best practices

Pharm Tech: Are there best practices that you would advise for formulators and developers to employ to avoid the potential issues that may arise from ingredient/excipient interaction with delivery systems and ensure consistency with the formulated product?

DeGrazio (West): We have determined a best practice to be the evaluation of the drug product vehicle design space, which considers various excipient combinations with the chosen prefilled syringe system. To implement this best practice, we have designed a program that models the potential interactions among the drug solutions and the prefillable system, and then confirms results through pertinent analytical testing. Employing this kind of program early in development provides clear direction on the best combination with which to move forward and provides the data to support the decision.

—Felicity Thomas

dren," adds Chin. Providing examples, Chin highlights that minitablets and syrups have been found to be the most acceptable formulation for toddlers and infants, whereas neonates were found to have increased swallowability of minitablets when compared with syrup (6–9). "For the older children, a preference for chewable and orodispersible preparations were observed when compared with multi-particulates," he notes.

When considering therapies that are inhaled, the most appropriate method of delivery can depend on the level of coordination, so, for example, younger patients that may struggle with coordination would be more suited to nebulizer therapy or a pMDI used with a spacer, explains Munro. For older children and adults, the delivery method can be more individual and based on patient preference, he continues, but the most appropriate delivery platform may also be driven by the technical requirements of the molecule.

"Smart nebulizer devices come into their own where there is a particular need for efficient lung delivery to maximize the probability of success for a given drug, and where the disease indication can tolerate the higher cost of goods associated with this type of device," Munro says. "Sometimes this indication is in niche diseases such as idiopathic pulmonary fibrosis (IPF), or in particular sub-categories of a broader disease (e.g., severe uncontrolled asthma) or for a particular development strategy (e.g., fast to clinic development for a biologic)."

Discussing biologics, Chin reveals that the advantages these large, complex molecules can afford over small-molecule therapies include more target-specificity and minimal side-effects, but delivery can be more difficult. "Oral delivery of biologics is far more challenging than it is for small molecules and because of this, biologics have conventionally been delivered in intravenous forms," he says. "However, there are technologies available to improve the permeability of high-molecular weight biologics and to prevent gastric degradation (e.g., enteric coatings). In addition, spray drying in combination with certain excipients is a promising

method for the stabilization of biologics that are usually formulated as liquids."

For Akalkotkar, targeted drug delivery approaches are more suitable for oncology drugs. "These approaches help reduce the risk of side effects," she adds. "Continued research is ongoing in this field to develop novel therapeutic modalities. Examples include, magnetic nanoparticles, pH sensitive carriers, and conjugated polymers."

In great demand

"Novel drug delivery systems offering impactful solutions for the development of new or improved therapeutics are in great demand currently, and are highly sought after by pharmaceutical companies," says Shanmugam. "In the next 5–10 years, we will see a push toward such systems that address a broad range of clinical and patient objectives, including higher efficacy and bioavailability enhancement, better safety, and improved compliance."

Therefore, as a result of industry demands, Shanmugam believes that OTFs will grow in importance thanks to the dosing capabilities, packaging, and film stability advantages they offer. "Also," he continues, "OTFs that are now being developed to enhance solubility can become instrumental in delivering poorly soluble new molecular entities to pediatric and geriatric populations, as well as in extending the lifecycle of such medications that are approaching patent expiration."

For Shook, the development of nanotechnology will be critical for developers to be able to deliver large and small molecules to a specific site of treatment. "Nanotechnology will ensure that the therapy is introduced and actively initiated at the right time and place to disrupt the disease with precision," he adds.

The role of connectivity in understanding patient behavior and adherence to medications is important for the future, according to Munro. Additionally, he explains that complex combination products and smart formulations will be vital for the inhalation space.

"Alongside the traditional small-molecule monotherapy products in development, there are complex combination products, large molecules, and biologics," Munro concludes. "All of these new molecule types are bringing fresh challenges in terms of formulation and the range of doses that may need to be delivered."

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Understanding Containment for Tableting

Matt Bundenthal

Risk levels should be considered when designing equipment to enhance operator safety.

Tablet manufacturing is evolving, and the use of highly potent active pharmaceutical ingredients (HPAPIs) is increasingly prevalent. The inhalation of hazardous, airborne particulates can represent a real risk for those operating the equipment used to compress final tablets. It is due largely to these facts that the concept of contained tableting equipment is gaining prominence in pharmaceutical manufacturing facilities.

Any discussion of containment involving pharmaceutical tablet compression is likely to include a number of common acronyms. The following are some of those most commonly encountered:

- Occupational exposure banding (OEB) is a process whereby APIs are assessed and categorized for toxicological concentration.
- Occupational exposure limit (OEL) is an upper limit on the acceptable concentration of an airborne particulate API, in terms of the risk associated with an individual's exposure to the API, usually expressed as a value of micrograms per cubic meter ($\mu g/m^3$).
- Permitted daily exposure (PDE) is the amount of a specific active substance for which the occurrence of an adverse effect is unlikely in an individual exposed to this dose, or to lower values, for a lifetime (1).
- Personal protective equipment (PPE) is clothing, respirators, etc. used to create a protective barrier between operators and potentially toxic substances.

Figure 1 depicts the various topics of consideration that come into play when operator safety is considered. A product should be initially assessed for the amount of dust it is capable of creating, as well as the amount of highly active substance it contains relative to its overall dosage (i.e., dilution). The manufacturer will also need to decide what protective measures to take with regards to the operator—which may well include the use of PPE—and how it will quantify the risk levels associated with a particular product (i.e., measurement protocols). Finally, after determining that a particular product does, in fact, constitute an exposure risk for the operator, consideration may be given to the use of specialized technology that includes features specifically designed to contain dust or allow for precleaning prior to breaching containment, for example, thereby mitigating the risk factors.

Different end users will employ different strategies for protecting their equipment operators, but what remains constant across manufacturers is a legal obligation for taking such measures. Containment solutions must ensure that established limit values for highly active ingredients can be reliably maintained during the manufacturing process. The International Society for Pharmaceutical Engineering (ISPE) Containment Manual acts as a guidepost for technical solutions pertaining to hazardous substance handling in pharmaceutical facilities and can provide further information (2).

OEB and OEL

Figure 2 depicts the relationship between OEB bands and OEL or PDE limits, illustrating how equipment users can identify the level of containment to be considered for various applications. It is important to mention that while the OEB and OEL categories do quantify limit levels, their interpretation and the way that various end users will seek to achieve operator safety can be highly variable.

Safety guidelines

Different containment requirements necessitate a wide array of equipment needs, and many tablet press vendors offer options that are suitably configurable. It is imperative to note that containment projects are inherently complicated, both from an equipment and facilities perspective. Consider the following steps.

Evaluate the API. The first step is to determine if a particular active ingredient is potentially hazardous enough to those

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- ICH Storage and Accelerated Stability Studies
- GMP/GLP Method Development and Validation
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Figure 1. Areas to consider for protecting the operator during tablet production with potentially hazardous ingredients.

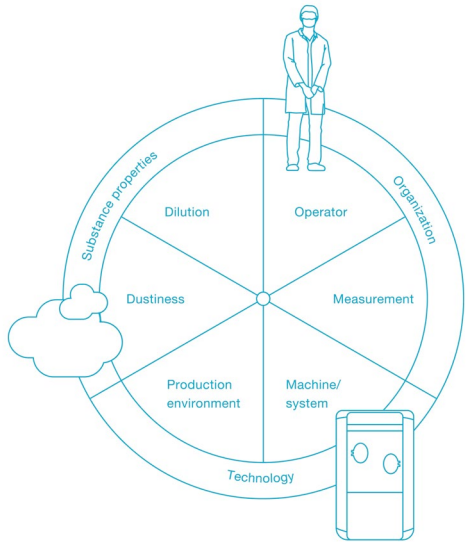
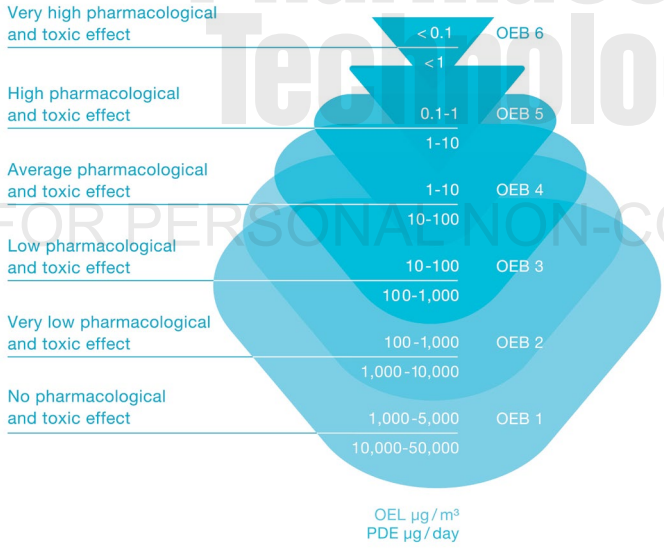


Figure 2. Occupational exposure limits (OEL) and permitted daily exposure (PDE) can be corresponded to occupational exposure bands (OEB).



working with it, such that it warrants the use of contained equipment in the first place. There are differing philosophies on how best to approach such situations, which can include the avoidance of the ingredient all together (essentially a fool-proof approach), the use of PPE alone (the least effective approach), or something in between. **Figure 3** illustrates this continuum.

Quantify the risk. Once a determination has been made that an ingredient does have associated risks, it is time to define them. The OEB data shown in **Figure 2** are the rule of thumb for pharmaceutical manufacturers seeking to quantify a risk level. These categories, when considered in addition to the drug load for a particular product (i.e., the ratio of active ingredient to the overall dosage or dilution), will lead to greater clarity in terms of what level of equipment containment is actually necessary.

Although the scope of this article does not allow for a detailed exploration of personal protective equipment (PPE), it should be noted that those having the most experience with compressing highly active substances generally elect to use some form of PPE, regardless of the efficacy of the contained system being utilized. PPE can be important given the fact that with virtually all contained systems, final cleaning will still include manual steps.

Choose a qualified vendor. Identify equipment manufacturers that can meet your needs and who, ideally, have a proven track record with such applications. Asking for surrogate test results is a good way of vetting for this purpose. Qualified vendors will not only perform such testing, but also offer systematic methodology for scientifically matching a specific containment target (when one has been clearly stated) to a well-defined equipment system. This testing can bolster internal risk-assessment processes the end user conducts under ISPE's Standardized Measurement of Equipment Particulate Airborne Concentration guidelines (3), as the methodology itself will result in a standardized, objective, and reproducible determination of a specific system's capabilities.

Select containment-specific features and attributes. Identify the level of containment the press will need to maintain and select the options necessary for reaching that goal. For example, an ingredient with an OEL level of 50 µg/m³ (OEB 3) will commonly require less containment than one with a level of 8 µg/m³ (OEB 4).

If a particular set of containment-related requirements necessitate dry-clean, low-dust production only, then a press fitted with glove- and rapid transfer ports, as well as need-specific process equipment, may prove to be the ideal fit. Glove ports typically utilize fail-safe technology that prohibits the operator from gaining access while a press is running. When the machine is in a static state, the ports provide access to the interior of the press for simple operations such as cleaning a punch tip or changing a fill cam, without breaching containment. A rapid-transfer port allows for either introducing a small component into the press or removing it, similarly without a breach. Utilizing split-valve technology for charging the press, in addition to high efficiency particulate

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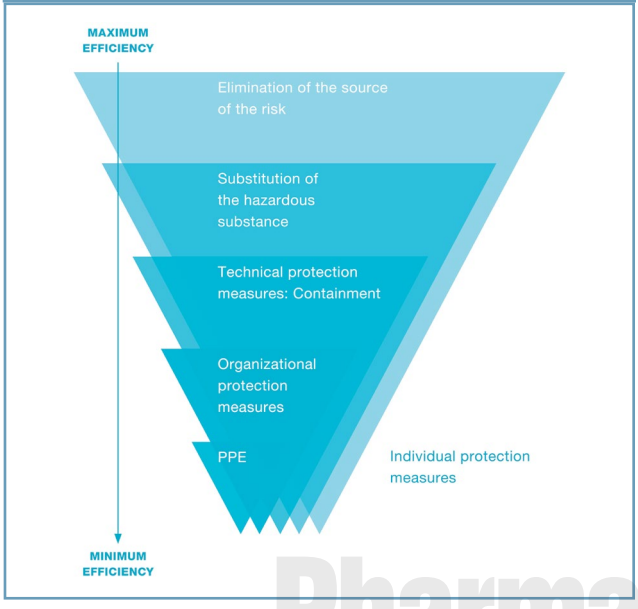
Figure 3. Methods for protecting operators from hazardous ingredients fall on a continuum of efficacy, with personal protective equipment (PPE) as the least effective.



air (HEPA) filtration and dust-tight discharge chutes, applicable models that are correctly configured can potentially provide containment levels of approximately 5 µg/m³ (i.e., the middle of the OEB 4 band).

Hazardous active ingredients necessitating wet cleaning, where the press will run itself through various wash and rinse cycles (i.e., wash-in-place systems), are often classified at the higher levels of the OEB 4 band and into OEB 5 or above. Such press systems are far more complex and are designed to introduce various forms of water and detergent into the machines. This set-up allows for the binding of airborne particulates with water molecules, which are then drained away before access doors are opened. Integrated, internal spray wands may be available, with which the operator can essentially pre-clean the compression zone prior to letting the automated wash system perform its function. For OEB 5 applications, process equipment such as de-dusters, metalcheck units, and quality control testers may be installed in separate but connected isolators, ensuring that the entire tableting system is fully contained and safe. When tackling these products that warrant higher levels of containment, sophisticated air management systems are available that provide automated safeguards against risk factors, such as power loss, and maintain predetermined set points (i.e., vacuum) across variable run conditions. The caveat to the latter approach is that project costs are generally much higher, as related equipment and facility considerations are proportionately more complex.

Act early. Due to this inherent complexity of containment projects, whether they necessitate dry- or wet-cleaning, they always present challenges extending beyond those of a non-contained endeavor. It is therefore strongly recommended that end users identify their equipment vendors as far in advance as possible. Making a selection early will allow for the commencement of project-critical dialogue between the end user and their chosen supplier. It should also be worth noting that contained presses often have lead-times of up to 50% longer than their non-contained counterparts.

Safety is the goal

The sole purpose of investing in contained compression equipment is to ensure the safety of one's operators. Nothing else could, or should, be of more paramount importance. Take the time to properly identify potential risk factors, methodically match those factors to suitable equipment, and create a safer, more efficient working environment.

Acknowledgement

The author would like to thank Dr. Martin Schöler (author of *Containment*, Fette Compacting GmbH, 2019) for his constructive insight and feedback during the creation of this article.

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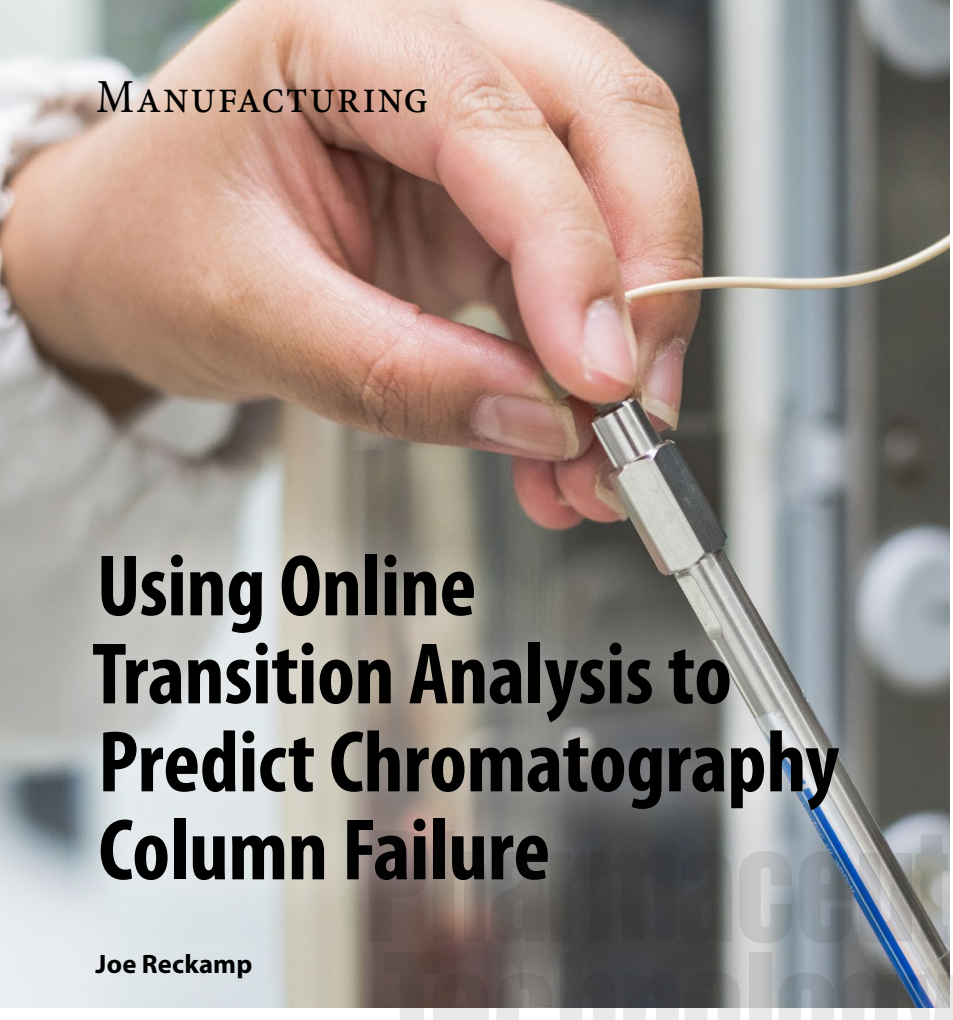

Using Online Transition Analysis to Predict Chromatography Column Failure

Joe Reckamp

Advanced analytics and modeling can be used to predict downstream failures, allowing for corrective action before batches are lost.

In the biopharmaceutical industry, quality and consistency are two of the most important attributes for any manufacturing process. In downstream bioprocessing, quality is dictated by separation purification unit operations such as filtration and chromatography.

Chromatography, the key purification unit operation in biologics synthesis, requires precise monitoring of column integrity and efficiency. Chromatography columns consist of packed resin or media that separate the solution's components based on chemical or physical properties such as size, charge, hydrophobicity, or affinity. As the chromatography column is cycled, the degradation of the resin ligand or fouling of the column can decrease the consistency and effectiveness of the purification process.

Transition analysis is commonly used to evaluate the condition, degradation, and efficacy of the chromatography column (1–3). Step change transitions in the column input solution, measured by conductivity or ultraviolet (UV) detection, are evaluated and reported as key performance indicators (KPIs). Typically, the height equivalent of a theoretical plate (HETP) and asymmetry (1,2) are the KPIs most frequently used to characterize chromatography column performance.

HETP defines the separation efficiency of the chromatography column, while asymmetry evaluates the normality of each peak to indicate the amount of peak fronting or tailing, either of which can result in reduced product quality and purity. These KPIs are helpful for monitoring column integrity and efficiency because higher HETP and abnormal asymmetry values, deviations from a value of 1.0, indicate resin degradation and signal potential batch failure. This article describes how data analytics can be used to cleanse input data, conduct transition analysis, create online dashboards, and develop predictive models to trend these KPIs over time. It also highlights alternatives to HETP and asymmetry that can be used to measure the separation efficiency and the normality or tailing of peaks (3).

Challenges

There are a number of challenges involved with developing transition analysis calculations, however. One problem is data quality. Transition analysis measures subtle changes in data trends. To identify and quantify these changes, the data must be collected at a sufficient frequency and the sensors must be accurately calibrated.

Process data are typically linearly interpolated between stored values, which does not accurately represent a transient state where the step change occurs, particularly when there is additional noise in the data. Calculating accurate KPIs often requires filtering algorithms to more precisely capture the transient shape of the data. In addition, it can be difficult to work with the complex differential equations needed for HETP calculation because they require moment analysis.

Moment analysis requires solving a nested set of equations and relies not only on the column data, but also on the added contextualization of the time period where the transition occurs. Identifying the transition periods automatically from continuously flowing time-series data to perform differential calculations across those time periods is challenging.

Furthermore, a considerable amount of time (i.e., many hours or days) is typically needed to conduct the analysis and alert operators of imminent column failure. Traditionally, these complex calculations have been performed

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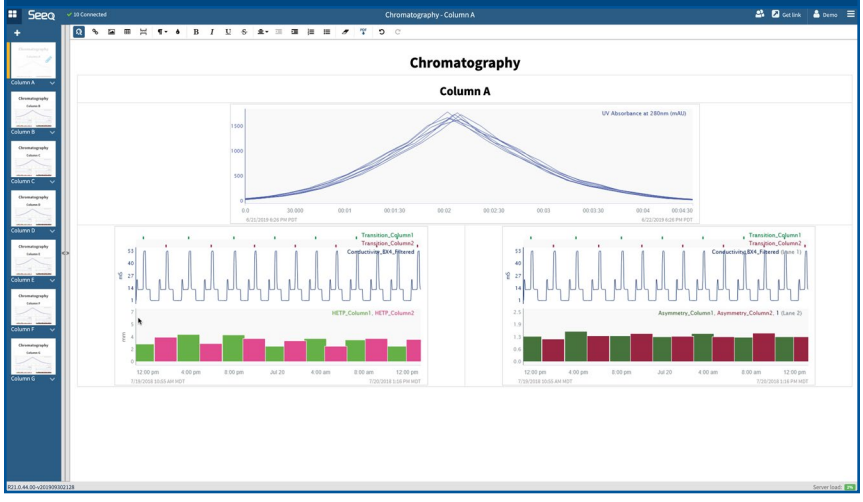
Figure 1: Online dashboards allow operators and experts to monitor multiple chromatography columns in near real-time by displaying HETP (height equivalence of a theoretical plate) and Asymmetry KPIs, along with chromatography peak overlays.



offline using mathematical software, which often results in excessive time to insight. As a result, operators must often react to column failure after it has happened, rather than being able to monitor columns and predict failure before it takes place.

Process analytics can be used to speed up the transition analysis process by allowing operators to connect directly to process data and perform calculations in real time. These data are typically stored in a process historian or an SQL database. Advanced analytics applications can set up live connections to data historians or SQL databases to view data and perform calculations like transition analysis as soon as the data are stored in the database. Live connections to the data enable the application to automatically find transition periods on set criteria, such as a shape or value, and to set KPI calculations that are executed upon completion of the transition period.

A number of pharmaceutical companies have used advanced analytics applications to remove outliers and cleanse conductivity data prior to transition analysis, dramatically improving the effectiveness of HETP trends over time by ensuring data quality. Data must be collected at a sufficient frequency and may require cleansing to remove outliers (e.g., signals generated when a sensor is not in use), or filtering to smooth out any noise in the signal. Transition analysis requires differential equations to quantify the change in conductivity with respect to volume over the entirety of the transition period.

As a result, HETP and asymmetry results can vary significantly depending on the frequency of the data and the type of interpolation used between data points. If data are not handled properly, false column failure alerts may be generated, or actual column failures may be missed.

The need for data cleansing

Chromatography column data requires cleansing prior to transition analysis calculations to remove outliers, focus calculations on only the transition time periods, and smooth the data. While numerous filtering algorithms exist, selecting an appropriate filter that accurately identifies and captures step changes, such as one using the Loess method, is important for transition periods.

These techniques make HETP calculations more consistent by isolating relevant data and removing noise, enabling engineers and scientists to increase the precision and rigor of transition analysis calculations, focusing calculations on only the transition time periods and smoothing the data. These three techniques make HETP calculations more consistent by isolating relevant data and removing noise, enabling engineers and scientists to increase the precision and rigor of transition analysis calculations.

The KPIs monitored in transition analysis are expected to have low variation while the column is intact. But noise or inappropriate data sampling frequency can result in significant changes in the transition analysis KPIs that may falsely trigger column failure alerts. Data cleansing is used to enable effective monitoring of column health by reducing the dependence of the KPIs on the data sampling parameters.

Creating an online dashboard

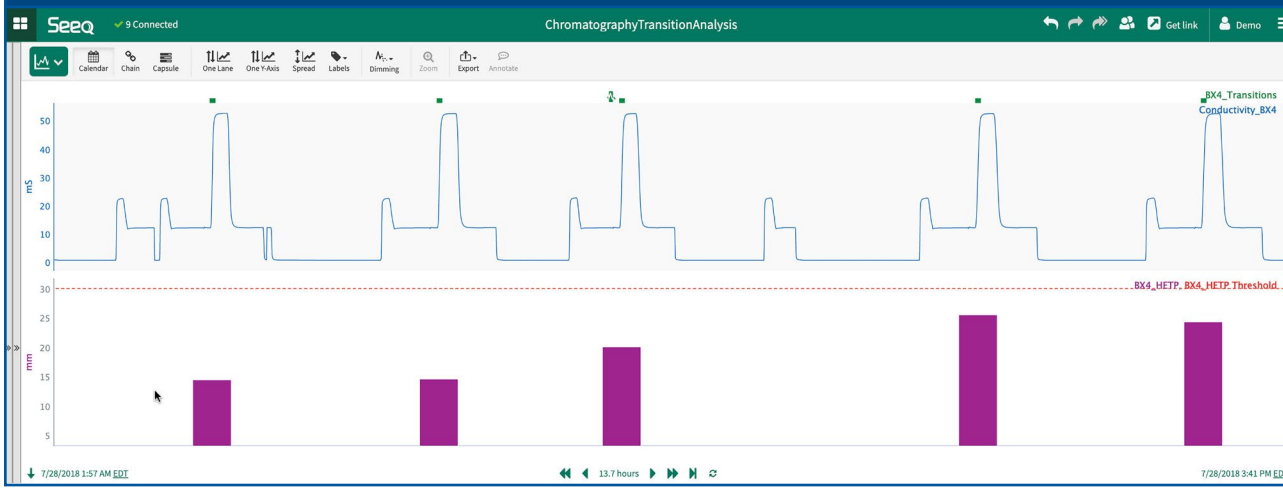
Transition analysis is most effective when calculations are performed automatically, online to minimize delay between data collection and access to calculation results. Results can then be shared with operators, who can prescribe actions such as regenerating the resin or repacking the column when the HETP or asymmetry values are out of specification to avoid quality deviations and lost batches. Using an advanced analytics application, these goals can be achieved by performing the transition analysis calculations and displaying the results in an online dashboard (**Figure 1**).

First, after data have been cleansed, context is added by identifying the phase transitions, using a manufacturing execution system (MES) or through analytical techniques to detect all similar data profiles in the conductivity signal. Some chromatography equipment, such as in multicolumn continuous chromatography, contains data from multiple columns. Changes in other signals, such as the differential pressures across each column, can be used by advanced analytics applications to associate transitions with each respective chromatography column.

A similar approach can be used for single column chromatography if the column is cycled numerous times. Both HETP and asymmetry calculations can be performed using the transition periods for each column. HETP is often calculated using moment analysis (3) to describe the change in conductivity over column volume during each transition period. Asymmetry is estimated by comparing

ALL FIGURES COURTESY OF THE AUTHOR.

Figure 2: Transition analysis HETP (height equivalence of a theoretical plate) and asymmetry values can trend toward column failure over extended periods of time. Models can be applied in an advanced analytics application to predict the amount of time until column failure.



the change in column volume between left and right sides of the conductivity transition peak. These calculations can be performed using a formula in an advanced analytics application.

Immediate access to results

While transition analysis can be performed in other calculation programs, the complexity of the calculations often results in significant delays between when data are generated and when results are found. In addition, the calculation process entails extracting data from historians, inserting the data into a calculation program, and communicating the results as separate steps. Any delays in this process can result in missed column failures, leading to lost or reworked batches, reducing product yield and resulting in millions of dollars in lost product. Advanced analytics applications streamline this workflow by connecting directly to data in leading historians and other databases, performing the calculations automatically as new data are collected, and communicating results through auto-updating dashboards.

Pharmaceutical companies have utilized advanced analytics applications to monitor chromatography column health by creating online production dashboards to monitor HETP and asymmetry. As a result, these companies have realized savings of up to 10 hours per week per unit when performing transition analysis calculations, with further financial benefits gained by applying predictive maintenance to limit unplanned downtime and subsequent decreases in batches produced. Tracking HETP and asymmetry over time or batches enables corrective action prior to column failure.

Advanced analytics applications enable subject matter experts to access process data, define the equations for transition analysis, and build models to forecast predicted HETP and asymmetry values. Predictive maintenance models of time series data utilize a time component to predict usage of the equipment. With transition analysis, an equation can be written to count the total run time of column usage since the last resin regeneration, and to then extrapolate that run time data into the future based on current utilization using formulae in an advanced analytics application. Multivariate regression, such as principal component analysis, enables the extrapolation of the regressed model to predict future values or predict equipment maintenance periods. With transition analysis, these models help users predict HETP and asymmetry values based on the run time of the current utilization of the chromatography columns and other process variables such as flow rates or concentrations (**Figure 2**). Predictive models can be used to forecast an appropriate maintenance window prior to column failure. Performing online transition analysis with predictive modeling can thus reduce downtime, product quality deviations, and lost batches.

Alternatively, scientists and engineers can use alternatives to transition analysis such as TransWidth and DirectAf (3). Trans Width is a measure of the separation efficiency or resolution of the peak, which is calculated from the change in volume across the transition period. DirectAf indicates the normality or tailing of the peak, which is calculated as the average volume differentials by comparing the beginning and end of the transition period at six points for each transition, and it can be used in place of asymmetry.

TransWidth and DirectAf have been shown to be less influenced by noise in the data and thus may be more robust metrics for detecting column integrity and efficiency. These techniques have allowed Just–Evotec Biologics to detect resin degradation and replace the resin prior to subsequent batches.

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A Q&A

A Patient-Centric Solution

Dr. Luigi Boltri
Director of Technology Development
Adare Pharmaceuticals

Dr. Chinmay Maheshwari
Director of Product Development and Pharmaceutical Technologies
Adare Pharmaceuticals

New oral dosage technology offers a solution to patients with swallowing difficulties.

Patient adherence can be improved through the development of innovative dosage technology, especially for patients who struggle to ingest standard oral dosage forms. Parvulet™, a recent acquisition by contract development and manufacturing organization Adare Pharmaceuticals, is one such technology. *Pharmaceutical Technology* sat down with Dr. Luigi Boltri, Director of Technology Development, and Dr. Chinmay Maheshwari, Director of Product Development and Pharmaceutical Technologies at Adare Pharmaceuticals, to discuss this new dosage solution.

PharmTech: What is Parvulet™?

Maheshwari: Parvulet is useful for administering therapies to patients who may find taking conventional dosage forms to be difficult. These patients may include infants, young children, geriatric patients, and others who prefer to take their medication in a semi-solid form. The technology encompasses a solid dosage form that can be in either a powder or a tablet that is gelable upon adding a small amount of water. This gel matrix has the consistency of a soft food and can be easily consumed by the patient.

PharmTech: Can you give us some more background into Parvulet and how it works?

Boltri: For many valid reasons, most drugs are currently administered using solid forms such as tablets and capsules. However, it is known that the deglutition process comprises of a preparatory phase in which the food bolus is chewed and wetted with saliva to a defined texture and rheology to activate the natural deglutition reflex.

It is not by chance that foods consumed by nearly all cultural groups tend to be soft in texture—porridge, rice pudding, quinoa, apple sauce, and Italian polenta, just to name a few. Therefore, it can be argued that human beings are not designed to swallow solid objects.

Parvulet starts out as a solid formulation, tablet or granules, then turns into a soft food by simply adding a few milliliters of water and waiting 20–30 seconds. It is important to note that no other human intervention is needed after water is applied, which further reduces the risk of human error or misuse.

This delivery design represents a major paradigm shift in oral drug administration.

PharmTech: What are the applications of this technology and how is it helpful?

Maheshwari: The main application of this technology is the ease of therapy administration, and patient compliance. Based on the current choices on the market, if a child needs medicine, one would either use a runny liquid formulation

such as solutions, suspensions, syrups, or solid dosage formulations such as capsules and tablets. Liquids are often difficult to handle, have stability issues, are bulky to carry, and can be bitter. Needless to say, there are difficulties in administration of such products to children, as well as concerns about accuracy of administered dose.

> This delivery design represents a major paradigm shift in oral drug administration.

Similarly, solids are not a preferred option either, as small children and even young adults do not prefer to swallow pills and capsules. Crushing these dosage forms can either alter their performance or impart bad taste and smell once crushed. With Parvulet and Adare's decades-long expertise in taste masking, we can develop products that are compact solids, easy to carry, and when intended to administer, these solids can be converted to soft food-like texture in a spoon or a small bowl and administered to the patients. The given dose can be precise and thus perform as intended.

Additionally, bitter-tasting drugs can be easily administered as well as with Parvulet. Various flavors and colors can be included to make the dosage more acceptable by the patients and children.

PharmTech: What makes this technology innovative or unique?

Boltri: Produced using a conventional manufacturing process, Parvulet leverages the natural swallowing mechanism by mimicking the texture and the consistency of natural food bolus, which is a simple but powerful concept. This technology overcomes current practices such as crushing tablets, opening capsules, and mixing the powder with food or a thick food vehicle such yogurt, jam, or pudding—all of which could impact product stability and dissolution properties.

Parvulet can be easily combined with Adare Microcaps®, a technology that uses microencapsulation to secure taste masking by preventing bitter drugs to be released in the mouth. The combination of these technologies generates a dosage form that can improve patient compliance and adherence to the therapy, which maximizes overall efficacy.

PharmTech: Does this technology have any limitations? And if so, what are they?

Maheshwari: One major limitation is acceptance from various drug developers and prospective partners. Undoubtedly, whenever there is a new technological trend, there are initial hurdles with acceptance and promotion of that technology, which results in a lag phase. However, once the initial development hurdles are cleared and a regulatory path is more clearly defined, the product concept should consequently be deemed useful and accepted by the end user.

PharmTech: What are the regulatory implications and needs regarding this application?

Boltri: It is important to recall recent FDA draft guidance on the use of liquids and soft foods as vehicles for drug administration, which states that only those liquids and soft food demonstrated to have no appreciable effect on drug product performance should be proposed as vehicles (1). It also states that consideration should be given to the complexity of the preparation procedure (1).

If the sponsor anticipates the use of liquid or soft foods as vehicles for drug administration during drug development or even during their market approval, data from *in-vivo* and *in-vitro* studies should be submitted.

Considering this, Parvulet's technology is well-equipped to match the requirements of this guidance. In fact, the swallowing vehicle is built into the formulation and can be designed to prevent any impact on the biopharmaceutical properties.

Reference

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Identifying the Structure of an Unknown Impurity in a Topical Gel

Jerry Neal, Jerry Mizell, Richard Durham, and Matt Casteen

It is not uncommon for pharmaceutical analytical chemists to observe unknown impurities during routine drug product testing using general chromatographic methods such as high-pressure liquid chromatography/ultraviolet or gas chromatography/flame ionization detection. Discovery of an unknown impurity triggers an investigation, along with a shift in priorities from routine to more specific specialized testing in order to be able to answer key questions about the impurity. This case study highlights analytical instrumentation and techniques that were used to identify an unknown impurity detected during routine release testing of a topical gel drug product.

Impurities in pharmaceutical products are defined as "substances in the product that are not part of the API itself or the excipients that are used to manufacture the drug product" (1). These impurities are unwanted chemical entities that remain with the API or finished drug product and may develop during manufacturing or upon storage.

An impurity can be inorganic or organic. In some cases, impurities can be residual traces of solvents that are used in synthesis or manufacturing. During routine drug product testing using general chromatographic methods such as high-pressure liquid chromatography/ultraviolet (HPLC/UV) or gas chromatography/flame ionization detection (GC/FID), discovering an unknown impurity triggers investigations and specialized testing in order to answer several basic questions about the unknown, including:

- What is it?
- Is it toxic?
- How much of it is present?
- Where is it coming from?

Answering these questions can be difficult without access to specialized instrumentation and analytical techniques that can provide structural information about the unknown, allowing a useful toxicological assessment to be made.

Classifying impurities

The impurity may be classified either as a degradation product resulting from chemical reaction of the API during manufacturing and storage, or as a foreign substance that was introduced into the product by contamination or adulteration. Classification of impurities permits the development of adequate control measures to minimize unwanted impurities in the final product. It is important to note that the presence of an impurity, in and of itself, is not necessarily problematic. The introduction of trace levels of impurities is inevitable during the manufacturing or storage of pharmaceutical products. In fact, scientists expect impurities to be present, hence the requirement that any and all of them be identified and controlled and their presence and concentrations monitored. In many cases, the presence of an impurity may not pose any safety, quality, or efficacy issues for the

Submitted: Sept. 12, 2019.
Accepted: Nov. 22, 2019.

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drug product. In theory, however, the presence of any impurity could influence the efficacy and safety of the finished product. At the very least, impurities confer no therapeutic benefit. In the worst case, they can be toxic. Several authorities, including the International Council for Harmonization (ICH) and FDA, regulate impurity levels in all pharmaceutical products.

Ensuring the purity of an API or finished drug product requires identifying, quantifying, and controlling any impurity once it has been observed. An impurity can be controlled by establishing appropriate control methods at all points where they enter or form during the manufacturing process. According to ICH guidelines on impurities in new drug substances and new drug products (1), identification of impurities below the 0.1% level is not necessary unless the potential impurities are expected to be unusually potent or toxic.

Materials and methods

This case study used the following analytical instrumentation and techniques to identify an unknown impurity that was detected during routine release testing of a topical gel drug product. The impurity was detected by a validated HPLC/UV method with a known impurity profile (**Table I**) and was out of specification for the product. The following analytical methods were used:

- Liquid chromatography–mass spectrometry/quadrupole time-of-flight (LC/MS/Q-TOF)
- Gas chromatography mass spectrometry / electron impact mass spectrometry (GC/MS EI/MS)
- Fraction collection
- Infrared spectroscopy.

Results and discussion

After detecting an unknown impurity during routine release testing, a pharmaceutical company requested that investigational testing be performed on its topical gel drug product to identify the impurity and determine whether it was an API degradation product, a process impurity, or a contaminant that had been introduced during the manufacturing process.

The HPLC/UV chromatographic impurity profile of the topical gel release lot is shown in **Figure 1**. When comparing the known impurity profile (**Table I**) to the HPLC/UV chromatogram (**Figure 1**), scientists observed that a single unknown impurity eluted past Impurity 11 (55.7 min.) at approximately 71 minutes. Other chromatographic peaks that were observed eluting after the unknown itself were considered evidence of impurities from solvents that were used to prepare the sample for HPLC testing and considered to be blank-related.

Outlining the process

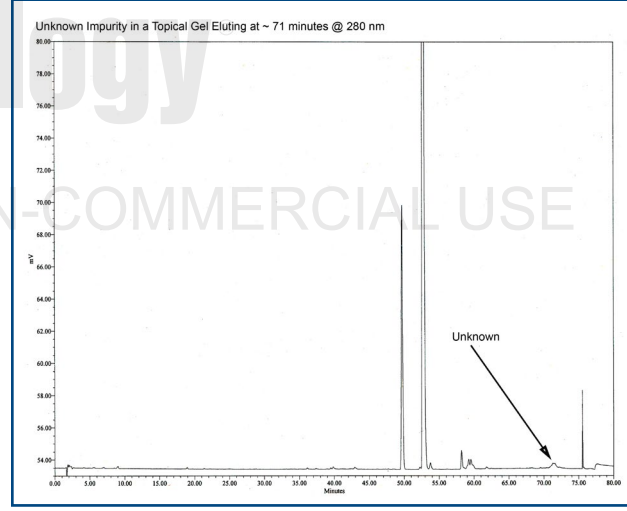
One of the most challenging problems encountered is the identification of unknowns at trace levels in pharmaceutical drug products. This is due mainly to the significant differences in detection limits for each analytical technique that is used to confirm unknown impurities. In this case, the first step in identifying the unknown impurity was testing the drug product by LC/MS using Q-TOF detection. This method provides key information about the identity of the unknown by generating highly accurate mass data. Having highly accurate mass information for the unknown significantly reduces the number of possible molecular formulas or compound identities generated by the molecular formula software.

While this testing provides key information about the unknown, it does not always provide positive identification of the unknown, because hundreds of compounds may share the same molecular formula. Additional experimental data are needed to rule out other compounds and eventually identify the unknown. With this impurity, the mass (M+1) of the unknown was determined to be 447.3476 from Q-TOF LC/MS experiments (**Figure 2**).

Table I: Unknown impurity profiles for topical gel using high-pressure liquid chromatography (HPLC) and ultraviolet (UV) detection.

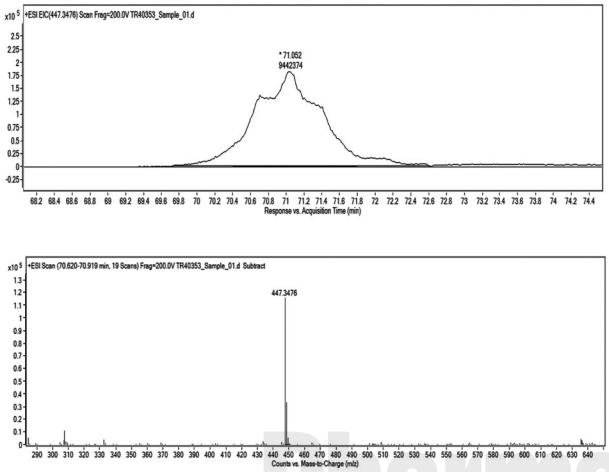
Impurity	Retention time (in minutes)	Relative retention time (in minutes)	Molar response factor	Molecular weight
Impurity 1	6.7	0.128	0.43	138.16
Impurity 2	32.2	0.614	0.99	314.42
Impurity 3	33.1	0.630	1.26	316.44
Impurity 4	34.8	0.636	0.67	314.42
Impurity 5	41.8	0.797	0.57	316.44
Impurity 6	43.7	0.800	0.57	316.44
Impurity 7	44.3	0.810	1.36	316.44
Impurity 8	51.3	0.940	---	220.35
Impurity 9	53.7	0.983	1.63	300.44
Impurity 10	54.1	0.990	1.36	300.44
API	54.6	1.00	---	300.44
Impurity 11	55.7	1.02	1.66	300.44

Figure 1: High-pressure liquid chromatography (HPLC) chromatogram of unknown impurity in a topical gel.



ALL FIGURES COURTESY OF THE AUTHOR.

Figure 2: HPLC Spectra. HPLC is high-pressure liquid chromatography, LC is liquid chromatography, MS is mass spectroscopy, and EI is electron impact. A. LC/MS +EI product ion scan of unknown in a topical gel eluting at approximately 71 minutes. B. LC/MS +EI product ion of unknown in a topical gel eluting at approximately 71 minutes (M+1 = 447.3476).



Using the unknown's accurate mass information and the molecular formula generator, the unknown was determined to have the molecular formula C28H46O4. The exact mass calculation for the molecular formula was 446.3396.

Using the exact mass from the Q-TOF LC/MS experiments and the molecular formula, scientists performed a National Institute of Standards and Technology (NIST) database search and identified a total of 88 potentially matching species within the database, with the top search result being diisodecyl phthalate (DIDP) (2).

Knowing the impurity's exact mass and having a molecular formula from the LC/MS data is invaluable in helping narrow down its identity from hundreds of potential compounds with the same molecular formula. Other analytical techniques must then be used to rule out or confirm the impurity's structural identity.

One disadvantage of using LC/MS data is that database libraries with searchable mass spectral data do not exist. However, extensive searchable database libraries are available for GC/MS testing. Thus, the next step in identifying the unknown was to test it by GC/MS. Obtaining electron impact (EI) mass spectra of the unknown would allow for positive identification with a database match.

The LC/MS Q-TOF experiments indicated that the unknown was potentially identifiable as diisodecyl phthalate, which is volatile and thermally stable enough to be detected by GC/MS. A potential problem associated with GC/MS testing, however, was the fact that, if the unknown proved not to be DIDP, it might not be sufficiently volatile to be detected by GC/MS.

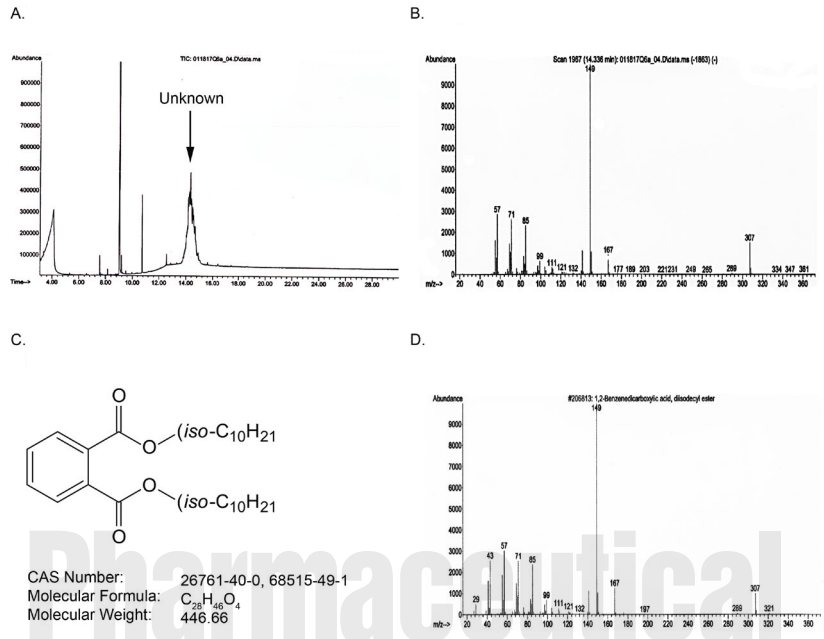
In addition, if the unknown were not present at a high enough concentration, it would not be possible to obtain electron impact mass spectra of sufficient quality to search against the database library. To enhance the probability of performing a successful GC/MS run, scientists prepared a concentrated sample of the drug product to ensure that the impurity could be adequately detected, since the sensitivity of the various analytical techniques used to confirm identity can vary significantly.

Table II: Conditions used for gas chromatography/mass spectrometry/electron impact (GC/MS/EI) testing.

Gas chromatograph:	Agilent 6890N
Analytical column:	Agilent DB-1ms capillary column 30 m x 0.25 mm, 0.25 µm (P/N: 122-0132)
Injection port type:	Split / Splitless
Injector temperature:	290 °C
Injection mode:	Split
Split ratio:	5:1
Carrier gas type:	Helium at 1.2 mL/minutes
Oven program:	60 °C for 0.5 min. to 300 °C at 20 °C held for 17.5 minutes.
Mass spectrometer:	Agilent 5975 Inert XL
Transfer line temp.:	300 °C
MS temp.:	230 °C (Source); 150 °C (Quad)
MS mode:	Electron Impact (EI), Scan
Scan range:	50–500 atomic mass units (amu)
Solvent delay:	3 minutes
Autosampler:	Leap Technologies PAL Combi-xt
Cycle:	Gas chromatography – injection (GC – Inj.)
Syringe:	10 µL
Sample volume:	1.0 µL
Air volume:	0 µL
Pre Cln Slv1:	3 strokes
Pre Cln Slv2:	0 strokes
Pre Cln Spl:	2 strokes
Fill volume:	5 µL
Fill speed:	2 µL/second.
Fill strokes:	5
Pullup del:	5 seconds.
Inject to:	GC Inj1
Inject speed:	50 µL/second
Pre Inj Del:	500 ms
Pst Inj Del:	500 ms
Pst Cln Slv1:	3 strokes
Pst Cln Slv2:	0 strokes

Multiple injections of both dilute and concentrated sample were made onto an HPLC/UV system to generate a chromatographic profile similar to that in **Figure 1**. The HPLC eluent from multiple injections was collected for approximately one minute on either side of the expected retention time of the impurity. The fractions were combined and further concentrated at least 10,000-fold to ensure adequate sensitivity for detection. Injections of the concentrated solution were made on the GC/

Figure 3: Gas chromatography/mass spectrometry (GC/MS) electron impact (EI) results.
A. GC/MS EI total ion chromatogram of concentrated unknown.
B. GC/MS EI spectra of concentrated unknown. C. Best database match - Diisodecyl Phthalate (DIDP).



MS using the conditions outlined in **Table II**. GC/MS results (**Figure 3**) confirmed that concentrated unknown electron impact (EI) mass spectra were consistent with the best database match for DIDP and the exact mass obtained by LC/MS Q-TOF experiments. Scientists used infrared spectroscopy to test the concentrated impurity, and the results further supported the probability of the unknown being DIDP. Fourier Transform-Infra-Red (FT-IR) spectra of the unknown did not contain spectral elements that contradicted the mass spectroscopy data and were also consistent with NIST reference spectra of diisodecyl phthalate (**Figure 4**).

As a final confirmation, a known standard of DIDP was prepared as a marker at multiple concentrations to estimate the concentration of unknown observed in the sample. The DIDP markers, along with a sample preparation, were injected using the original HPLC/UV assay conditions (**Figure 5**).

Figure 4: A comparison of Fourier-Transform-Infra-Red (FT-IR) spectra A and B.
A. Concentrated unknown impurity B. National Institute for Standards and Technology (NIST) spectra for diisodecyl phthalate (DIDP).

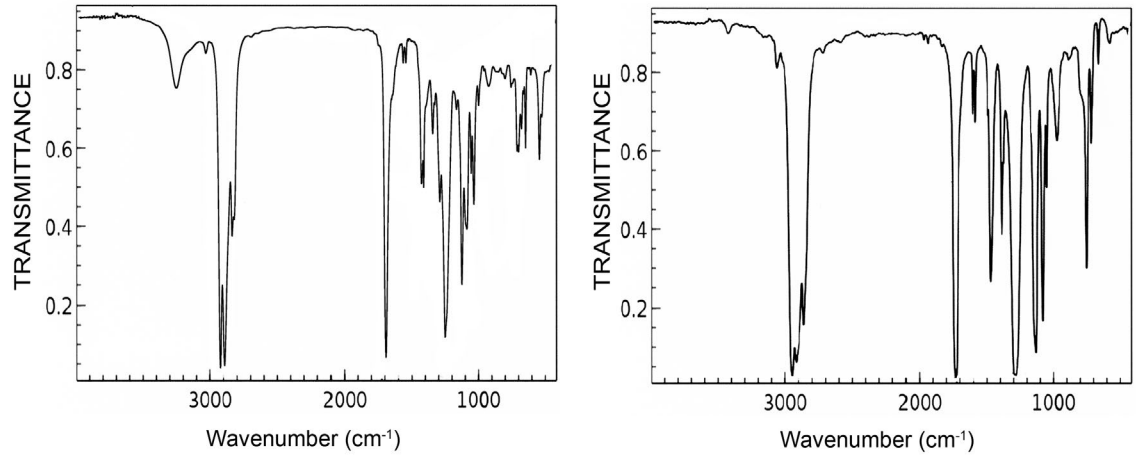
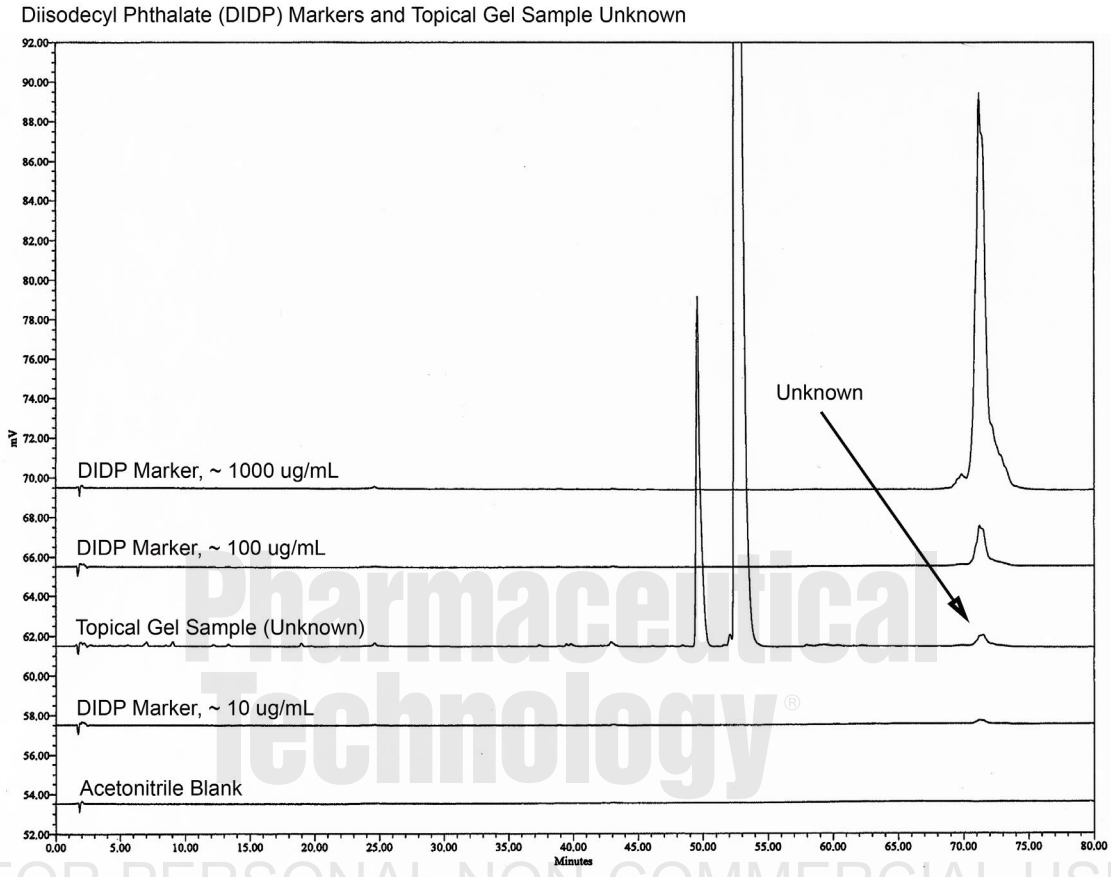


Figure 5: High-pressure liquid chromatography (HPLC) and ultraviolet (UV) overlay (markers and unknown). Reflects results for diisodecyl phthalate (DIDP) markers and a sample of topical gel unknown.



Evaluation of all the experimental data collected from the investigational experiments demonstrated that the unknown impurity detected in the topical gel drug product during release testing was DIDP (**Figure 3c**).

It should be noted that commercially available DIDP actually is a mixture of two phthalates. The other component is diisononyl phthalate (DINP). DIDP is composed of a complex mixture of branched C9-C11 isomers containing mainly C10 isomers of C28H46O4. Significant amounts of toxicological data for DIDP are available for review (3).

DIDP is one of eight individual phthalate esters that the US Environmental Protection Agency (EPA) has deemed appropriate subjects for developing assessment and management strategies. It is the main plasticizer used for polymers in wire and cable applications. It also is used in anti-corrosion and anti-fouling paints, sealing compounds, and textile inks (4). Major identified sources of DIDP internationally include food and pharmaceutical packaging as well as printing inks (5). DIDP also is used as an additive in the production of plastics to make them more flexible.

In this case, the source of the impurity was not definitely determined; however, scientists believe it was unlikely to be a degradation product of the API, since the molecular weight of DIDP is higher than that of the API. Instead, the impurity was most likely a contaminant that resulted when the API or drug product came in contact with a source of plastic that was introduced during the manufacturing process. To date, no other batches of this drug product have contained this impurity.

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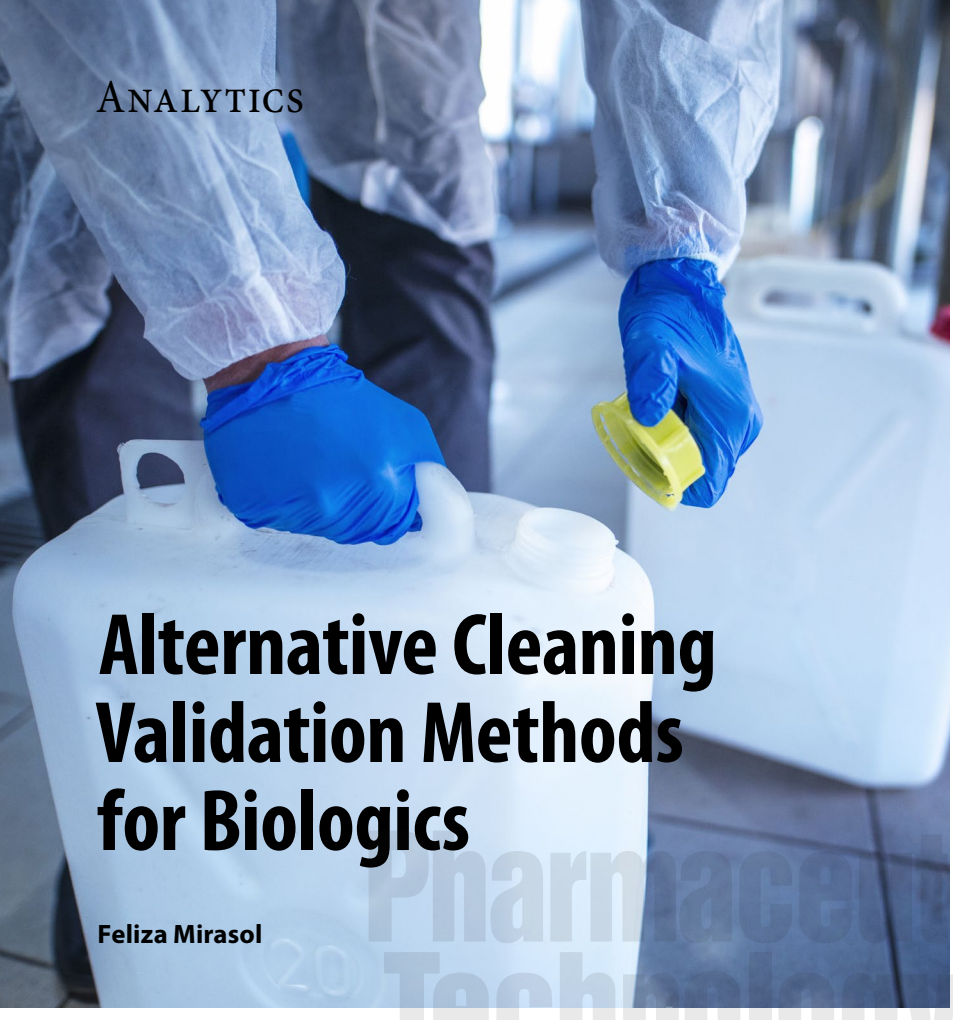
Jerry Neal, **BS**, is senior analytical chemist; **Jerry Mizell**, **BS**, is director of analytical services; **Richard Durham**, **PhD**, is chemistry, manufacturing and control (CMC) quality liaison; and **Matt Casteen**, BS, is team leader, all with Metrics Contract Services.



Alternative Cleaning Validation Methods for Biologics

Feliza Mirasol

Because conventional cleaning methods can risk product loss, biopharmaceutical manufacturers are often reluctant to use PDE/ADE limits to validate cleaning processes.

Cleaning validation for biologics, particularly those that are manufactured in commercial stainless-steel equipment, has always been tricky. One worrisome issue has been the potential loss of product as the result of the cleaning process. Cleaning processes can degrade protein molecules, and biologic products—such as therapeutic antibodies—have been known to degrade and denature under extreme conditions, such as high heat and high or low pH. This can often result in loss of pharmacological activity. Yet, the cleaning of biomanfacturing equipment often requires that equipment surfaces be exposed to extreme pH and temperatures to ensure sterilization.

FDA cleaning requirements

FDA expects manufacturers to have written procedures on how their cleaning processes will be validated (1), and expects the validation procedure to specify the personnel responsible for performing and approving the validation study. Companies must also indicate staff members who will be responsible for establishing the acceptance criteria for the validation and the timing for when revalidation will be required.

The agency further expects companies to prepare specific, written cleaning validation protocols before carrying out studies that they expect to perform on each piece of manufacturing equipment. The written protocols should address important issues, such as the company's sampling procedures, the analytical methods that will be used, and the sensitivity of those methods.

Fortunately, advances in analytical technology have made it possible to detect even very low levels of residue left behind from manufacturing and cleaning processes, according to FDA. However, when residue or contamination is not detected, that may be due to a limitation in the sensitivity of the analytical method used.

Absence of detectable levels of residue or contamination is not itself a guarantee that a piece of equipment or the entire manufacturing system is clean. Because of this, the agency recommends that companies challenge the analytical method used for detection by combining it with sampling methods. This allows manufacturers to show that contaminants can still be recovered from equipment surfaces after cleaning. After all, a negative test (i.e., where no contaminants are detected) could be due to poor sampling technique.

Sampling techniques are important for determining contamination levels, and FDA accepts two general types: direct surface sampling and rinse solutions (1). Direct surface sampling allows accessible but hard-to-clean areas to be evaluated, so that data can be used to establish an acceptable residue or contamination level per given surface area.

Dried residue, or residue that is insoluble, can easily be sampled by physically removing it. However, FDA has cautioned manufacturers that, in order to do direct sampling, they must first determine early on in their cleaning validation program what type of sampling material they will use and how the material will affect test data because there is potential for the sampling material to interfere with testing.

For the rinse sample method, advantages include use of a larger surface area for sampling and ability to test inaccessible systems (e.g., ones that cannot be routinely disassembled). However, the residue or contaminant may not be soluble, or may be obstructed by the physical structure of the equipment. As a result, evaluation of any system's cleanliness should not rely solely on evaluation of the rinse solution, but rather evaluation of the equipment itself. The rinse solution

should not simply be tested for water quality, but rather for the presence of specific contaminants.

Data must be recorded and documented during the sample testing procedures. Testing uncleaned equipment will establish what an unacceptable result would look like when indirect testing methods are used.

Where alternative methods are justified

Alternative cleaning validation methods involve using a gauge other than permitted daily exposure (PDE) or acceptable daily exposure (ADE), or changing the limits set by regulators for these standards. It has been argued that protein molecules are degraded by the cleaning processes used to meet PDE or ADE limits (2), which has led to a search for alternative cleaning validation methods.

In the European Medicines Agency's (EMA's) guideline on setting health-based exposure limits (3), the agency states that it would be acceptable to use approaches other than PDE/ADE limits to determine health-based exposure limits, provided that the alternative approaches are "adequately and scientifically" justified. EMA also understands that, because the cleaning methods for "therapeutic macromolecules and peptides" can result in the degradation or denaturation of those molecules due to their exposure to extreme heat and/or pH, "the determination of health based exposure limits using PDE limits of the active and intact product may not be required" (3).

The worst-case product

Loss of biological product during cleaning processes can be costly, and especially challenging when a company is testing its cleaning validation method on a potentially new biologic product. To help mitigate expensive losses, companies may look for alternatives to their molecule that they can use as a "worst-case product" scenario for their cleaning validation methods.

In one study, a worst-case product scenario was tested for the cleaning validation of brolucizumab (4), Novartis' Beovu, prior to its approval by FDA in October 2019 for treating wet age-related macular degeneration (5). In the study, five molecule candidates for worst-case product were subjected to cleanability and solubility tests, with the caveat that a worst-case product must be more difficult to clean than the actual biologic product. This would ensure that acceptable cleaning settings would be established for the bioreactor when manufacturing the actual biologic product (4).

Loss of biological product during cleaning can be costly.

Going through this exercise helped the researcher demonstrate the multidisciplinary nature of cleaning validation, which is one aspect of good manufacturing practices (GMP) regulations that is still not well understood or gets little attention (4). FDA's requirements largely focus on the need to record and document all steps used in cleaning processes. To that end, a company must be meticulous in its cleaning validation documents, including defining the equipment that is cleaned as well as the equipment used in cleaning processes; demonstrating understanding of the given drug's properties; and describing analytical methods used to determine the level of cleanliness (or presence of contaminants). Sample residue collection from surfaces must also be recorded. The overall approach to cleaning validation, therefore, requires expertise in various disciplines and cooperation among those disciplines.

Recognizing residues

Air-liquid residues can be detrimental for biologics manufacturing and can come from a variety of sources, including hydrocarbons, polymers, mineral silicates, lubricants, and siloxanes (found in valves, gaskets, and tubing) (6). Hydrocarbons such as steramide, erucamide, and oleamide, are mold-release agents used to prevent caking of powders. They are often used in manufacturing the bags (e.g., those used for storage and transport) and biologics equipment.

Polymers such as nylon, polytetrafluoroethylene, and silicone are necessary components of equipment used in raw material manufacturing and are also used in bags or containers meant for raw material storage. These substances can be a source of raw material impurities. Likewise, mineral silicates, lubricants, and siloxanes can also be sources of raw material impurities, all of which can appear in bioprocess preparation tanks (6).

Common cleaning approaches that pharmaceutical manufacturers use to combat these residues include increasing spray (e.g., employing a rotating spray device), raising cleaning temperature to around 75 °C–85 °C, and using a formulated cleaning agent. In addition, the industry may increase the concentration of the cleaning agent and/or use an oxidizing cleaning agent or a detergent additive combined with an alkaline cleaning solution (so long as temperature is kept between 50 °C and 65 °C) (6).

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A Q&A

Oncology Product Manufacturing in a Nondedicated Facility

Wendy Saffell-Clemmer
Lead Scientist and Senior Director
Baxter BioPharma Solutions

The increase in targeted oncology therapies has led to fewer units per product, making production in dedicated facilities less practical.

Outsourcing complex biologic products to an experienced contract manufacturing organization can improve efficiency and reduce costs. Measures to prevent cross-contamination make it possible to manufacture cytotoxic and noncytotoxic products in the same facility, according to Wendy Saffell-Clemmer, lead scientist and senior director at Baxter BioPharma Solutions. *Pharmaceutical Technology* recently sat down with Saffell-Clemmer to discuss the advantages of manufacturing immuno-oncology therapies in multiproduct facilities. She also offered some strategies to overcome potential risks and discussed cleaning process development and validation.

Pharmaceutical Technology: In the past decade, what changes have occurred in the immuno-oncology pipeline?

Saffell-Clemmer: There have been several changes in the oncology pipeline. Ten years ago, chemotherapy with cytotoxic small molecules was the only pharmaceutical option available for the treatment of cancer. A big change occurred in 2010 when the first immunotherapeutic for cancer received regulatory approval. Since then, therapies have continued to become more targeted to specific patient populations within indications.

The types of immunotherapeutic products have also evolved. Products now include monoclonal antibodies and different variations such as bispecific antibodies, fusion proteins, and antibody–drug conjugates. In the United States alone, more than 1,800 immunomodulator therapies are in active development today.

Pharmaceutical Technology: How have these changes made production in a multiproduct facility more attractive?

Saffell-Clemmer: The increase in targeted therapies has led to decreased numbers of units per product. This can make production in a dedicated facility less practical. Outsourcing to a contract manufacturing organization that may have more experience in handling complex biologic products has its benefits. It is a good option for improving efficiency, getting to product launch faster, and reducing costs.

Pharmaceutical Technology: What is the greatest risk to using a multiproduct facility?

Saffell-Clemmer: There are definitely concerns about cross-contamination, which can be a risk for any type of pharmaceutical manufacturing in a multiproduct facility. However, this risk can be avoided through good facility design and a robust approach to cleaning validation.

Pharmaceutical Technology: Can a line used to produce cytotoxic drug products be used for noncytotoxic products?

Saffell-Clemmer: Yes, absolutely. Good cleaning validation practices, combined with appropriate engineering and procedural controls, make it possible to manufacture cytotoxic and noncytotoxic products in the same facility.

Pharmaceutical Technology: What are some best practices for facility controls to prevent cross-contamination?

Saffell-Clemmer: State-of-the-art engineering controls are really important. These can prevent cross-contamination among products as well as protect employees who are working at the facility. At Baxter BioPharma Solutions' facility in Halle Westfalen, Germany, for instance, we use isolators and restricted access barrier systems, which are equipped with separate HVAC and air exhaust systems.

We also try to automate tasks as much as possible. These types of tasks include automated lyophilizer loading and unloading, automated capping, and automated inspection to reduce human interactions and potential for exposure. It also reduces any potential for tracking product into nonproduct areas.

In addition, any filled and sealed vials are passed through an automatic decontamination process where they are rinsed prior to packaging. We also use product-dedicated filling equipment and single-use disposable products to prevent cross-contamination.

Pharmaceutical Technology: Are engineering controls alone enough to prevent cross-contamination?

Saffell-Clemmer: No, absolutely not. As with any other operation at a pharmaceutical manufacturing facility, it is critical to have a comprehensive risk-based program. This is clearly spelled out by the European Medicines Agency, which has excellent guidance for determining health-based exposure limits for residual active substances.

The health-based exposure limit is the permissible daily exposure. It is critical to conduct a risk assessment before introducing any new product into a shared facility. The risk assessment should account for the permissible daily exposure as well as properties of the active pharmaceutical ingredient and its formulation. For example, the solubility of a particular product may make it more difficult to clean or remove from a surface.

This risk assessment determines—before it is introduced—if a new product is suitable for the facility and if it represents a worst case for its product type at that manufacturing unit. If the new product is not a worst case, it can be safely manufactured and cleaned using processes that are already validated and in place at that facility.

If the new product is a worst case, then the facility has an opportunity to create a plan for cleaning process development and validation. That plan must be executed prior to introduction of the new product to protect the other products at the facility.

Pharmaceutical Technology: What are the components of a cleaning validation program?

Saffell-Clemmer: First, as I mentioned, it is important to understand the health-based exposure limit (permissible daily exposure) for a particular product. Once we know what that limit is, it can be used to calculate an analytical limit, which would be applied to any final samples taken from the equipment for testing.

Sampling is typically done either by swab sampling, where a swab is used to interact with the surface of the equipment, or by rinse sampling, where a specific volume is poured over the surface of the equipment. Before testing, we account for variables such as the area that will be swabbed, as well as the volume that the swab will be placed in. We also need to understand things such as the surface area of the equipment.

After performing this calculation to understand what level of product we could potentially be testing for, we need to develop a test method with sufficient sensitivity. When that method becomes available, additional testing must be done to show that the product can be recovered from product contact surfaces.

We do that by spiking the product on to samples of product contact surfaces such as stainless steel or glass. Cleaning validation requirements must be established by understanding the process; determining critical process parameters; and incorporating knowledge of the equipment design, how frequently the equipment will be used, and whether the equipment is product dedicated.

A manufacturer that really understands its equipment knows which areas will be more difficult to clean and should receive particular attention during the cleaning validation process. After that is understood, a performance qualification of the cleaning process will be delineated in a protocol, which will include a description of sample locations and procedures. For example, the protocol may state that a procedure must be executed a minimum of three times in three different runs. Then, the samples acquired during this procedure will be tested for product residue using the validated method.

In addition to that process, it is really important to include a hold time for dirty equipment so that it is known if the product is more difficult to clean after a specific time period. It is also critical to monitor the cleaning validation process.

This is not a one and done activity. Rather, the qualification studies should be repeated on a regular basis—often annually—for the worst-case product in any single product class.

Comparison of Pharmaceutical Excipients and Food Ingredient Requirements

Luke Grocholl, Priscilla Zawislak, R. Christian Moreton, and Katherine L. Ulman

With ingredients sold to multiple markets, excipient manufacturers must understand the different regulatory requirements for pharma vs. food.

Manufacturers of pharmaceutical excipients often serve other markets in addition to the pharmaceutical industry. The excipient qualification process, quality systems supporting excipient manufacture, and regulatory scrutiny associated with pharmaceutical excipients offer confidence to potential customers in other regulated industries that the pharmaceutical excipient grade material could be qualified to meet their needs. The reality, however, is that significant differences often exist between regulated industry requirements, and neither suppliers nor customers can assume a single material qualification can meet every markets' requirements.

Many ingredients used as pharmaceutical excipients have applications in dietary supplement or food ingredient markets. The common sugar alcohol, mannitol ($HOCH_2(CHOH)_4CH_2OH$), for example, can be used as a pharmaceutical excipient, a non-dietary ingredient in dietary supplements, or a food additive. Mannitol monographs are accessible in the *United States Pharmacopeia's National Formulary* (*USP–NF*), *European Pharmacopoeia* (*Ph. Eur.*), and Ja*panese Pharmacopoeia* (*JP*), as well as the *Food Chemicals Codex* (*FCC*) and the European Union (EU) Food Additive regulations (Reg. (EU) 231/2012). Mannitol, with its sweet taste and pleasant mouthfeel, may serve the same purpose in confectionaries, chewable dietary supplements, or oral medications.

Each market application, whether food, dietary supplement, or pharmaceutical, has its own requirements, and although some of the requirements may overlap, pharmaceutical excipient manufacturers must understand and implement the requirements relevant to the intended uses before supplying into the aforementioned applications. Similarly, manufacturers of food additives and/or non-dietary ingredients need to understand and implement pharmaceutical requirements prior to supplying mannitol for drug product use. It is incorrect to assume that materials meeting food additive and/or non-dietary ingredient standards will also meet pharmaceutical excipient requirements. Likewise, it is also incorrect to assume that product approved for use as a pharmaceutical excipient will automatically comply with food or dietary supplement requirements.

FDA's food additive definition (1) does not include generally recognized as safe (GRAS) substances; however, all food ingredients (including food additives, GRAS substances, and non-dietary ingredients for dietary supplements) are held to the same good manufacturing practice (GMP) requirements. For the sake of brevity, in this article, food additives, GRAS substances, and non-dietary ingredients for dietary supplements will be referred to collectively as food ingredients. Pharmaceutical excipients will be referred to as excipients.

Excipient, dietary supplement, and food ingredient markets are regulated, having requirements for quality management systems with material specifications and qualifications. Some markets have voluntary GMPs and other certification programs as discussed in the following. While there is considerable overlap in requirements for the different markets, there are also significant differences. No single quality management system or certification scheme satisfies the demands or requirements for all three markets, and some applications may have market-driven

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Table I: Sources for guidelines and certification programs, food and pharmaceutical excipients.

Guidance/guidelines	Website
NSF/IPEC/ANSI 363–2016 Good Manufacturing Practices for Pharmaceutical Excipients	ansi.org
EXCiPACT Certification Standards for Pharmaceutical Excipient Suppliers: Good Manufacturing Practices, Good Distribution Practices	excipact.org
Joint International Pharmaceutical Excipient Council–Pharmaceutical Quality Group Good Manufacturing Practices Guide for Pharmaceutical Excipients	ipec.org
Food Chemicals Codex	foodchemicalscodex.org
International Food Additives Council	foodingredientfacts.org
The Global Food Safety Initiative	mygfsi.com
Food Safety Systems Certification 22000	fssc22000.com
Safe Quality Food Institute	sqfi.com
International Featured Standards	ifs-certification.com
ISO 22000 Food Safety Management	iso.org
World Anti-Doping Agency	wada-ama.org
International Council for Harmonization	ich.org

requirements not considered for the other applications. **Table I** lists pertinent guidelines and certification programs mentioned in this article.

GMP requirements

There are well-established GMP standards for regulated markets. For excipients, the NSF/IPEC/ANSI-363 and EXCiPACT excipient GMP standards, or the *Joint International Pharmaceutical Excipient Council–Pharmaceutical Quality Group GMP* guide for pharmaceutical excipients should be followed. In contrast to food ingredients, pharmaceutical products are not limited to the oral route of administration. For non-oral routes of administration, additional GMP requirements are based on intended uses.

Food GMP conditions are mandatory for food ingredients. In *Current Good Manufacturing Practice, Hazard Analysis, and Risk Based Preventative Controls for Human Food* (2), FDA requires that all food must be manufactured in compliance with food GMP requirements. Finished dietary supplements are subject to *Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling or Holding Operations for Dietary Supplements* (3) dietary supplement GMP requirements; non-dietary ingredients are subject to 21 *Code of Federal Regulations* (*CFR*) 117 Part B (2) like all food ingredients.

The manufacture of chemical and mineral food ingredients may vary considerably from production requirements for agricultural food ingredients. Similar to excipients, food ingredients are often manufactured in chemical or mineral manufacturing facilities.

As such, it is not always clear to these manufacturers how to apply food GMP requirements to food ingredients. For this reason, the International Food Additives Council (IFAC) developed a GMP guide (4) for the food ingredient industry. Similarly, the Global Food Safety Initiative (GFSI) recommends the Food Safety Systems Certification FFSC 22000, Safe Quality Food Institute, or International Featured Standards as applicable food safety schemes for the manufacture of (bio) chemicals. The FSSC 22000 is based on ISO 22000 Food Safety Management requirements and adds additional elements appropriate to food ingredient manufacturers. Regardless of the certification standard used, application of food ingredient GMPs is sometimes quite different than for finished foods. Appropriate controls for food ingredients are based on identified and potential material hazards.

Although some quality management systems (i.e., GMPs) for excipients may exceed requirements needed to meet food ingredient GMPs, it is incorrect to assume excipient GMPs meet all food ingredient requirements. It is often easier to obtain acceptance of a food-grade material for use as a pharmaceutical excipient than for an excipient to comply with food regulatory requirements. Like excipients, food ingredients must undergo rigorous toxicological and safety evaluation prior to being approved for use in food; however, excipients, unlike food ingredients, may be evaluated based on their intended route of administration. In addition, whereas direct contact equipment and packaging supplies for excipients must be qualified based on the excipient being handled—including verification activities and identification of potential risks—food contact materials must follow FDA rules limiting the types of materials that can be used.

Table II illustrates some of the differences between food ingredient and excipient GMP requirements.

Other regulatory requirements

In addition to GMPs, food ingredients and excipients are subject to other regulatory requirements including the following:

- California Safe Drinking Water and Toxic Enforcement Act of

Optimizing Equipment Availability for Capsule Fillers

ON-DEMAND WEBCAST: Aired Tuesday, March 24, 2020

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

Event Overview

Modern encapsulation is encumbered by some well-established, but inefficient processes that limit overall equipment effectiveness. This webcast will demonstrate that there is room for availability-based improvements within the capsule-filling sectors of the pharmaceutical and nutraceutical industries. Learn what the common equipment bottlenecks are and how engineering developments can maximize equipment availability. Experts will provide insight into how to minimize cycle, set-up, and changeover times and how to define optimal parameters for each process step.

Key Learning Objectives

- Understand capsule-filling equipment bottlenecks
- Review engineering solutions to improve overall equipment effectiveness
- Understand how to define optimal parameters for each process step
- Learn how the decoupling of process steps and use of additional stations can reduce conversion and cleaning times

Presenters

Matt Bundenthal
Senior Manager
OSD Systems

Johan Van Evelghem
Senior Expert
Oral Solid Dosage Forms

Moderator

Jennifer Markarian
Manufacturing Editor
Pharmaceutical Technology

Who Should Attend

- Capsule-filler users from the pharmaceutical, nutraceutical, and nutritional industries

For questions or concerns,
email mdevia@mmhgroup.com.

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Table II: Key differences between food ingredient good manufacturing practices (GMPs) and excipient GMPs.

Food ingredient GMPs	Excipient GMPs
Primary focus: Identify and control hazards.	Primary focus: Verify process controls are sufficient to reproducibly produce excipients of consistent quality.
Written food safety plan available at all food facilities, which includes the preventive controls for identified food safety hazards.	Assessment of risks is required; however, a single documented risk assessment plan is not required.
Identity of preventive controls qualified individual (PCQI) responsible for: • Preparation of the food safety plan • Validation of the preventive controls • Reanalysis of the food safety plan	No equivalent requirement.
Activities can be managed by shared responsibility. Quality unit is responsible for oversight, but responsibility can be delegated.	Quality unit independent of manufacturing is responsible for: • Approval of documents that impact product quality • Approval of significant changes* that may impact excipient quality • Approval of suppliers • Release of finished excipient • Approval to reprocess and/or rework • Approval of returned excipient for resale • Review and approval of manufacturing, packaging, labeling, and testing records prior to approval.
Minimum personnel gowning/hygiene defined in regulation.	Personnel gowning/hygiene determined by risk assessment.
Allergen control plan required.	Allergen control is customer driven but not required by GMP.
Documented recall plan, which must include conditions and process for informing the public.	Documented recall procedure; public notification is not required.

*Significant change is defined as "any change that has the potential to alter an excipient's physical, chemical or microbiological property from the norm, and/or that may alter the excipient's performance in the dosage form" (5).

1986 (commonly called Prop 65) for the reporting of known carcinogens
- Pesticides and potential pesticide residue
- World Anti-Doping Agency
- Bovine spongiform encephalopathy/Transmissible spongiform encephalopathy (6) reporting requirements
- Applicable *USP* general chapters (for excipients)
- Applicable FCC general chapters (for food additives).

Excipients and food ingredients require analytical testing, often described in published monographs. Although there may be some overlap in attributes, test methods, and specifications described in the monographs, significant differences often exist.

For instance, food and food ingredients' heavy metal requirements typically focus on arsenic, cadmium, mercury, and lead. For pharmaceutical products, elemental impurities (7) are emphasized, which does not apply directly to excipients, but rather, to the final dosage form of which the excipient is a component. As of Jan. 1, 2018, heavy metals specifications were no longer required for excipients in the United States and European markets unless specific metals are included in the excipient's monograph. Excipients have requirements for residual solvents (8); however, in the United States, no specific residual solvent requirement for food ingredients exists. This is not to say that there is no consideration for solvents in food ingredients. When appropriate, food safety risk due to potential residual solvent should be evaluated.

Regulatory agencies, such as FDA, sometimes inspect excipient and food ingredients facilities for cause; however, only food ingredient manufacturing facilities are required to register with FDA under the Bioterrorism Act of 2002 (9). Under the Food Safety Modernization Act (FSMA), food ingredient facilities are subject to additional FDA requirements intended to protect against intentional adulteration (10). FSMA requirements include implementing a food defense plan targeted at preventing intentional adulteration intended to do mass harm to the public and food fraud mitigation programs targeted at protecting against economically motivated adulteration. Although similar intentional adulteration concerns may exist for excipients, a written plan to address intentional excipient adulteration is not explicitly required.

Importers of food ingredients must confirm foreign suppliers comply with US food requirements per the Foreign Supplier Verification Program (FSVP) (11). FSVP requires food ingredient importers to verify that their suppliers have controls in place for meeting US food safety requirements, including implementing supplier verification activities to mitigate risks identified for each imported food. There is no corresponding regulatory requirement to verify GMP of foreign manufacturers of excipients. Pharmaceutical customers should evaluate the risks associated with imported excipients.

Integrated Preformulation Studies for Fast Advancement of Drug Candidates to Human Clinical Studies

LIVE WEBCAST: Wednesday, April 15, 2020 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

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

Event Overview

The development cost and timeline for a new drug is increasing due to high attrition rates caused by inadequate physicochemical and biopharmaceutical attributes, unacceptable safety, and sub-marginal efficacy. This development attrition rate can be reduced by strengthening efficacy and toxicity screens and establishing a developability screen to enable selection of developable compounds to move to the clinic. It is critical to select right formulation principles for efficacy and toxicity screens, and equally important to run developability screens by:

- Physicochemical characterization of new chemical entities
- Salt form and polymorph form selection
- Preclinical formulation development
- Integrated pharmacokinetic testing and profiling
- Drug delivery technologies to enable oral bioavailability of poorly water-soluble compounds

Key Learning Objectives

- Learn how to select the most developable drug candidate for development
- Learn how to quickly develop Phase 1 formulation
- Learn how to apply drug delivery technologies for enhancing the oral bioavailability of poorly water-soluble molecules

Presenters

Liang Mao
Director, Developability and Formulation Research
WuXi STA

Andrew Phimister
CMC Consultant
Seaview Pharma

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Who Should Attend?

- Head of New Drug Development
- Head of Pharmaceutical R&D
- Head of Formulation Development
- Head of CMC
- Formulation Scientist

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Excipient manufacturers must implement quality management system requirements for each market served.

Material origin considerations

Because ingredients used in any of these markets could be derived from raw materials of natural origin, additional restrictions to prevent exploitation of endangered species (12,13) need to be considered. There are also more specialized requirements to address illegal logging (14) intended to protect vulnerable environments (15). In addition to controls on flora- and fauna-derived materials, conflict mineral concerns require supply chain control on some inorganic materials (16,17). These conventions and regulations are impacted by material origin and harvesting for excipients and food ingredients.

Consumers also may want food ingredients to have attributes that are not defined by safety or quality. Despite the lack of scientific evidence, "natural," "organic," and "genetically modified organism (GMO)-free" are all perceived as "healthier" and verification can add significant consumer-recognized value to food ingredients. Although there is no regulatory definition of "natural" for most food ingredients, flavors have a clear regulatory definition (18). The United States Department of Agriculture (USDA) regulates organic claims, labeling, and practices (19). Furthermore, USDA defines the requirements on labeling bioengineered foods: food containing bioengineered genetic material, which consumers commonly associate with GMO (20).

Consumer demands for natural, organic, and GMO (bioengineered food) are less likely for dietary supplements and currently are very limited for excipients. Although sustainable and fair-trade supply chain verification may be very important for foods, similar concerns for dietary supplements or pharmaceuticals are less likely.

Some consumers desire vegan or vegetarian ingredients, and certain regions such as India (21) require vegetarian labeling on food products. These same consumers typically do not hold pharmaceuticals to the same requirement.

Religious considerations

Religious requirements for food are very clear to the extent that in some countries these requirements are written into law. Kosher and halal are the most common religious requirements, and recognized religious agencies provide detailed requirements on meeting these standards. Many religious scholars recognize kosher/halal alternatives are not available for all pharmaceuticals; however, the pharmaceutical's benefits are medically necessary and may have no suitable alternatives. As such, although halal or kosher ingredients may be desirable for pharmaceutical excipients, acceptance by patients is not a strict requirement, particularly when there is no suitable halal or kosher alternative. There may be other religious dietary requirements, and the degree to which they ascribe those to dietary supplements or drug products may vary.

Summary

Although there may be considerable overlap in quality management systems and material specifications/requirements for substances sold for use as food ingredients, non-dietary ingredients, and excipients, many significant differences remain. No single quality management system or certification scheme satisfies ingredient requirements for the three markets. Therefore, manufacturers who supply into two or more of these markets need to understand and implement quality management system requirements to meet each of the markets they serve.

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The Path To Patient Safety – Addressing Industry Concerns and Solutions for Primary Packaging Component Selection

Striving for Zero Defects: Use of Quality-by-Design Principles for Manufacturing Parenteral Packaging Components to Mitigate Risks of Drug Product Contamination

ON-DEMAND WEBCAST: Aired, Tuesday, April 7, 2020

Register for the entire series for free at: http://www.pharmtech.com/pt_p/design_principles

Event Overview

Visible particles are a concern for the pharmaceutical industry. In the last few years, a quarter of all sterile injectable drug recalls were linked to particulate found in finished drugs. This poses a significant challenge to address quality requirements and to comply with regulatory authorities in various geo-regions. This webcast will focus on innovations in the manufacturing of parenteral packaging components to address the demanding needs for packaging sensitive drugs, such as biologics.

Topics of discussion will include:

- Common concerns in the pharmaceutical industry surrounding parenteral packaging
- A quality-by-design approach to manufacturing components to mitigate industry concerns that relate to particulates and silicone contamination
- Analytical tools utilized to ensure packaging integrity and product quality
- Advancements in products and processes to achieve best-in-class specifications, with a focus on 'zero-defects'

Key Learning Objectives

- Understand the risks that face the pharmaceutical industry today from a drug packaging perspective, and discuss strategies to mitigate these risks
- Introduce a QbD approach to product manufacturing and product design for pharmaceutical components with a focus on particulate reduction
- Review solutions for manufacturing high-quality packaging components to meet the needs of biologics and sensitive molecules

Who Should Attend

- Formulation scientists and packaging engineers
- Device development engineers and managers
- Technical functions surrounding drug delivery systems
- Extractable and leachable experts
- Quality/regulatory personnel in parenteral drug delivery
- Procurement professionals

Presenters

Rahul Thakar, PhD
Technical Key Account Manager
Datwyler

Elke Geuzens,
Technical Key Account Manager
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Moderator

Rita Peters
Editorial Director
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Packaging Preserves the Cold Chain

Hallie Forcinio

More sustainable and functional packaging protects temperature-sensitive drugs.

Proper storage and transport temperatures for drugs, especially biologics, are essential to protect product efficacy and patient safety. "As strong growth continues across the global pharmaceutical industry, the sub-category of temperature-controlled products is surging ahead—growing at twice the rate of the industry overall," said David Williams, president of Pelican BioThermal in a press release (1).

Joe Cintavey, product specialist at W.L. Gore, agrees, noting, "The pipeline of biologic drugs in development are becoming more temperature-sensitive, resulting in an increase in storage of bulk drug substance at frozen temperatures (-40 to -70 °C)."

Rory Davidson, Business Development Manager at Almac Pharma Services, adds that labeling, packing, and distributing cell and gene therapy products often requires products to be stored and processed at ultra-low temperatures (-20 to -80 °C), with the products only being defrosted immediately prior to use. "If these products are not kept in exact conditions, they become unusable. We have seen some cases of product becoming unusable within a minute of being out of frozen conditions and so we need to be able to handle and process product at these ultra-low temperatures as quickly and efficiently as possible," notes Davidson.

Packaging trends

In addition to the growing number of temperature-sensitive products, three trends are driving the need for temperature-controlled packaging, according to a survey by Pelican BioThermal. First, quality demands increase as more sensitive products bring logistics complexity and greatly expanded risk. Yet, while awareness of temperature-controlled requirements is high, the survey shows temperature excursions happen frequently (1).

Second, the distribution range is expanding as products move further and through more climatic zones. More than half of survey respondents (51.8%) regularly ship products internationally, creating an increasingly complex web of local, regional, and international connections that require a broad range of transport modes (1).

The third trend identified in the survey is the need to optimize the total cost of ownership (TCO) due to relentless competition and margin pressures. A full 70% of survey respondents agree that TCO is "important" or "very important," while 10% consider only basic packaging costs and transport rates. This exploration of TCO is spurring interest in reusable containers, with 79% of survey respondents saying reusable containers—though more expensive than single-use containers—are worth the investment. More than one-third of respondents (37.6%) are already using reusable rental programs in their cold-chain logistics operations, and 25% are actively exploring this option (1).

As a result, validated, off-the-shelf, or customized protective packaging options continue to evolve for all temperature ranges, including controlled room temperature, refrigerated, frozen, and cryogenic. "The challenge is optimizing the design, materials, and components to minimize overall size and weight of the shipping solutions," says Mark Barakat, general manager of Cryopak, a subsidiary of Integreon (formerly TCP Reliable). He continues, "Achieving peak performance while minimizing size, weight, and cost is typically contradictive." Cold-chain engineering experience and tools like thermal modeling software and testing equipment play important roles in optimizing temperature-controlled packaging.

Meeting requirements

There is also strong demand for more sustainable designs, including re-use programs to reduce the carbon foot-

Hallie Forcinio is packaging editor at *Pharmaceutical Technology*, editorhal@sbcglobal.net.

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print. Interest in temperature-controlled packaging also is being impacted by changing regulations and standards. For example, "Temperature profiles issued by ISTA [International Safe Transit Association] have changed within the past five years," reports Barakat.

"Regulations governing these types of highly sensitive products are growing stricter," adds Adam Tetz, director of worldwide marketing at Pelican BioThermal. "For example," he says, "China has become particularly strict and requires real-time tracking on all pharmaceutical shipments."

Many local governments want to reduce or eliminate the use of expanded polystyrene foam (EPS), a common insulating material, because it is rarely recycled. "California and New York are limiting the amount of EPS foam that can be delivered into their states," says M. Ryan Corbin, director of marketing at Kodiakooler. These requirements are forcing makers of temperature-sensitive drugs and biologics to look for alternatives.

In addition to insulation, temperature-controlled packaging includes single-use and reusable parcel and pallet shippers, thermal pallet covers, and phase-change materials. Sometimes, customized designs are needed, especially for products that will experience particularly hostile conditions or need to be maintained at cryogenic temperatures. Regardless of the application, optimized temperature-controlled packaging depends on the answers to three questions: Where is it being shipped? What temperature must be maintained? How long does that temperature need to be maintained? In addition, "Seasonal temperature changes can substantially affect the internal facility environment and shipping environment," warns Joe Luke, vice president of sales and marketing for Reed-Lane, a New Jersey-based provider of contract packaging services.

Testing

To ensure packaging will perform as specified, Cryopak tests it against extreme ambient temperature profiles in its ISTA-certified lab following protocols and internal standard operating procedures. "Our shipping systems are then qualified with repetitive testing to assure consistency and performance repeatability," explains Barakat. "The real shipment is then monitored with temperature data loggers to prove operational performance and quality assurance," he concludes.

To test the durability of reusable, passive thermal packaging systems, Pelican BioThermal is developing a mechanical test method. In addition to mimicking the real-world use environment, the test method also allows assessment of the impact of dynamic use on thermal performance. Tetz reports that results are promising. He says, "The test standard would give pharmaceutical manufacturers even more confidence in choosing reusable thermal packaging over single-use options to reduce costs and advance environmental initiatives."

"Current standards assess parcel thermal packaging systems during one intense shipment from point A to point B," explained Bill Mayer, director of research and development at Pelican BioThermal. "Throughout the development of this new test method, we addressed the challenges of exposing systems to the multi-leg and multi-mode shipping route and more of an average trip with parcel thermal packaging used multiple times" (2).

Cold-chain options

Innovations in temperature-controlled packaging center on sustainability, performance, and cost. To improve sustainability, OptumRx, a pharmacy care services provider, has transitioned from rarely recycled foam packaging to recyclable packaging made from renewable cotton-based Kodiakotton from Kodiakooler, which was recently acquired by Airlite Plastics. The Kodiakotton insulating material is biodegradable, compostable, reusable, and recyclable. OptumRx projects the new packaging will save millions of gallons of water, pounds of carbon dioxide, and kilowatt-hours of energy (3). "OptumRX has had great success with our sustainable products," reports Corbin. "Part of the initiative is ongoing education for their consumers on the benefits of recyclable materials," he adds.

In addition to Kodiakotton liners, Kodiakooler offers the patented Kwikpack system. This is a bundled kit of two Kodiakotton liners with an easy-to-remove, recyclable band. The liner bundle cuts insertion time and results in a packout-ready shipper in less than six seconds (4).

Fiber-based options, which can be recycled in the corrugated or waste-paper streams, also are popular. To address this market, Thermo Fisher Scientific has developed the Invitrogen Paper Cooler. The 100% paper alternative to EPS foam coolers meets thermal requirements for overnight shipments (5). Another paper-based product, ClimaCell insulation from TemperPack, is designed to replace EPS insulation and reduce packaging waste. In addition to being recyclable in the corrugated stream, the ClimaCell material protects temperature-sensitive shipments for up to 80 hours. The material also is moisture-resistant and can be customized with printed graphics/messages (6).

Another player in the insulation market, va-Q-tec, has opened a US headquarters and production facility in Langhorne, PA, to manufacture its small boxes and containers. The location also serves as a rental and repair station. The company, which is headquartered in Germany, specializes in vacuum insulation panels and phase-change materials that offer five-day temperature protection without the need for external energy sources. A rental service business offers a fleet of cold-chain containers and boxes (7).

Reuse is possible with the AcuTemp Plus Series of shippers from CSafe Global through its Repaq program. Proprietary, high-performance ThermoCor vacuum-insulated panels control payload temperatures. Simple to deploy, the shippers are available in multiple sizes and temperature profiles with integrated track-and-trace options (8).

Although reusable packaging has gained ground, one-way shippers remain a viable choice and continue to evolve. AeroSafe Global, a supplier of reusable shippers, has added a disposable option

to its portfolio. The A20 insulated shipper is designed to serve shipments needing protection for 24 to 48 hours. It is fully prequalified to ISTA 7D summer and winter profiles. Minimal components simplify packouts (9).

Gore Sta-Pure flexible freeze containers from Gore PharmBIO Products are designed to protect high-value bulk drug substances from container breakage or leakage during frozen handling. "Traditional single-use bags are constructed from materials that typically become brittle when exposed to temperatures below -40 °C, which can lead to cracks or leaks in the bags," explains Cintavy. The proprietary high-strength fluoropolymer material used for the Sta-Pure flexible freeze containers is durable after freezing at -86 °C (-123 °F) and offers the convenience and scalability of a single-use system that efficiently uses freezer space. In addition to durability, the container's chemically inert, biocompatible, high-purity fluoropolymer composite film has a low extractables profile (10).

Gore Sta-Pure flexible freeze containers come in sizes from 50 mL to 12 L with tubing and connector options to meet different pharmaceutical and bioprocess applications. A hard-shell carrier is available for easier handling. If carbon dioxide or oxygen permeation is a concern, an optional, vacuum-sealable, secondary barrier wrap minimizes ingress (11).

Reed-Lane recently added cold storage (2–8 °C) capabilities and a dedicated climate-controlled room for vial and ampule kitting at its packaging facility in Wayne, NJ. Temperature and humidity sensors constantly monitor the cold storage area to document conditions and ensure there are no product-damaging temperature excursions. "Most crucially, our environmental monitoring solutions are able to provide email alerts should any specified environmental conditions be exceeded," says Luke. He explains, "Additional sensors are deployed to provide alerts pertaining to ... power outages, which would result in an immediate onsite power generator startup to maintain specified temperature continuity."

The dedicated room for kitting temperature-sensitive products includes space for labeling vials and ampules and assembling them with other components such as printed literature. Its location adjacent to the cold storage area minimizes intra-facility travels and exposure to temperature excursions.

Introductions from Pelican BioThermal include a new version of its ProEnvision web-based asset management track-and-trace software, which allows integration of its CoolPall Flex bulk shipper into the Internet of Things. The CoolPall Flex shipper serves refrigerated, frozen, and room temperature ranges. A high level of flexibility allows the system to address different time, weight, and payload requirements.

For cryogenic products, SAVSU Technologies has expanded its portfolio of dry vapor shippers, which maintain biologic payloads at -196 °C during storage and transport. Positioned between the DV4 and the DV10 shippers, the DV7 unit offers seven days of thermal autonomy and a more compact form factor with a payload capacity similar to the DV10 shipper. With its smaller size, the DV7 shipper is easier to handle and store and less expensive to ship (12).

Cryoport Express Advanced Therapy Shippers from Cryoport have been developed to meet demand from biopharma customers and in anticipation of more stringent government regulations. The shippers are dedicated to human use and certified as such. Validated to ISTA 3A and 7E Transportation Standards, a new vapor plug design further doubles the holding time if shippers are mis-orientated during transit. The shippers also provide complete traceability of use history and assurance that each dewar is requalified for each trip for physical suitability, cleanliness, liquid nitrogen capacity, and shipment hold times. Validated cleaning processes reduce the risk of cross-contamination during use, delivery, and distribution (13).

Future possibilities

Sustainability continues to be a major driving force with suppliers and users of temperature-controlled packaging. As a result, work continues on developing designs that meet performance requirements that will be more renewable, recyclable, reusable, and/or compostable. Kodiakooler, for example, is working on biodegradable EPS foam. "We are constantly looking for ways to reduce the carbon footprint of temperature-controlled packaging materials," says Corbin.

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A Q&A

Data Integrity for Laboratory Instruments

Heiko Haack
Specialist Manager, Lab Weighing
Sartorius

Laboratory instruments can be key to safeguarding data integrity.

Data integrity in the analytical laboratory is an area of increased focus for regulators such as the FDA. Standalone instruments, in particular, have special requirements. These are especially important if the instrument will be integrated into a networked laboratory. *Pharmaceutical Technology* recently sat down with Heiko Haack, Specialist Manager of the Lab Weighing Division at Sartorius, to discuss data integrity challenges and what to consider when buying a new laboratory instrument.

Pharmaceutical Technology: Why is data integrity so important, and why is there such a focus on data integrity compliance by regulators?

Haack: In the pharmaceutical industry especially, every variable measured creates data that serve as the basis for important decisions such as quality decisions like batch release. During past GMP inspections, regulators identified a number of violations in data manipulation and other data issues. These problems have led to the current focus by regulators on data compliance.

Pharmaceutical Technology: What major violations were found during inspections?

Haack: Several types of violations can occur. A major one is that data are not fully and accurately documented. In addition, we often find that critical deviations (such as operating steps not correctly followed) are not investigated, or perhaps there is no user management or access control. It can also be the case that data are not recorded contemporaneously.

Pharmaceutical Technology: Given those examples, what should be done to avoid violating data integrity in daily processes?

Haack: The ALCOA principles should be followed, for both paper and electronic documentation. The ALCOA principles provide everything needed to be fully compliant.

The acronym ALCOA is defined by the US Food and Drug Administration and relates to data, whether paper or electronic. It stands for five principles:

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate.

These simple principles should be part of your daily data life cycle and data integrity initiatives.

Pharmaceutical Technology: How can a computerized laboratory instrument be helpful?

Haack: As humans, we unfortunately make mistakes. Automation reduces manual errors and increases efficiency tremendously. In addition, access and user management helps control role-based usage and provide traceability together with an audit trail because each audit trail entry must be traceable to the individual responsible for creating, changing, or deleting the record. A computerized instrument also allows safe transfer of electronic data, as well as storage with restricted access to avoid data manipulation.

> “A computerized instrument also allows safe transfer of electronic data, as well as storage with restricted access to avoid data manipulation.”

Pharmaceutical Technology: What should be taken into account when buying a new instrument?

Haack: The instrument should include technical controls to fulfill 21 CFR Part 11 requirements. Of particular importance, instruments should include audit trails, user and access control management, electronic signatures, and safe data transfer and handling.

Furthermore, it should be possible to automate work processes as much as possible on the instrument to avoid manual errors. Sartorius offers small applications, called QApps, for this purpose that can be loaded onto the balance. These reloadable application programs guide the user step-by-step through specific workflows. It is thus guaranteed that the procedures described in the corresponding standard operating procedures are observed at all times.

Pharmaceutical Technology: What exactly is meant by safe data handling?

Haack: Safe data handling means ensuring that stored data are safe and secure, without manipulations, from the beginning throughout the entire lifecycle of the data. It is important for an instrument to enable easy and safe data transfer into a LIMS or ELN system, as well as fallback (temporary storage) if the connection is lost.

Pharmaceutical Technology: How can an instrument be integrated into a LIMS/ELN?

Haack: An instrument can be integrated into a LIMS/ELN in a variety of ways. In particular, bidirectional communication with an open protocol (especially “REST Webservice” via LAN or WLAN) allows for direct integration. The biggest advantage in this scenario is the elimination of middleware that would otherwise increase costs and efforts. Other possibilities are to directly generate files, such as PDF, on the balance, which enables direct and paperless documentation in a document management system. Although this method does not offer the same possibilities for further processing as the transfer of measured values including all metadata, like the REST Web service, but it can often be implemented easier and faster in a first step.

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Being Vigilant in Supplier Oversight

Susan Haigney

Risk assessments, audits, and good communication between sponsor and supplier are key elements of supplier oversight.

The bio/pharmaceutical industry is a global network that ties together an array of developers, manufacturers, and suppliers. Bio/pharmaceutical companies, therefore, may source APIs and excipients from companies thousands of miles away. This global aspect of the industry, naturally, creates a complex supply chain that could leave patients vulnerable if not properly overseen. The discovery of nitrosamine impurities, including N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), found in angiotensin II receptor blocker (ARB) medicines (1) in 2018 is an example of how ingredient issues can affect patients and the supply chain and the importance of testing ingredients. Now, the global COVID-19 coronavirus pandemic has the potential to disrupt supply chains, site inspections, and other activities associated with supplier qualification and oversight.

Sponsor companies and manufacturers are responsible for ensuring the components they use are safe and effective. FDA has cited companies for failing to test their incoming API and raw materials "to determine their identity, purity, strength, and other appropriate quality attributes" (2). According to a spokesperson for IPEC-Americas, sponsor companies must verify the quality of materials, which includes qualification of the supplier through on-site good manufacturing practice (GMP) audits and/or a third-party GMP certification. Incoming materials should have their identification verified and the quality department should give its approval to release the materials for use. This includes performing—at a minimum—an identification test, and may include other tests necessary to ensure the quality for the intended use as per 21 *Code of Federal Regulations* 211.84(d)), advises IPEC-Americas.

Risk assessments of both suppliers and materials should also be performed, according to IPEC-Americas, with a specific focus on the intended use of the material. The risk assessment should also evaluate possible concerns with efficacy, variability, safety, and quality. And this evaluation should not end with the risk assessment. The sponsor should "[establish] a process for continued monitoring of the supplier and the quality of incoming materials," according to IPEC-Americas.

Qualifying suppliers

How do sponsor companies choose and monitor material suppliers to ensure the ingredients they are purchasing are fit for purpose? Linda Evans O'Connor, vice president and chief of staff at Lachman Consultant Services, Inc., suggests that sponsors start by obtaining information from the supplier about its capabilities and compliance history through a questionnaire. Material samples should also be obtained to determine if they are fit for their intended purpose. Site audits should be performed, and quality agreements should be put in place, she says. Finished product trials should be performed if the materials meet the requirements. Batches should then be tested for stability. Periodic monitoring of the supplier should be performed with data reviewed on a predefined basis in addition to performing surveillance audits, according to O'Connor. IPEC-Americas stresses, however, that an appropriate risk assessment cannot be performed without onsite audit information.

Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates, says that companies should begin the qualification with an onsite audit. "Once the audit is performed and any identified concerns resolved, the two parties, purchaser and supplier, can enter into a quality agreement. After the quality agreement is approved, the purchasing company can start the process of 'qualifying' the supplier. This qualifi-

cation usually involves testing of the material to confirm the supplier's certificate of analysis (CoA) is accurate and develop a history that demonstrates the ability of the supplier to continually provide a suitable product," says Schniepp.

The supplier should then be placed on an approved supplier list, according to Schniepp. "The initial qualification for a supplier to be considered an approved supplier usually involves complete confirmatory testing on the first 10 lots of material received and then a periodic check and confirmation by the purchaser of the entire testing regimen listed on the CoA received from the supplier."

Performing audits

Peforming audits of material suppliers is key for ensuring the quality of materials, but how often should these audits be performed? O'Connor suggests that a risk-based approach should be used to determine when and how often a supplier is audited. "Many factors can go into the risk model, such as type of material (e.g., API, excipient, sterile, non-sterile, complex dosage form, etc.), location, past regulatory or audit history, recalls, quality of incoming goods, complaint history, importance to the business of the materials (i.e., Is this an API for your blockbuster drug and lack of supply would have a material impact on the business?). A minimum frequency per material type should be defined (i.e., for an API, every two years)," O'Connor says.

IPEC-Americas agrees. "Whether the supplier is an excipient manufacturer, contract manufacturer, distributor, or service provider (e.g., a contract testing lab), the initial audit frequency should be based on results from the initial supplier/excipient risk assessment along with any additional mitigation measures identified. Based on on-going monitoring, a sponsor company should determine whether to adjust the audit frequency."

A quality risk management plan is key, agrees Schniepp. Frequency of audits should be based on the criticality of the material and the past performance of the supplier. "This plan should identify supplier vulnerability (i.e., single source, secondary supplier, etc.), which should help determine audit frequency. The quality agreement should reflect the risk plan but there should always be a contingency to allow for-cause audits as needed. Laboratories used by either the supplier or the purchaser should be audited and included as an element of the risk plan," says Schniepp.

Auditing under difficult circumstances. Having a consistent and properly executed audit program is paramount to maintaining the timeliness and integrity of the supply chain, says Schniepp. Audits, and the information obtained during them, allow one to assess a supplier's risk, especially during crises such as the COVID-19 pandemic. "Having the baseline knowledge of your suppliers' operations will help assess where critical resources need to be allocated during a crisis period. While not ideal, audits can still be performed on suppliers through the use of questionnaires and video conferencing. If visuals are required for the

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Oral Peptide Delivery Utilizing Specialized Encapsulation Technologies

ON-DEMAND WEBCAST: Aired Wednesday, April 1, 2020

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

Event Overview

Technological enhancements in peptide discovery and synthesis are emerging to meet the increasing number of incidences of cardiovascular and metabolic diseases. However, targeted delivery of peptide drugs within the therapeutic range remains a significant challenge for the biopharmaceutical industry. Parenteral administration—including intravenous, subcutaneous, and intramuscular injection—remains the primary method for commercialized therapeutic peptides.

From a patient perspective, oral administration is a preferred drug delivery method, providing improved patient compliance and facilitating outpatient therapy for chronic indications. Non-invasive delivery methods such as oral administration have increased over the past five years through the innovation efforts at start-up and big pharma companies. Indeed, the September 2019 approval of Rybelsus, (semaglutide) from Novo Nordisk is seen as a game changer within the industry as it allows oral delivery of high molecular weight (>1300 MW) peptide delivery.This webcast will cover the physicochemical requirements for peptides and biological oral delivery barriers. Both aspects are crucial to de-risk pharmaceutical development and increase the success rate of first-in-human trials using innovative approaches.

Key Learning Objectives

- Understand physicochemical attributes of peptide for oral routes administration
- Review performance criteria for peptide formulation
- Learn about biological hurdles to overcome low oral bioavailability of formulated peptides

For questions or concerns,
email mdevia@mmhgroup.com.

Presenter

Dr. Hassan Benameur
Chief Scientific Officer
Chemical Division
Lonza Pharma & Biotech

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Who Should Attend

- Pharmaceutical formulation scientists
- Product development management focused on peptide drug and delivery applications
- Innovation and Life cycle management

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Sterile Filling Challenges for Early-Phase Product Development

ON-DEMAND WEBCAST: Aired Thursday, March 19, 2020

Register for this free webcast at: http://www.pharmtech.com/pt/early_phase

Event Overview

Getting your product to the clinic fast is always a key driver in pharmaceutical product development. Producing it right the first time is another key driver. In this webcast, Pii will discuss options for delivering on both of these critical requirements and will talk about the challenges clients have in producing efficient and flexible sterile product filling solutions.

Key Learning Objectives

- Review the experience, technologies and solutions necessary to maximize yield and reduce contamination risks in small-scale sterile filling operations
- Gain knowledge on how to get drugs faster to clinic and how to get them done properly the first time through
- Learn about Pii's, AST GENiSYS® R technology, and how this technology can support your clinical product requirements

Who Should Attend

- Formulation and process development scientists working on early-phase, sterile, drug product development programs
- Industry consultants and CMC professionals requiring small-scale sterile filling operations

Presenters

Samuel Chia
Director Aseptic Manufacturing
Pii

Joe Hoff
Chairman & CEO Automated Systems
Tacoma (AST)

Moderator
Amber Lowry
Managing Editor
Special Projects

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Operations — *Contin. from page 73*

supplier assessment, the use of an electronic device or video streaming options could be employed. Bottom line, to keep the supply chain viable during crisis mode we need to think outside of our normal operating procedures and experiences," says Schniepp.

If travel is limited due to global situations such as the COVID-19 epidemic, O'Connor suggests getting creative. "For example, performing a virtual audit, while not ideal, is a possibility, and would require cooperation of the sponsor and the manufacturer. Document review and interviews can be performed remotely. Companies could even look at virtual facility tours using appropriate technology. However, these types of audits are not ideal, and shouldn't replace on-site audits. Another solution is to partner with a local company that has the local resources to perform the on-site portion of the audit. This will allow on-site audits to occur even when international travel bans are in effect," says O'Connor.

The role of CoAs

CoAs provide manufacturers with detailed information about materials including material manufacturer, quality testing information, specifications, batch numbers, and other information (3). FDA has been known to cite companies for incomplete or incorrect information on CoAs (4). So, how reliable are these documents and how much emphasis should sponors put on them when it comes to ensuring material quality?

O'Connor suggests that sponsor companies create a library of CoAs or labels so they can verify that the information is correct. "Also, maintaining

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Manufacturing APIs and the Supply Chain

Pharmaceutical Technology spoke with Jens Andersson, purchasing director at Cambrex Karlskoga, about the best way to ensure the security of the bio/pharmaceutical materials supply chain.

PharmTech: What is the contract manufacturing organization's (CMOs) responsibility in ensuring the quality of materials they use in the production of APIs?

Andersson (Cambrex Karlskoga): Cambrex prefers to take full responsibility for ensuring the quality of the raw materials that are used in our manufacturing processes. Ultimately, we are responsible for the quality of the final API produced at our sites and ensuring that it meets customers' specifications. Therefore in our opinion, it makes sense that we take the responsibility to source raw materials of the correct quality to undertake the campaign or product. We also find this process to be quicker and more cost-effective than if the end customer undertakes the sourcing and sends material to us, as we can use our own supplier network and can use suppliers with which we have a well-established relationship without having to necessarily qualify new suppliers.

PharmTech: What are the steps and/or best practices for qualifying suppliers?

Andersson (Cambrex Karlskoga): There are several steps that are undertaken when we qualify suppliers, with the first being to evaluate the quality of raw materials against the specifications to ensure that they meet both the stated purity and the demands of the project we intend to use the materials for. Then we send questionnaires to the suppliers that cover a wide range of topics, from quality to health and safety practices, as well as environmental policies and responsibilities, and ethical guidance of the company. If needed, audits are carried out on-site by our QA [quality assurance] specialists for suppliers of raw materials with critical impact on the final product quality, such as the main building blocks of the final API.

PharmTech: How often should suppliers be audited?

Andersson (Cambrex Karlskoga): For critical raw materials and services we re-evaluate suppliers every two years. We carry out on-site audits every two to three years depending on how critical the raw material or service is; however, audits can also be initiated outside of the regular schedule for other reasons, such as quality or supply issues.

PharmTech: What additional challenges do high-risk materials pose? Does the oversight of these suppliers intensify?

Andersson (Cambrex Karlskoga): The main challenge is that for suppliers of critical raw materials we need to make a much more thorough initial qualification and risk assessment. This can be time consuming and, at times, it can be difficult to get the data and information needed. At Cambrex, we do have a robust supplier network where we have been able to establish strong relationships over a number of years that mitigates this risk.

PharmTech: When there have been reports of suppliers falsifying certificates of analysis (CoAs), how can a pharma company or contractor be sure the information they are receiving from a supplier is correct? Is this why testing of materials is important?

Andersson (Cambrex Karlskoga): For critical raw materials, we will always carry out our own analyses to confirm the vendor's CoA and ensure the quality of the material. For less critical raw materials such as common solvents or regularly used bulk acids and alkalis from reliable and trustworthy vendors, goods can be received only on CoA, but we will undertake random tests to ensure the CoAs.

PharmTech: What should a pharma company or contractor do when FDA puts a supplier on import ban? Should companies have a backup plan to prevent product shortages?

Andersson (Cambrex Karlskoga): A company needs to be proactive and should always aim for dual sourcing capabilities for critical raw materials, so that any risk of supply is minimized. A risk assessment should always be carried out to evaluate the danger of interrupted deliveries.

PharmTech: What has the recent NDMA impurity issue taught the industry about materials quality and the importance of testing materials?

Andersson (Cambrex Karlskoga): Given that the situation with the NDMA is still ongoing, it is too early to say what lessons need to be learned from it. However, in 6–12 months the situation will hopefully be clearer, allowing for a detailed review to take place and evaluation of any future risks to be made. It is paramount that patient safety is the highest priority so the industry as a whole has a duty to ensure that decisions are made that do not compromise this in any way, and that any oversights that have been made previously do not happen again.

—Susan Haigney

Biomanufacturing: Demand for Continuous Bioprocessing Increasing

Eric S. Langer

But are innovations sufficient to increase adoption? CMOs are demanding better continuous bioprocessing options.

In nearly all other manufacturing technologies, cost considerations dictate that continuous production will be the rule. But in bioprocessing, the normal evolution from batch to continuous operations has not moved as quickly as many had expected.

Continuous processing upstream has been around for decades as perfusion (e.g., fiber-based perfusion bioreactors for fused-cell hybridoma culture in the 1980s). But that's essentially the only continuous-adapted upstream unit process, with such things as culture media and additives preparation still done in batch processing. In some respects, perfusion has overall been a commercial failure. Sales of the leading alternating tangential flow (ATF) perfusion systems from leading suppliers, after more than 15 years, are under $20 million. And continuous processing downstream is still largely lacking and, where implemented, involves just a few of the many unit processes involved in downstream processing. Multi-column, countercurrent, and other variations of continuous chromatography units are just starting to enter the market. The classic and still predominant approach to bioprocessing, both upstream and downstream, remains batch processing, with manufacturing batch fluids essentially moving incrementally en-masse from one process step and set of equipment to the next.

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Downstream processing continues to create bottlenecks in production, and improvements in batch processing are not really emerging. Therefore, the industry continues to seek solutions from innovators for better continuous processes that offer further process intensification and lower costs. In fact, 70.6% of bioprocessing professionals are either testing continuous bioprocessing downstream technologies or considering them. This is up from 68% based on data from our 2016 Annual Report (1).

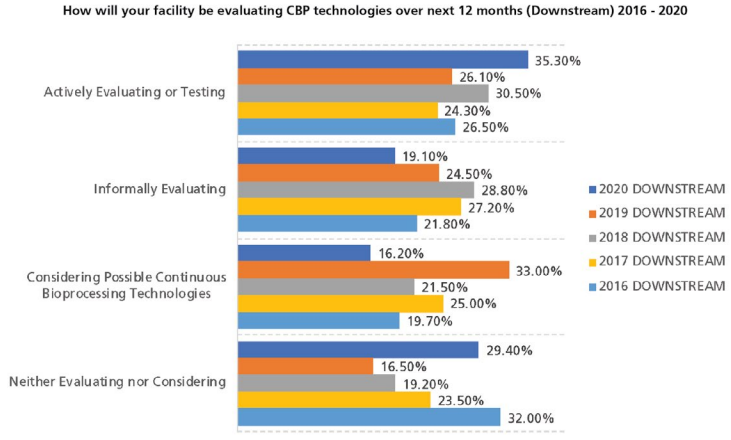
According to BioPlan's *17th Annual Report and Survey on Biopharmaceutical Manufacturing Capacity and Production* (2), there has been a slow increase in assessment of the various continuous bioprocessing options over the past five years, and the data support ongoing interest in the coming year (see **Figure 1**). Approximately 55% of facilities surveyed are actively or informally evaluating continuous processing technologies in the coming year.

Although there are a number of technologies providing process intensification and continuous purification steps, it appears that more robust continuous chromatography technologies, such as simulated moving bed (SMB) and periodic countercurrent chromatography, are generally not yet ready yet for commercial-scale adoption (other than adoptions performed using single-use upstream equipment generally limited to 2000-L scale).

Outsourcing and continuous bioprocessing

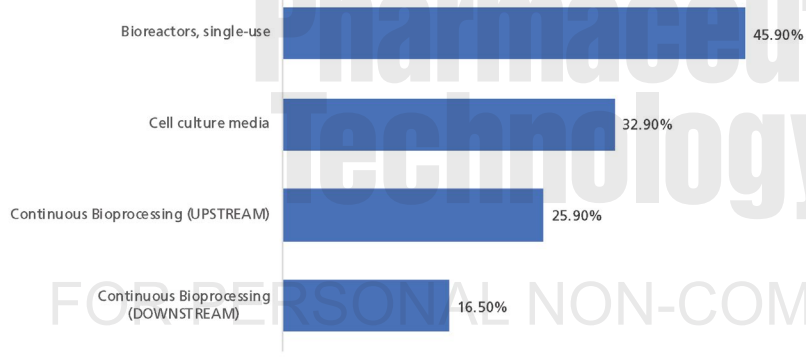
Contract manufacturing organizations (CMOs) are often on the leading edge of new technology adoption. For continuous bioprocessing and process intensification, BioPlan's Annual Report shows that significantly more CMOs will be testing these technologies over the next 12 months (53% of CMOs will be evaluating downstream options, vs 38% of biomanufacturing facilities). On the upstream side, again it is the CMO outsourcing organizations that are seeking better products and more

Figure 1: Facilities evaluating continuous bioprocessing (downstream) technologies in the next 12 months (2016–2020).



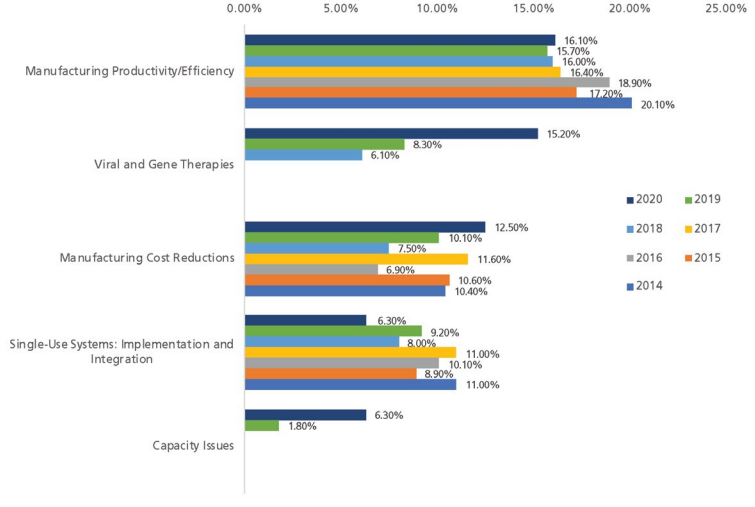
Source: 17th Annual Report and Survey Biopharmaceutical Manufacturing, Preliminary Data March 2020, BioPlan Associates, Inc., Rockville, MD

Figure 2: New expenditures, 2020.



Source: 17th Annual Report and Survey Biopharmaceutical Manufacturing, Preliminary Data March 2020, BioPlan Associates, Inc., Rockville, MD

Figure 3: Single most important biomanufacturing trend (2014–2020) (Selected Findings).



Source: 17th Annual Report and Survey Biopharmaceutical Manufacturing, Preliminary Data March 2020, BioPlan Associates, Inc., Rockville, MD

improvements. More CMOs than biomanufacturers (40% vs 28%) are indicating they want vendors to focus greater efforts on developing continuous upstream technologies (1).

Budgets for adoption of continuous bioprocessing

BioPlan's annual report for 2020 also evaluated adoption of bioprocessing technologies based on new technology purchases. When evaluating new expenditures, industry decision-makers were asked about new technologies they were budgeting for. Of the nearly 20 technologies identified, the top technologies this year included single-use bioreactors (noted by 45.9% of respondents), followed by cell culture media including optimization, and then continuous bioprocessing (upstream), and continuous bioprocessing (downstream), according to preliminary data.

BioPlan data in general indicate that the direction of the industry is more toward single-use novel devices, those that allow rapid transitioning from project to project, and options for continuous bioprocessing. Some of these technologies also support the increasing demand for biologics that may be called for in smaller quantities.

Figure 2 shows the economic commitment decision-makers are focusing on continuous bioprocessing, as evidenced by companies' top three new expenditures including both upstream and downstream continuous bioprocessing equipment, which was noted by a robust 25.9% and 16.5% response from decision-makers.

Trends making continuous bioprocessing attractive

Several technological advances and related trends are making continuous bioprocessing attractive. Some established bioprocessing facilities are being retrofitted and upgraded for more continuous operations.

There are many benefits to operating bioprocesses continuously rather than in batch mode, with many of these similar and complementing those of single-use and modular systems:

ALL FIGURES COURTESY OF THE AUTHOR.

- Reduced costs: Operating continuously allows use of significantly smaller-scale equipment, with a smaller volume bioreactor.
- Increased productivity: Because much of the bioprocessing equipment is operated continuously, there is little need for large transfer/storage vessels and no halts between processes. Bioprocessing thus tends to move much more smoothly.
- Improved quality: Biological molecules are expressed continuously, and compared to batch culture, continuous culture tends to be more controllable, less intense and stressful, including less shear and media nutrient levels kept constant.
- Increased flexibility: Continuous manufacture enables more adaptability and efficient facility utilization, similar to the advantages of single-use devices. Bioprocessing also becomes much more portable, and facilities more cloneable.

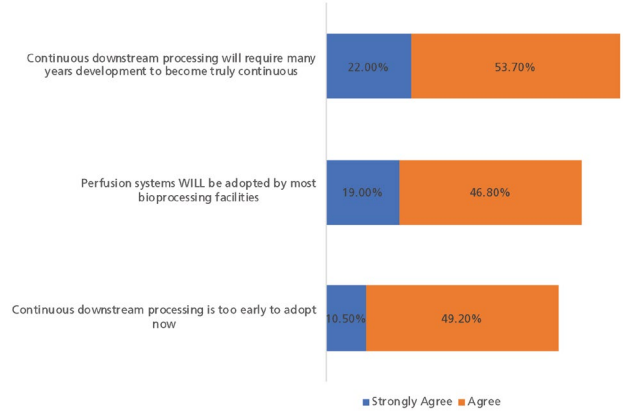
Many upcoming continuous bioprocessing technologies are very novel. For example, a single 50-L bioreactor is expected to be able to manufacture the same quantity of product, often at better quality, comparable to a 5000-L bioreactor over the same time period. Case studies and other reports of such performance will further promote rapid adoption. There will be increasingly rapid adoption of single-use systems for new commercial manufacturing over the next five years; and continuous bioprocessing, particularly upstream processing, is expected to follow a similar trajectory. Use of continuous bioprocessing is likely to further increase with the arrival of more hybrid systems that use bolt-on-type technology, which retrofit components unit operations for existing systems. Other conventional downstream continuous adaptable technologies, such as centrifugation, will also see increasing adoption in coming years. Potentially revolutionary capillary fiber perfusion bioreactors and other new technologies, including those for downstream processing, will be likely coming online and be more widely adopted for commercial manufacture over the next 10 years.

Continuous processing trends in bioprocessing

When respondents were asked about their 'single most' important biomanufacturing trend, or operational area on which the industry must focus its efforts, upstream and downstream continuous bioprocessing declined dramatically over the past six years, from 9.1% to 1.25% for upstream, and 10% to 4.7% for downstream continuous bioprocessing (**Figure 3**).

While this might imply that interest in continuous bioprocessing is waning, combined with the increased expenditures in the area, it suggests that continuous bioprocessing is becoming a more mainstream bioprocessing area, and therefore, less trend-relevant, thus, the lower trend 'score.'

Figure 4: Perspectives on continuous bioprocessing and process intensification (Selected Data) (2).



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing, April 2019, BioPlan Associates, Inc., Rockville, MD [2]

Implementation of continuous bioprocessing

Although this is beginning to change, implementation of continuous bioprocessing is and has been slow (see **Figure 4**). At best, a few unit process/steps both up- and/or downstream have been implemented as continuous by a minority of facilities. Some commercial biopharmaceutical products that essentially require perfusion's generally milder/less intense processing conditions, including Factor VIII (the largest recombinant molecule biopharmaceutical) and coagulation factors, have been manufactured for decades using perfusion (other products use continuous centrifugation).

BioPlan studies have shown approximately 5% of bioreactors that are over desktop-size use perfusion, mostly for feeder, not production, bioreactors. There is more adoption of perfusion for early stage vs. large/commercial-scale manufacturing. BioPlan studies have shown that few processes are scaled-up, particularly for commercial good manufacturing practice (GMP) manufacture, using perfusion in continuous upstream bioprocessing CP USP. Perfusion adds considerable mechanical complexity and regulatory uncertainties (i.e., it is avoided for GMP manufacturing, expert staff are needed, etc.), as well has having limited equipment options and universal industry inertia restraining adoption.

Survey data suggests that bioprocessing professionals may believe continuous processing is more ready for broad adoption for more unit processes than it currently is.

Large-scale continuous downstream processing, particularly chromatography operations, remain rare. Even where continuous downstream processing has been implemented, it involves at best only one or few out of the usual multiple chromatography and other downstream processing unit processes/steps having been implement as continuous.

Survey data suggests that bioprocessing professionals may believe continuous processing is more ready for broad adoption for more unit processes than it currently is. Notably, continuous processing equipment manufacturers and users report that many of the problems long associated with perfusion and continuous bioprocessing have been resolved in recent years through the application of innovative technologies, including new developments in single-use equipment.

On the other hand, perfusion processing is now significantly less complex, less prone to contamination, and more readily scalable than previously. Negative assessments from within the industry of continuous perfusion fed-batch processing overall may reflect a lack of direct exposure or experience with continuous technology.

In BioPlan's annual report, for example, key areas where most respondents reported they perceive perfusion as presenting more concerns (vs. fed-batch) included:

- Process operational complexity (perfusion noted by 72% as more operationally complex vs. batch)
- Contamination risks
- Upstream development and characterization time
- Process development control challenges
- Process development general challenges
- Validation challenges
- Need for greater process control
- Cell line stability problems
- Ability to scale-up process.

Interestingly, while approximately 76% believe downstream continuous bioprocessing will be a long time in coming, 66% believes that perfusion systems will be adopted by most bioprocessing facilities. This shows the expectation that continuous bioprocessing is here for the long haul, but widespread adoption may not be in the near future.

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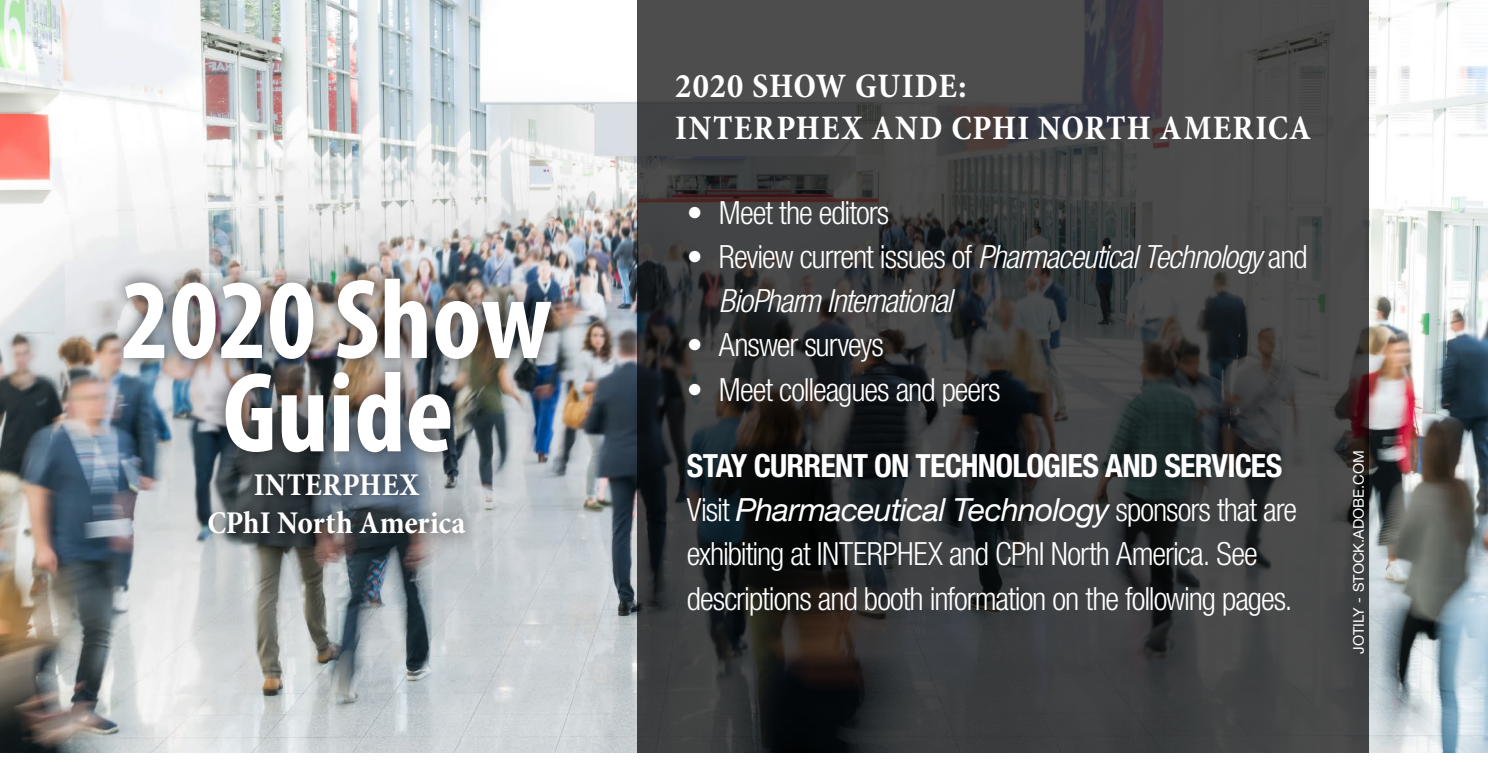

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a relationship with suppliers is key. Anything unusual needs to be flagged," says O'Connor.

Building trust between the sponsor and supplier is important, agrees IPEC-Americas. "A robust supplier qualification program, including an onsite GMP assessment of a supplier, by either the sponsor or a qualified third party, and development of a partnership with the excipient supplier are necessary to establish and build trust in the validity of their CoA."

Annual confirmation testing of CoA results is also necessary, says IPEC-Americas (5). "Full testing of an excipient is required until a robust supplier study has been completed and a reduced testing program has been approved. Only once trust has been established can the sponsor move to a reduced testing program. However, identification testing is always required to ensure the identity of incoming materials."

To establish that the quality testing information included in the CoA is accurate, incoming materials must be tested against the requirements in the CoA, Schniepp insists. "The best way to ensure the CoA is accurate is through complete testing. In cases of falsification of the CoA, results testing is mandatory to make sure the material is suitable for use; however, it must be coupled with a review of the supplier's overall quality system. Even if the material meets the testing qualifications listed on the CoA, it may not be suitable for use due to other potential GMP violations that might be present at the supplier facility," she says.

"In the case of falsification, the purchaser should be concerned with data integrity issues that lead to the falsification in the first place. If a purchaser suspects a supplier is falsifying the results on a CoA they need to initiate a for-cause audit and quarantine the suspect material until they can confirm it was satisfactorily manufactured following cGMP expectations. Passing test results does not confirm compliance to cGMPs," Schniepp explains.

The role of CMOs

Many drug sponsors engage contract manufacturing organizations (CMOs) to conduct drug production steps. So what is the CMOs responsibility in ensuring that materials are safe and effective?

O'Connor says that while both sponsors and CMOs share responsibilities, the sponsor has the "ultimate" responsibility of its supply chain. "Sponsors and CMOs share responsibilities, but the selection, qualification, and oversight of suppliers is the sponsor's responsibility, whereas day-to-day testing is generally the CMOs/CDMOs, although sometimes that goes to the sponsor as well. The sponsor has ultimate responsibility for the entire supply chain, so even if it delegates part of that responsibility to the CMO/CDMO, it is ultimately responsible."

Sponsors must ensure that they have signed agreements in place with any CMOs and/or CDMOs they are using that identifies the responsibilities of each party when it comes to ensure the quality of materials, according to a spokesperson for IPEC-Americas.

Both sponsors and CMOs/CDMOs must have an active role, according to Schniepp. "The specific level of involvement of the sponsor may depend on the confidence they have in the CMO/CDMO organization. The CMO/CDMO should make sure they involve the sponsor in decisions involving material quality so the sponsor is aware of the impact on their product," says Schniepp.

Ensuring quality is about vigilance

Maintaining a safe supply chain is crucial in the bio/pharmaceutical industry. The efficacy and safety of the materials used in drug products is of utmost importance. And it is the sponsor's responsibility to ensure the quality of all materials used in their products. Sponsors must not rely on others to ensure quality, says O'Connor. Also, not all suppliers should be treated the same. "Clearly, some suppliers have greater risk than others, either based on the product type, location, etc. These suppliers should receive more scrutiny," she says. Sponsors also must not cut corners or do what is convenient, says O'Connor. For example, she notes, it is inconvenient, but necessary to audit suppliers in China and India. In addition, sponsors should also not make supplier decisions based on price or availability instead of quality and safety, says IPEC-Americas.

Communication is key to supplier oversight, says Schniepp. "Both parties need to be willing to talk as frequently as needed to address issues before they manifest into a disruption in the supply chain. The frequency of these conversations are not necessarily defined in a quality agreement. They are important in establishing an open relationship between the supplier and the purchaser so issues can be solved before supply chain disruption occurs. Not all problems can be solved through the terms included in the quality agreement and both parties must be willing to work outside the defined 'communication schedule' of the quality agreement to avoid unnecessary supply-chain interruptions."

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Events Update

The global coronavirus pandemic has forced the postponement of many industry events. The dates listed below reflect the scheduled and rescheduled dates for major bio/pharma industry events as of March 25, 2020. For the latest information, contact the event organizer, or visit PharmTech.com/events.

BIO International Convention
June 8–11, 2020, San Diego, CA
www.bio.org/events/bio-international-convention

CPhI China
June 22–24, 2020, Shanghai, China
www.cphi.com/china/en/home.html

CPhI Southeast Asia
July 1–3, 2020, Bangkok, Thailand
www.cphi.com/sea/en/home.html

INTERPHEX 2020
July 15–17, 2020, New York
www.interphex.com/Register/

69th PDA Annual Meeting
July 20–22, 2020, Raleigh, NC
www.pda.org/conference/2020-pda-annual-meeting/home

CPhI North America
Sept. 9–11, 2020, Philadelphia, PA
www.cphi.com/northamerica/en/home.html

CPhI Japan
Sept. 30–Oct. 2, 2020, Osaka, Japan
www.cphi.com/japan/en/attend/register-to-attend.html

CPhI Worldwide
Oct. 13–15, Milan, Italy
www.cphi.com/europe/en/home.html

AAPS 2020 PHARMSCI 360
October 25–28, 2020, New Orleans, LA
www.aaps.org/pharmsci/annual-meeting

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products on manufacturing lines that are more than 30 years old and the analytical results rely on outdated methodology (5). The age of the line usually indicates that the processes being run on those lines are non-automated and require human driven steps. In these situations, it is critical a company demonstrates it has a quality mindset because of the human/product interface. The best way to address this issue in an inspection is to demonstrate that the company has a plan to update its facility over time. The plan should indicate what needs to be updated and a timeline for implementation.

Investigations/CAPA

The need for a robust investigation/CAPA process is clearly defined in global regulations, but it seems the industry still struggles with conducting and documenting root cause when it comes to investigations based on FDA 483 observations (6). The purpose of an investigation is to identify the root cause of a deviation and take appropriate action to correct the issue across the manufacturing/product line. The best way to demonstrate proper control of this process during an investigation is to ensure you have a robust investigation process, which routinely identifies root cause and that once the correction is made, it does not recur (7). The ability to demonstrate this depends on the understanding and training of the people involved in the investigation process and data that shows the problem was addressed and solved (8, 9).

Risk management

Every company should have a quality risk management plan (10). A well-written and well-implemented quality risk management plan is an integral and valuable element of an effective quality system. Quality risk management plans are important because they help improve a company's ability to provide quality product to patients. They are contingency plans with identified actions that help to ensure a continuous supply of product to the market that meets the expectations of being safe, effective, and available. They are dynamic documents that require integration into and data inputs from all departments in order to be successfully implemented at a company (11). Having the plan available for discussion and demonstrating a knowledge of the plan, how it is incorporated into the culture, and making sure it is revised as needed to reflect current practices is critical to having a successful outcome should you be audited on this topic.

The bottom line is that the regulatory landscape is changing, and it is conceivable that companies will begin to be audited on programs and process that are more subjective than tangible. To be prepared for an audit that touches on the intangibles of a functioning quality management system, companies should begin to formulate programs and systems that address the aforementioned topics.

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Critical Knowledge for Preparing Audits

Addressing data integrity, quality culture, aging facilities, investigations/corrective actions and preventive actions, and risk management is key when conducting audits, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am preparing my site for an audit and have prepared and trained our employees on the usual topics (training program, standard operating procedures [SOPs], change control, etc.). I am concerned that this traditional approach may not be enough in the current regulatory environment. Can you offer some guidance into other issues I should focus on in preparing for the audit?

A. This is a great question and shows an insight into the changing regulatory landscape. I think it will be critical in the coming years to focus on addressing certain intangible topics during routing regulatory audits. These topics should be addressed as part of your company's overall improvement plans and programs.

I would focus on the following topics as a part of preparing for any routine audit: data integrity, quality culture, aging facilities, investigations/corrective actions and preventive actions (CAPA) and risk management. I am of the opinion that these topics will become routine areas of focus for regulatory inspections regardless of the affiliation of the regulatory authority performing the audit. These topics are not new to the industry. There has been much discussion on their impact on drug shortages. It is my opinion that developing robust programs addressing these issues and incorporating them into everyday routine operations will improve the drug shortage situation, improve a company's operating performance, and improve the outcome of regulatory inspections for the company.

FDA has been publishing guidance on these issues over the years, and now as the agency gets ready to finalize the New Inspection Protocols Project (NIPP), it is time to revisit some of these recommendations and implement some of the advice offered. The intent of the NIPP program (1) is to provide inspectional assessments to support tracking and improvement of performance across pharmaceutical manufacturers and products and enhance the production, utility, and consistency of the establishment inspection reports.

Data integrity

Every company should have a program to address data integrity issues that includes guidance on what data integrity is, how to recognize it, how to prevent violations, consequences for violating the company's data integrity policy, etc. The program should also address the frequency and effectiveness of employee training on this topic. The program should demonstrate an understanding of regulatory expectations as well as an explanation of how those expectations are incorporated into the data integrity program. The program needs to go beyond the concepts of ALCOA (attributable, legible, contemporaneous, original, accurate) and include the four new attributes in ALCOA+ (complete, consistent, enduring, available) (2, 3).

Quality culture

The concept of quality culture came about with the introduction of quality metrics. FDA introduced the concept of collecting quality metrics in 2013 (4). Since that time, the industry and regulatory authorities worldwide have embraced the idea that in order to rely on the metrics collected, the company needs to have a culture that supports an open, transparent reporting of "deviations, errors, omissions and aberrant results at all levels of the organization, irrespective of hierarchy" (3). There has been work done by the Parenteral Drug Association and Uni-versity of St. Gallen suggesting the there is a correlation between mature quality attributes and quality culture behaviors. To address the issue of a quality culture during a regulatory inspection, the company should be able to demonstrate their quality system is functional and identifies gaps so the company can implement changes to ensure continuous improvement.

Aging facilities

Aging facilities are of concern because they can lead to drug shortages. It is hard to achieve compliance to current regulatory expectation when manufacturing new and novel

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