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Development
Challenges in IND Applications
Coprocessed Excipients
Patient Centricity

Manufacturing
Cell and Gene Therapies
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COVER STORY

16 Automating Aseptic Processing Reduces Contamination Risk

Industry experts discuss the need for stricter environmental controls.

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FEATURES

DEVELOPMENT

19 Early Development Challenges in IND Applications
Collecting relevant data, planning ahead, and communicating with regulatory bodies in pre-IND meeting programs can help companies to avoid roadblocks in IND applications.

24 Development of Coprocessed Excipients
The right processes used with the right excipient combinations address evolving formulation needs.

27 Focusing on the Patient in Drug Development
Putting the patient at the forefront of drug development is essential, particularly to ensure medication compliance is optimized.

MANUFACTURING

29 Coming Together to Enable Cell and Gene Therapy Manufacturing
Precompetitive consortiums seek solutions to industry-wide challenges.

32 Considerations for Cleaning Lipid Nanoparticles
This article explores the concerns with cleaning pharmaceutical products utilizing LNP delivery vehicles and provides a general cleaning recommendation based on laboratory and field testing.

OUTSOURCING

45 When Is It Appropriate to Outsource Bioanalysis Work to a CRO?
When considering whether to outsource work to a CRO, there are a number of factors to assess, including the type of work that may be outsourced, regulatory considerations, and needs for the study.

WEIGHING UP BIG PHARMA

47 Big Pharma in the Balance
Is AI a panacea for pharma’s productivity gap?

ANALYTICS

43 Ensuring Patient Safety through Elemental Impurity Analysis
Analyzing elemental impurities in drug products is much like other analytical testing—primarily aimed at ensuring patient safety.

PEER-REVIEWED RESEARCH

36 IVPT Data Analysis with FDA Statistical Approach to Assess Bioequivalence
This article describes the in-vitro permeation test study data processing procedures and FDA statistical mathematics of evaluating a generic topical drug product, acyclovir cream, against its reference product.

Continued on page 6

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FROM THE EDITOR

10 The Next Pandemic

Authorities and governing bodies have lost the public's trust when it comes to pandemic response.

REGULATORY WATCH

14 FDA to Continue Inspection Efficiencies After Pandemic

FDA will use virtual site visits even after resuming active inspections.

ASK THE EXPERT

50 Productive Client-CDMO Relationships

Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, discusses the basics for maintaining an acceptable working relationship between a client and their CDMO.

DEPARTMENTS/PRODUCTS

8 Note from the CEO
12 Product Spotlight
49 Marketplace
49 Ad Index

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As we reach the midpoint of the year, it’s appropriate to reexamine the topics we’re addressing. I’d like to point to a special podcast Pharmaceutical Technology conducted where Editorial Director Chris Spivey talked with the director of FDA’s Office of Pharmaceutical Quality (OPQ), Dr. Michael Kopcha, and his deputy directors Dr. Sau Lee and Dr. Cindy Buhse about advancing the science of pharmaceutical manufacturing. Discussion encompassed the framework for regulatory advanced manufacturing evaluation (FRAME), quality management maturity ratings (QMM), advanced versus traditional manufacturing, and re-shoring drug manufacturing to the United States. But I particularly want to highlight the emerging technology program (1).

These new technologies initially were brought to FDA by industry and are, therefore, a fascinating window into where the industry believes it is heading. In this respect, Mike Kopcha said on the PharmTech podcast that, “…to address current and potential future innovations … we worked with NASEM (National Academies of Science, Engineering and Medicine), they held a public workshop, brought in industry experts in this area, to be able to talk with us about what was going on in the industry, what’s on the horizon over the next five to 10 years. … I can list some of the more significant ones … end to end manufacturing, distributed manufacturing, point-of-care manufacturing (as the name implies, doing manufacturing right at the point of care where the patient or consumer actually is), and artificial intelligence, in order to understand what the regulatory framework should look like, we needed to know what these technologies were … so we knew what we were going to be asked to evaluate, and eventually regulate.”

Our new series, “Weighing Up Big Pharma” directly addresses large company performance vis-à-vis their ability to leverage artificial intelligence (AI). With batch values occasionally rising to $3 million dollars, and data streams proliferating both in terms of total amounts but also depth of insight, it is totally logical that pharmaceutical manufacturing has increased the use of AI. Multivariate mechanistic modeling and digital twin strategizing are two areas that leap to mind. But predictive maintenance and advance failure warning systems play an increased role in reducing costs. One example is water purity control. Having to fix a plant’s water system after a problem not only means, electronic or mechanical including by photocopy, recording, or information storage and retrieval without permission in writing from the publisher. Authorization to photocopy items for internal/educational or personal use, or the internal/educational or personal use of specific clients is granted by MultiMedia Pharma Sciences LLC for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Dr. Danvers, MA 01923, 978-750-8400 fax 978-646-8700 or visit http://www.copyright.com online. For uses beyond those listed above, please direct your written request to PTTpress@mmhgroup.com with “Permissions Department” in the subject line. MultiMedia Pharma Sciences LLC provides certain customer contact data (such as customers name, addresses, phone numbers, and e-mail addresses) to third parties who wish to promote relevant products, services, and other opportunities that may be of interest to you. If you do not want MultiMedia Pharma Sciences LLC to make your contact information available to third parties for marketing purposes, simply email mmhinfo@mmhgroup.com and a customer service representative will assist you in removing your name from MultiMedia Pharma Sciences LLC lists.

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Under the helm of Charles Hennessy, Senior Vice President of Content Silas Inman, and Global Medical Affairs & Corporate Development Executive Vice President Mike Hennessy, Jr., as the President and CEO of MJH Life Sciences®, the company continues to be the go-to source for cutting-edge information on the latest trends and technologies in the pharmaceutical industry. The company’s flagship publication, Pharmaceutical Technology, provides in-depth analysis and insights into the evolving landscape of pharmaceutical manufacturing, regulatory affairs, and digital technologies.

In this issue, we delve into the advancements in artificial intelligence (AI) and its impact on pharmaceutical manufacturing. The podcast with FDA’s Office of Pharmaceutical Quality (OPQ) directors offers valuable insights into how AI is shaping the future of the industry. The series “Weighing Up Big Pharma” highlights the performance and AI adoption across large pharmaceutical companies, offering a comprehensive view of the industry’s progress.

As we reach the midpoint of the year, it’s crucial to reevaluate the topics we’ve covered so far. The emerging technology program initiated by NASEM (National Academies of Science, Engineering and Medicine) underscores the industry’s commitment to harnessing the power of AI to enhance manufacturing efficiency, predict chronic diseases, and support health equity. With batch values reaching unprecedented levels and data streams multiplying, AI’s role in pharmaceutical manufacturing is more critical than ever. The discussion with FDA’s OPQ directors on the PharmTech podcast provides a clear direction on how industry expectations are evolving, setting the stage for future innovations.

Moving forward, we continue to explore various aspects of AI in pharmaceutical manufacturing, from predictive maintenance to digital twins. The focus on end-to-end manufacturing and point-of-care solutions is essential in addressing the productivity gap and ensuring patient safety. As we look towards the future, the importance of regulatory frameworks and data protection cannot be overstated. Our commitment to providing comprehensive coverage of the pharmaceutical industry’s latest developments ensures that our readers are well-informed and equipped to navigate the rapidly changing landscape of technology and innovation.
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FDA to Continue Inspection Efficiencies After Pandemic

Jill Wechsler

FDA will use virtual site visits even after resuming active inspections.

Although FDA announced in February 2022 that it was resuming “normal, routine domestic surveillance” of drug and medical product manufacturing facilities, many of the innovations and modifications for site inspections adopted during the COVID-19 pandemic will continue to play a visible role in agency compliance and enforcement operations. FDA’s Office of Regulatory Affairs (ORA) delayed or cancelled most onsite inspections during the past two years due to travel restrictions and infection concerns, but now seeks to resume active inspections where needed and practical (1).

This shift, however, does not signal an end to FDA’s wider use of paper document reviews and of virtual site visits, or Remote Interactive Evaluations (RIEs), in ramping up oversight of biopharma manufacturing and research operations. These strategies notably reduced agency inspection costs, while enabling timely detection of compliance issues, and FDA sees value in continuing its expanded reliance on documents and records, on inspection reports from trusted regulatory authorities, and on wider use of remote real-time review of records and plant operations to provide assurance of proper manufacturing and clinical research operations (2).

Judith McMeekin, associate commissioner for regulatory affairs, pointed out during a presentation sponsored by the Alliance for a Stronger FDA on April 6, 2022 that ORA saved nearly $40,000 in 2020 and 2021, providing resources to develop a foreign travel planning system, expand personnel training, enhance information systems, and upgrade labs. FDA analysts are comparing the benefits and shortcomings of onsite inspections vs. record requests to develop criteria for revising or continuing these alternative practices.

More flexible inspection programs could gain from legislation before Congress to reauthorize FDA user fees and update agency operations and policies. The bill includes a provision to clarify FDA’s authority for collecting manufacturing records from medical device makers in advance or in lieu of field inspections and also for clinical study sites under FDA’s bioresearch monitoring program (FDA already has such authority for drugs). The measure also clarifies agency use of inspection findings of trusted foreign regulatory authorities in determining the need for preapproval inspections (PAIs). The bill requires FDA to post more information on the findings from drug and device inspections, such as warning letters and import alerts. And to expand unannounced FDA inspections of foreign drug establishments, the legislators propose a new pilot program to increase such site visits and to evaluate the impact on both domestic and foreign facilities (3).

Dealing with RIEs
In response to these developments, FDA has worked to better explain its criteria for selecting and methods for conducting more remote and alternative facility assessments. At the recent FDA Generic Drugs Forum, staffers from the Office of Pharmaceutical Manufacturing Assessment (OPMA) in the Center for Drug Evaluation and Research (CDER)’s Office of Product Quality (OPQ) explained that FDA will weigh the need for an on-site inspection based on a risk-based assessment of product, process, and facility risks (4). This involves scrutiny of records and other manufacturer information from trusted regulatory authorities.

Such information on a firm’s compliance history, process risks, manufacturing experience, and previous alerts, recalls, and complaints will help determine whether a PAI is needed or if FDA can assess the firm’s capacity for risk mitigation and GMP compliance from company and regulator records. When FDA considers an RIE advisable, it will discuss the logistics, scope, and expectations with the manufacturer, request needed documents from the firm in advance, and outline its main questions or concerns and the logistics for conducting a remote facility tour. Such virtual site visits also can help all parties prepare for a future onsite inspection, if warranted, but do not qualify as formal inspections per se. They are voluntary for the company, but a refusal to cooperate with an RIE request could delay product approval.

Jill Wechsler is Pharmaceutical Technology’s Washington editor, jillwechsler7@gmail.com.
OPMA staff fellow Alexander Gontcharov described an RIE for a foreign manufacturing facility utilizing a new unit of operation to produce delayed-release tablets and capsules. This involved four three-hour sessions with a facility “walk-through” utilizing a laptop on a cart with external cameras and microphones. Another RIE for a new unit producing new ointments and liquid products had three four-hour sessions that used a portable tablet PC with Wi-Fi connections. FDA investigators viewed warehouses, labs, and production areas, as well as document control systems. Inspection findings may be specified in a close-out memo, or FDA may later send a letter identifying difficulties found at the facility and if an on-site inspection is needed.

The shift to remote assessments is reflected in the rise of warning letters that involve alternative inspection tools, according to the 2021 annual report from CDER’s Office of Compliance (OC) (5). While FDA exercised enforcement discretion in multiple cases to avoid shortages of critical medicines, OC reports a rise in drug adulteration warning letters based on sample testing and on information from records requests. In addition, OC conducted more than 45 remote regulatory assessments of clinical sites under the agency’s biomedical research compliance program. An FDA draft guidance published in April 2021 advises manufacturers on how the agency seeks to conduct this growing range of remote evaluations (6).

Overall, FDA advises manufacturers to recognize the importance of RIEs and to query about any unclear agency information requests. While FDA recognizes that RIEs are not equivalent to full inspections and that the agency only can see what the firm makes available, these alternative tools have cut the need for on-site PAIs in half and helped the agency meet user fee approval goals for 90% of applications this past year.

References
Automating Aseptic Processing Reduces Contamination Risk

Meg Rivers

Industry experts discuss the need for stricter environmental controls, whether to incorporate single-use technologies, and areas for improved automation.

Packaging sterile drug products into sterilized containers via sterilization or aseptic processing continues to be both an absolute necessity and a challenge for the bio/pharmaceutical industry. But where there are challenges, there is room for innovation as well as room to grow.

“Aseptic processing is one of the most challenging manufacturing processes in pharmaceutical development,” says Robert W. Lee, PhD, president CDMO division, Lubrizol Life Science Health, a contract development and manufacturing organization (CDMO) located in Bethlehem, Pa. and provider of clinical and commercial aseptic processing. “Sterile is sterile. It is binary.”

One of the reasons aseptic processing, specifically, is so challenging is due to a lack of proper training as well as a lack of comprehensive understanding of the techniques. This can then lead to regulatory intervention.

“In aseptic processing, a lack of understanding of the importance of aseptic techniques and one’s impact on the environment can lead to an array of complications and compliance issues,” says Simren Ahmadi, quality specialist, GMP, Lubrizol Life Science Health. “For example, just last year, FDA issued 25,483 observation forms in relation to aseptic processing. Virtually, all these observations were regarding poor aseptic operational practices that were put in place by the facilities.”

According to Ahmadi, to adopt better aseptic practices and minimize regulatory observations, organizations must change how they view aseptic processing. Namely, to look at it not as an operation, but as a culture.

“When a facility adopts an aseptic culture, personnel begin to understand the ‘why’ behind aseptic processing and their impact on the environment. Explaining that aseptic techniques and behaviors are critical to avoid contamination and produce a sterile product for a patient while illustrating the impact one has on the environment enables personnel to understand why good aseptic technique is so important,” continues Ahmadi.

“This promotes more comprehensive risk assessments, validations, qualifications, etc. by taking aseptic processing into consideration, which in turn identifies weak areas of a process before complications or compliance issues arise. Additionally, promoting an aseptic culture allows personnel to develop an audit mindset and know what to look for when it comes to aseptic processing. Personnel can continually look for areas for improvement through their daily job functions or by simply walking on the floor and have any compliance issues addressed internally.”
Nonetheless, whether an organization views aseptic processing and sterilization as a culture or simply as a necessary step in the manufacturing process, the need for either isn’t up for debate.

“Sterility is an obligatory critical quality attribute for parenteral preparations; sterility cannot be assured by testing, but by use of well-designed, validated, and controlled manufacturing processes. Most modern therapeutics are parenteral preparations that are not suitable for terminal sterilization; instead, aseptic processing, whenever feasible, in combination with sterile filtration, has to be pursued,” says Hanns-Christian Mahler, CEO, ten23 health, a Switzerland-based CDMO with a specialty in the development and sterile manufacture of complex pharmaceuticals, such as biologics.

Environmental controls

To have sterile end products, environmental controls must be in place. Quality assurance (QA) departments have their work cut out for them to perform risk assessments. Many processes must be established and standardized, and all employees must follow those processes faithfully.

“[QA] departments ensure aseptic processing will work as intended by performing risk assessments on the locations, methods, equipment, and frequency for the aseptic processing that will be conducted,” says Christopher DeHart, director of quality, Lubrizol Life Science Health. “In-depth quality risk assessments identify the risks involved with the aseptic process to be conducted and determine what controls need to be put in place to minimize these risks.”

DeHart breaks down these controls further:

- **Facility design:** This should include room classifications, HEPA filters, first air, and airlocks.
- **Building management:** Working in conjunction with the facility, this includes monitoring the movement of the airflow, pressures, temperature, and humidity in real-time. This ensures the HEPA filters and airlocks are working as intended.
- **Procedures and trained personnel:** To minimize the risk of microbial contamination, procedures and training programs should be in place so that aseptic techniques are understood and followed. These procedures should cover gowning, personnel/material/equipment flow, viable and non-viable sampling, reading plates, autoclaving, cleaning, and more.

Rainer Glöckler, head of new technologies, swissfillon—a ten23 health company that offers a range of services for sterile filling and finish of liquid active ingredients—breaks down environmental controls into three relevant categories:

**Lack of proper training and understanding can lead to regulatory intervention.**

- **Isolator:** To ensure aseptic conditions of surfaces in the isolator, rodac plates are required; active air samples are needed to identify any living contaminant; passive air samples (settle plates) identify any particle in the laminar-air stream; and lastly, continuous particle measurement and fingertip end-of-batch tests are performed on all gloves installed on the isolator.
- **Room:** Rodac plates are used to ensure aseptic conditions of surfaces in the cleanroom; active air samples are used to identify any living contaminants in the air; and continuous particle measurement is also performed.
- **Clean media:** This includes a full routine control for particles, bio-contaminants, chemicals, and conductivity for water for injection.

Joerg Zimmermann, VP of Vetter Development Service External Affairs, Vetter Pharma-Fertigung GmbH & Co KG—a CDMO specializing in the fill/finish of sterile injectables and head-quartered in Ravensburg, Germany—stresses the importance of a functioning cleanroom system.

“Before we get to the aseptic operation, we must first ensure that we have a functioning cleanroom system that provides a controlled environment for safe production. This includes tight controls on temperature, humidity, and differential pressure,” says Zimmermann. “Of utmost importance is airflow management to minimize the contamination risk. Air flows are visualized during the qualification of the cleanrooms to ensure unidirectional flow from the ceiling to the floor, and from the core filling area to the background. This needs to be done in static and dynamic conditions.”

Another aspect that should be noted is the importance of a sterile, Grade A, ISO 5 environment.

“Aseptic processing should be executed in a classified space with minimum characteristics for particulate and microbial control, consistent with ISO 5,” adds Kenneth Laderman, PhD, manufacturing director, Eurofins BioPharma Product Testing, a laboratory that supports small batch sterile GMP manufacturing in San Diego, Calif. “Maintaining this classification will require a routine cleaning and environmental monitoring program as well as controls over gowning, material movement, and personnel movement.”

Lee adds that, in addition to an ISO 5 environment, it’s also acceptable to use a fully closed process in an ISO 7 environment. This is where the entire product contact pathway is sterilized using steam-in-place methodology. Afterward, sterile API and sterile-filtered excipients are added aseptically to the closed system and the remainder of the process is conducted aseptically.

**Single-use technologies and flexibility**

When interviewed by Pharmaceutical Technology, Eurofins BioPharma Product Testing, Lubrizol, and ten23 health confirmed using single-use technologies in some of their aseptic processes. As with most things, there are both benefits and risks in doing so.
“Single-use systems [SUS] are advantageous, as they reduce the need for cleaning validation/verification activities for your process,” says DeHart. “In addition, the materials come certified sterile, reducing the need for a validated autoclave cycle for your processing equipment. In terms of a CDMO business model, the cost of the [SUS] can be passed to the client, enabling a cost-effective way to provide sterile manufacturing activities.”

Laderman states that Eurofins utilizes single-use technology for many product contact surfaces.

“As a CDMO, single-use technology facilitates the processing of multiple APIs within the same facility,” says Laderman. “In the absence of this technology, it would be necessary to execute a new cleaning validation for each molecule introduced into the manufacturing suite. By maintaining a single-use isolated system, the process is streamlined, decreasing time for project execution as well as turnaround time.”

According to Lee, Lubrizol uses SUS for small-volume sterile solution processing because this technology provides sterility assurance and flexibility as well as saves time. Lee adds that while SUS can be expensive, avoiding cleaning validation can lead to cost savings, depending on the application.

Meanwhile, Mahler at ten23 health states that the company uses single-use technologies for compounding/formation down to the filling needle.

“[SUS] offer various advantages from a pharmaceutical perspective, including avoiding the risk for cross-contamination and avoiding related cleaning validation activities,” says Mahler. “However, [SUS] are a significant concern to us from a sustainability perspective, and we believe that biopharmaceutical solution providers should research new, more sustainable options.”

Companies should consider the following when using (or considering using) SUS in aseptic processing, according to Lee:

- Are the materials of construction compatible with the API?
- Depending on the complexity of the process as well as the product, SUS may not be advantageous, or a hybrid approach may be more ideal.
- What are the lead times for materials? This can be anywhere from eight weeks to one year.

Single-use technologies and SUS seem to have simplified processes and provided an alternative approach to more traditional methods in the realm of aseptic processing and sterilization. But one of the key disadvantageous is the supply chain. Similar to Lee, Zimmermann shares that recent shortages related to the pandemic have revealed that when a single-use component, for example, isn’t available, production comes to a stop.

To have sterile end products, environmental controls must be in place.

“There are some products where everything in compounding and in the liquid path is single-use, and we have others where it makes more sense to do a hybrid approach, with only the tubing and the filters being disposables,” says Zimmermann. “One thing that most people are not aware of is that the capacity for gamma-radiation, the method of choice for most [SUS], is under extreme pressure. This is causing companies to reconsider the processes on a strategic level. Another aspect that is coming into greater focus is the waste management of [SUS]. At the moment, the standard of disposal is incineration, which is not the most sustainable method.”

**The greatest risks**

The greatest risk in aseptic processing is, of course, contamination, which can lead to a possible rejection of a batch, loss in revenue, product shortages, etc. And what is the greatest risk for contamination? People.

Both Zimmermann and Mahler state that the highest risk in aseptic processing comes from operators. Intense training can help to avoid contamination along with proper, sterilized gowns and testing the operators.

Laderman adds that well-designed systems for cleaning and air handling will minimize the risk as well as gowning procedures and training of personnel. Eurofins BioPharma Product Testing, specifically, uses a robotic, gloveless isolator to limit the product’s exposure to the operator.

In addition to the inherent risks that humans pose, there are other avenues leading to contamination. Potential causes for contamination, according to Ahmadi, can be anything from poor aseptic technique to equipment.

“A facility must have robust validations, qualifications, risk assessments, investigations, etc., as well as a robust aseptic techniques training program. These documents and programs must also be periodically reviewed to ensure they remain compliant,” Ahmadi says. “An organization must also ensure the facility design of critical areas can be easily cleaned and that personnel have the room and means to work aseptically. Additionally, [QA] should maintain a presence on the floor to promote good aseptic techniques and conduct walkthroughs of critical areas to ensure the facility is in good order and personnel are practicing good aseptic techniques.”

**Better automation**

Like any part of the manufacturing process, aseptic processing has room to improve automation and has made significant progress in recent years.

“Automation requires flexibility, both in scale and duration of the function, while limiting the need for direct contact with the operators,” says Laderman. “Most automated systems are iterative by nature, as consumables utilized by the process will need to be resupplied. Decreasing the frequency of the resupply will minimize the chances for contamination.”

Contin. on page 21
Early Development Challenges in IND Applications
Meg Rivers

Prior to submitting an investigational new drug (IND) application to FDA, there is much for companies to plan and consider in advance. Collecting the appropriate data and determining just how much data are required to prove a drug product is reasonably safe for initial testing on humans are some of the challenges facing companies in the pre-clinical stage of development and planning for IND activities.

According to Mara Holinger, SVP, regulatory affairs, Veristat, the drug product, biologic, or other proposed assets should be tested in in vitro and in vivo to demonstrate that the product is efficacious in a therapeutic model.

“Next, or in parallel, a contract development and manufacturing organization (CDMO) needs to be selected,” Holinger continues. “The drug product formulation needs to be carefully considered and then manufactured per good manufacturing practice (GMP) standards. The drug product will need to undergo toxicity studies, typically in two animal species, for both acute and repeat dose testing. These studies are generally required to be conducted per good laboratory practice (GLP) standards.”

Additional testing that might be required, depending on the product type and indication, include the following:
- genotoxicity
- reproduction toxicity
- carcinogenicity.

It is also essential that all necessary information is collected for the drug substance, the drug product, and the non-clinical and clinical investigations, Paola Tocchetti, senior VP, head of global regulatory affairs, Evotec, explains. Some of the required information includes an investigator brochure, a clinical protocol, all IND sections in electronic common technical document (eCTD) format.

“It is our best practice to have all these documents included in an internal tracking system, an ‘IND tracker’ allowing us to follow the progress of the IND documents preparation according to the set timelines. The IND tracker also enables us to order priorities for any critical paths,” says Tocchetti.

Planning for an IND
As might be expected, some believe the best time to plan for IND activities is as early as can be managed.

“The regulatory strategy should be in place as early as possible in the development process—ideally at the step when the candidate is nominated for development,” says Tocchetti. “This is then followed by the IND edition, which requires the drug substance, drug product, and non-clinical reports. The health authorities’ regulations are the driving factor for the drug development process; for example, compendial tests from [the United States] and European Pharmacopoeia and regulated toxicology programs to support the first-in-human study must be performed.”

Meanwhile, Kevin Hennegan, senior regulatory strategist, Veristat, shares that there isn’t a single answer for when to start planning for an IND application, explaining that most companies should think about a regulatory plan once there are data to support a possible clinical benefit for an investigational product.

“To set the IND up for success, I think the two most important things a company can do are to engage an experienced regulatory professional (either an employee or a consultant) who can help you navigate the process; and take advantage of the free advice offered by FDA through the pre-IND meeting program,” Hennegan explains.

But the data are not the only important factor for INDs. A clear presentation of data is also critical. Hennegan
adds that the success of an IND submission depends largely on how clearly the data are presented—in addition to complying with regulatory guidance.

“For a regulatory reviewer, it is important that the document that he/she receives is coherently worded, linguistically correct, [and] consistent in terms of content and connection between the different sections. The goal is to provide a document that the reviewer ‘enjoys’ reading,” says Tocchetti. “We also find that the timely and accurate input of all the R&D functions and the integrated management of their different contributions is crucial to ensure the success of an IND submission.”

Pitfalls and misconceptions

From a manufacturing perspective, selecting a CDMO is a common pitfall. According to Hennegan, CDMOs can create significant delays in programs if they are low-performing.

“One other pitfall that is sometimes missed is not thinking product quality through all the way to delivery to the patient,” says Hennegan. “If there is a dilution device required for delivery, you will need to provide data that those processes do not adversely affect the product.”

Hennegan further breaks down potential pitfalls into non-clinical and clinical:

- **Non-clinical**: One pitfall is species selection. Costly additional studies can result from failing to perform toxicology studies in a relevant species. Meanwhile, costs can also be increased—without adding value—when selecting burdensome species. Selecting the best species to use should be discussed in a pre-IND meeting.

- **Clinical**: Measures must be put in place to mitigate risks to the study subjects—such as frequent vital sign assessments, safety labs, follow-up visits, and rules for stopping a study—which can be done through risk analyses of the first-in-human protocol.

Tocchetti adds the most common pitfalls they have come across:

- The reviewer can’t determine if the administration of a drug product in the clinical study is safe due to a lack of information in the IND.
- The most recent FDA and European Medicines Agency guidelines aren’t adhered to when designing the nonclinical development.
- GMP and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines aren’t followed, and a reason why the rules were not followed isn’t documented properly.
- The quality level of the drug substance and/or drug product quality level isn’t sufficient to administer it to humans.
- The findings of toxicology don’t support dosing in humans.

Moreover, one significant misconception for IND applications, according to Holinger, is the turnaround time.

“[I’ve] worked with several sponsors that believe the IND writing and submission process can be completed in a month or two. If a sponsor is starting from scratch (does not have a previous IND to reference), it typically takes four to six months to write an entire IND, pull together all of the documents, and publish/submit the IND,” says Holinger. “Another misconception I’ve come across is the assumption that an IND is a single document. INDs need to comply with eCTD standards including administrative information (module 1), summaries (module 2), CMC/quality (module 3), non-clinical testing (module 4), and clinical (module 5).
Excelling in the IND application process

“Companies who excel [in the IND application process] have an integrated and multidisciplinary approach to IND planning and execution,” says Tocchetti. “Thus, a tightly integrated approach and expertly coordinated delivery strategy enable them to carefully perform risk-management and rapid decision-making. The increase in quality allows for timely delivery of a robust and comprehensive regulatory data package for IND submission without ever needing to compromise on quality because of lack of time.”

In addition, the probability of a successful IND is increased by running a pre-IND meeting with the relevant regulatory agency, such as FDA, according to Tocchetti.

Proper planning and project management, according to Erin Flynn, regulatory strategist, Veristat, are also key to excelling in the IND application process.

“Proper planning and project management are critical aspects of IND preparation that are often underrated,” says Flynn. “The IND is a granular collection of documents that can sometimes be composed of upwards of one hundred individual documents, with multiple authors, and often with overlapping review cycles. It is imperative that all authors are aligned on product-specific details in order to maintain consistency throughout the IND and present the best face forward to the FDA. Project management is also key. It can be easy to get off track or overwhelmed by the sheer number of documents to prepare; so, effective tracking and timeline management streamline the IND preparation process.”

IND applications expected to decrease

When looking ahead for 2022 and beyond, both Holinger, Hennegan, and Flynn predict the number of IND applications for COVID-19 vaccines will decrease. In addition, they predict a potential increase in the number of INDs for personalized therapies, along with a general increase in INDs for mRNA-based products.

Meanwhile, Ralf Geiben Lynn, PhD, MBA, senior business development director, Evotec, foresees regulatory changes for large molecules.

“As more and more innovative treatments arise, we expect that the FDA guidance documents in non-traditional non-small molecule fields like biologics or gene-therapy products [to] evolve and mature,” says Lynn. “Thus, it is expected in the future, that the sponsors and specialized CROs will continue to keep up-to-date with these new treatments.”

Where the future of IND applications is headed, only time will tell. But one trend is clear: planning ahead whenever possible has the potential to provide a positive impact on INDs and their success rate. PT

Cover Story  —  Contin. from page 18

Laderman shares that Eurofins BioPharma Product Testing utilizes an automated robotic filler, which offers the lowest levels of extraneous particulate matter and the highest of sterility assurance. However, it’s dependent on the standardized nested vials and caps. Laderman believes that automation will continue to improve and be more readily adopted once additional vial types and sizes are available in standardized formats.

Similarly, when asked about opportunities for improved automation, Zimmermann points to the use of robots.

“Whatever can be automated, should be automated,” says Zimmermann. “The use of robots in cleanroom settings is increasing and constantly adding new tasks executed by robots. For us, this is not new, as we have been using robots since 1994. However, on new developments like the Flexi-cell that we are progressing with a partner, the robot does three distinct operations: set-up of the fill-line, the filling and stoppering process, and environmental monitoring. This makes the aseptic operation less risky and more robust. Automated environmental monitoring is considered for even more applications, but also remote troubleshooting via robot arms is being considered as well.”

Glöckler, on the other hand, looks to filling equipment without any glove intervention during aseptic processing as an area of improved automation. While the risk of contamination may be lessened, Glöckler adds that any problem in the isolator has the potential to impact process performance.

“Continuous online particle and bioburden testing replacing Settle plates, active air, and continuous particle measurement are in a development stage but still not accepted by authorities,” says Glöckler.

“Aseptic processing is better automated in that there is less human contact with the product, significantly lowering the possibility of contamination,” says Ahmadi, weighing in on the aseptic processing automation. “Automated aseptic processing removes the need for an operator to have close contact with the product and minimizes the number of operators needed in and out of critical areas. However, if automated aseptic processing is utilized, additional controls need to be put in place to ensure the equipment remains sterile. These controls include intervention procedures, cleaning validations, maintenance, etc. Aseptic processing is also better automated because it can produce more products in a shorter amount of time and minimizes the number of materials that need to be autoclaved. However, if the equipment is not functioning properly, there will be a loss of revenue in downtime.”

While we can’t banish humans entirely from the process floor, minimizing the risk associated with their presence is a major goal. Where the aseptic processing industry goes next, only time will tell. But it seems that single-use technologies and robotics will play a role in what’s on the horizon. PT
A Modern Alternative to Enzymatic Capping of mRNA

How TriLink developed its CleanCap® technology, an mRNA capping method, and made it scalable to support the global vaccine supply

PHARMTECH: Who is TriLink Biotechnologies, and what do you do?

POLING: TriLink Biotechnologies is a contract development and manufacturing organization (CDMO) focused on making mRNA drug substance. We are a key raw material supplier in the mRNA vaccine supply chain that also supports the Pfizer-BioNTech COVID-19 programs.

TriLink was founded in 1996 as an oligonucleotide and small molecule manufacturer. We pivoted to mRNA in 2005 – 2006, further expanding in that market in the 2010s. Our expertise in mRNA manufacturing has enabled us to grow and support various developers in the mRNA space.

PHARMTECH: Why is mRNA so important as a therapeutic?

POLING: mRNA is a new modality in the therapeutic biologics space with a unique opportunity to be a standard platform for manufacturing drugs for many different indications. mRNA serves as a transient message that can be delivered to patients to code for proteins that have functional activity. Prophylactic mRNA vaccines, in particular, are coded for specific antigens that the body can respond to and create an immune response similar to how the COVID-19 vaccine works. Like the spike protein found on the SARS-CoV-2 virus, it’s about making a small protein that trains our cells to respond to a prospective SARS-CoV-2 infection that would otherwise cause COVID-19.

mRNA can also be used in therapeutic indications, such as gene replacement, allowing for specific genes to be expressed at higher levels to help with protein deficiencies. Another application that we see mRNA being used for is gene editing, where specific gene-editing payloads are delivered as an mRNA product, and then encoded to carry out their gene-editing activity in the target cell type(s).

mRNA-based research is diverse in application potential, but, importantly, the core central manufacturing process is consistent regardless of the drug indication a pharmaceutical company may want to build.

PHARMTECH: What is an mRNA cap?

POLING: An mRNA is a long linear piece of nucleic acids with a head and a tail. The head of an mRNA is called the cap, which protects the mRNA from degradation. Because it is a long string of nucleotides, it can be degraded from either end, so having a cap at that head protects the structure.

TriLink developed a cap analog that is incorporated into the mRNA while being manufactured. Older methods required multiple steps to add a cap after the mRNA had already been produced. CleanCap is produced at the same time the mRNA is being made, which enables a more robust manufacturing process, improves yield, and in some cases, improves mRNA performance based on the structure of the cap used.
TriLink BioTechnologies, part of Maravai LifeSciences, is a CDMO focused on overcoming challenges in the synthesis and scale-up of mRNA, NTPs, and nucleic acids, including its proprietary CleanCap® mRNA capping technology. TriLink is headquartered in San Diego, California, and offers GMP and general mRNA, oligonucleotide, and plasmid manufacturing to support therapeutic, vaccine, and diagnostic clients.

**PHARMTECH:** Why is making an mRNA cap with CleanCap better than other methods?

**POLING:** Most importantly, CleanCap technology offers increased yield compared with older methods. Some early generation cap analogs have been around for 20 years but significantly hinder the overall yield—manufacturers and developers in this space would have to do two to five lots, in parallel, to get enough drug substance to dose a single patient. CleanCap reagents, comparatively, get you more than four times the yield from a single reaction.

The other great thing about CleanCap reagents is the no need for multiple enzymatic modifications after the mRNA has been made. All the modifications needed to get a natural cap structure are done in a single-pot reaction. The individual changes are done at the same time the mRNA is manufactured, which reduces the likelihood of triggering an unwanted innate immune response in vivo. If you’re introducing a foreign mRNA into an animal model or human patient, the host immune system will respond to it. However, mRNA capped with CleanCap evades that response in some capacity. This way, the mRNA is much more efficacious when used in a patient scenario.

**PHARMTECH:** When did you start working on making CleanCap a GMP material?

**POLING:** We’ve been making CleanCap for six years; we first synthesized the molecule in 2016. In mid-2020, we were tapped by Pfizer and BioNTech to use CleanCap in their mRNA clinical trials, so we invested in a more robust manufacturing process and a cleanroom facility. We transferred our manufacturing capabilities into an ISO manufacturing space, put in-process controls, validated our analytical methods, etc., and scaled up almost nine times what the original yield was from our bench-scale reactions. Since then, we have supported the manufacturing of over 5 billion doses of the Pfizer BioNTech vaccine, and CleanCap is now available as a GMP molecule for the entire market.

**PHARMTECH:** How is this different than what your competitors are doing?

**POLING:** Our main competitors are using enzymatic systems that modify the cap structure of the mRNA after it’s been manufactured. Two vendors currently have GMP enzyme offerings, but they’re not able to scale those enzymatic processes that are dependent on bacterial fermentation, purification, and clarification of the recombinant proteins. They’re not able to overcome the challenges that come with meeting the demand for large-scale vaccine programs or the hundreds of different clinical trial programs that are underway. CleanCap has allowed us to serve the entire market with a GMP solution for mRNA.

**PHARMTECH:** What is next for TriLink’s portfolio?

**POLING:** We spent a lot of time developing our internal capabilities to make something suitable for clinical trials, and the cap is one piece of the nucleic acid puzzle. The other piece is around modified nucleosides and nucleoside triphosphates. In the Pfizer BioNTech and the other mRNA vaccine platforms, they use a modified nucleoside triphosphate called N1-Methylpyrouridine, a molecule that TriLink has been making for 15 years. We’re taking our research-grade material and elevating it to the standards of GMP so that it can be used in clinical manufacturing.

We’re excited and proud of our ability to continue to serve the mRNA market. We’ve added a lot of robustness to our manufacturing process, and we’ll be launching a GMP version of N1-Methylpyrouridine in the summer of 2022. Expanding our GMP raw material offering means the researchers we support are one step closer in their drive to move mRNA therapies forward.
Development of Coprocessed Excipients

Cynthia A. Challener

The right processes used with the right excipient combinations address evolving formulation needs.

Coprocessed excipients are blends of different excipients subjected to physical processing that leads to modifications of their physical structures without causing any chemical changes. They possess unique functionality that cannot be achieved through simple blending and are increasingly important for addressing formulation issues posed by the highly complex APIs under development. Adoption of coprocessed excipients has been slow, however, because even when prepared using compendial excipients, they are considered “novel” by regulators. The lack of a separate excipient approval process means that drug developers must take on elevated risk when using such “novel” excipients in the formulation of drug candidates.

Reducing complexity and increasing functionality

Oral solid dosage forms are traditionally formulated with combinations of individual excipients with differing functionalities (filler, binder, disintegrant, lubricant, flow-aid, solubilizer, etc.), says Ashish Joshi, pharma technical and business manager at BASF Pharma Solutions. The processes used to formulate these excipients into an oral dosage form are complicated as well as time-, energy-, and labor-intensive (e.g., granulation, spray-drying, roller compaction, etc.). In addition, the use of many individual excipients requires bracketing or optimization studies and has the risk of non-uniform distribution, which can adversely affect final product performance.

The ideal process for tablet formation is direct compression, as it eliminates the need for granulation or other prior processing steps, according to Joao Marcos Assis, global technical marketing manager, BASF Pharma Solutions. “Direct compression formulations, however, typically require multiple excipients to achieve good flowability, high bulk density, excellent compressibility, and fast disintegration (for immediate release formulations) because individual materials do not possess these multiple attributes,” he observes.

Coprocessed excipients can be used to overcome these formulation challenges through their enhancement of the resulting material’s performance and processability, Assis says. “By reducing manufacturing complexity and thus drug development time, coprocessed excipients can significantly expedite time-to-market,” he continues. Furthermore, API and coprocessed excipients normally fulfill the minimum functional requirements for tableting, consolidating quality-by-design efforts by simplifying the formulation. Analytical testing and material handling and warehousing needs and documentation requirements are also reduced.

Several applications

The benefits of using coprocessed excipients are increased when multiple excipients can be coprocessed together. “Initially, most coprocessed materials were based on just two excipients, but increasingly coprocessed products being introduced to the market comprise multiple excipients,” notes Yeli Zhang, technical service manager at IFF Pharma Solutions.

The ability to combine many individual excipients and functionalities into a single high-functionality excipient enhances the ease of formulation and final performance as well as enables process simplification and cost-savings, Joshi adds. “Consequently, the major trend in developing coprocessed excipients is to reduce the number of individual excipients used in a formulation, with a focus on improving the flow-properties, compressibility, disintegration, and lubrication of oral solid dosage forms using a single coprocessed excipient,” he comments.
This trend is particularly true with coprocessed excipients intended for us in orally disintegrating tablets (ODTs). “Many companies are launching coprocessed excipients targeting this segment that combine a number of excipients because ODT formulations require a high number of excipients and are typically formed using direct compression,” adds Vinay Muley, research and development leader at IFF Pharma Solutions. Joshi agrees that single coprocessed excipients can provide not only good flow, compressibility, and fast-disintegration, but also excellent taste and a pleasant, non-gritty mouthfeel.

Coprocessed excipients are also increasingly being used to convert more complicated, labor-intensive formulation processes such as wet granulation into quicker direct-compression processes without affecting the final product quality or performance, according to Joshi. He also notes that coprocessed excipients are being used to improve the efficiency of continuous manufacturing operations given that only a limited number of feeder ports are typically available and it is crucial to precisely control the flow rate of excipients as they are added.

Different excipient combinations
Developers of coprocessed excipients can theoretically use any material in their products, but most commonly, excipients that already have pharmaceutical monographs are selected because these excipients have a history of being used in pharmaceutical product formulations, according to Zhang. The key when selecting different ingredients to use in a particular coprocessed excipient is to choose those materials that will provide the functionality required to address customer needs, Zhang observes. Coprocessed excipients can improve drug processability and/or drug product performance. “Mainly excipient developers are looking to solve particular customer problems or provide particular benefits, and excipients are chosen that can maximize the needed functionality,” she says.

Ideally, adds Muley, the materials used to create coprocessed excipients will also have synergistic interactions that lead to enhancements in functionality, so that the coprocessed excipient will not only simplify formulation, but provide improved performance. Joshi adds that in addition to having complimentary and/or synergistic functionalities, the individual excipients chosen should be amenable to use in commonly available commercial processes (agglomeration, spray-drying, etc.) and behave reproducibly under the processing conditions. Ingredients used in coprocessed excipients also need to be nonreactive and inert so they do not undergo any chemical changes during production, according to Muley.

Some coprocessed excipients specifically aim to improve the performance of the drug product.

Typically, one or more fillers are coprocessed with binders, glidants, or disintegrants depending on the intended purpose of the product, according to Diogo Gomes Lopes, product development scientific team leader, Softgel and Oral Technologies at Catalent. “Coprocessed excipients that are intended to overcome any manufacturing limitations of the API, such as poor compressibility or poor flowability, are often composed of fillers, which are coprocessed with binders or glidants,” he explains. These types of coprocessed excipients also have the potential to increase drug loading in the drug product, allowing for production of a smaller dosage form that is more acceptable to the patient, Gomes says.

Some coprocessed excipients specifically aim to improve the performance of the drug product. Here again, Gomes points to coprocessed excipients for the manufacture of ODTs. “These coprocessed excipients allow for immediate disintegration of the tablet after administration while providing sufficient mechanical strength for packaging and transport,” he notes.

The materials chosen for coprocessing can include both small molecules, such as sugars and esters, and polymers such as polyvinyl acetate copolymers, microcrystalline cellulose (MCC), and starch. Coprocessing such varied materials together can lead to improved functionality, including greater processing properties as well as improved content uniformity, palatability, stability, and enhanced sustained-release performance.

Processing methods provide intimate mixing
Several methods are used to manufacture coprocessed excipients. The one feature they all have in common, according to Zhang, is that they involve physical processing of two or more excipients such that they interact with each other on a micro level, providing intimate mixing.

The most common methods include spray drying, flash drying, co-extrusion, granulation, high-shear granulation, fluid bed granulation, and roller compaction. “All of these processes are well known and are standard operations in pharmaceutical manufacturing,” Assis underscores. The key advantage is that under the mild conditions—moderate temperature and pH values, for example—chemical reactions between the ingredients can generally be excluded. It is important, he emphasizes, to determine the potential for incompatibilities between the different excipients used that could lead to chemical changes and avoid any combinations that might present reactivity concerns.

One exciting new method that could play a role in the production of coprocessed excipients, according to Muley, is 3D printing. Fused deposition modeling, he notes, is a good example of an additive manufacturing method very applicable to the production of coprocessed excipients. “The use of such methods is at the very preliminary
stage, with exploration of the technology just beginning,” he says. Such approaches fit well with the push by FDA to adopt more efficient production technologies.

**Design-of-experiment studies valuable**

Although the development of coprocessed excipients does not involve combinatorial chemistry to impart many different chemical and molecular changes, there still are a large number of excipients to choose from. “Increasing functionality by modifying physical interactions only can present challenges, and pre-formulation studies using a design-of-experiment (DoE) strategy can be very helpful at the initial development stages,” Muley observes.

Computational methods can also be used to better support formulators during the development of drug products using coprocessed excipients, according to Silke Gebert, project engineer, BASF Pharma Solutions. For example, she points to ZoomLab, BASF’s Virtual Formulation Assistant for predicting and optimizing formulations using advanced algorithms and thereby expediting drug development. “Marketed coprocessed materials, new products, and prototypes can be characterized using the ZoomLab-logic to generate a chart that identifies each material’s favorable and less favorable properties, such as particle size distribution, compressibility index, and flowability,” she explains.

**Moving toward all-in-one solutions**

The need to accelerate drug development and also increase the efficiency and reduce the cost of drug manufacturing is driving excipient suppliers to seek more comprehensive coprocessed product solutions. “The most significant development in the coprocessed field relates to the growing focus on all-in-one coprocessed excipients,” Gebert contends.

All-in-one excipients, Gebert explains, are strategically designed multifunctional materials containing all the functionalities required to produce tablets: diluent/filler, disintegrant, binder, and lubricant at a minimum. “These materials are processed to achieve optimal bulk density, flowability, blend processability, drug uniformity, excellent compressibility, fast disintegration, and outstanding product performance,” she says. The drug manufacturing process then only requires blending the API and the all-in-one coprocessed excipient, then compressing the blend.

For these all-in-one products, Assis notes that common fillers include lactose, mannitol, and MCC; binders are often PVA-polyethylene glycol copolymers, PVP, or pre-gelatinized starch; disintegrants can be crospovidone, crosscarmellose, or starch glycolate; and lubricant choices include sodium stearyl fumarate and magnesium stearate.

The higher cost of coprocessed excipients can be an issue.

“Each ingredient in these compositions needs to be expertly selected with the end-use in mind,” Assis stresses. Furthermore, the excipient manufacturing process needs to be designed specifically to reduce chemical and physical instabilities.

Continuous tableting processes will benefit the most from the use of all-in-one coprocessed excipients, says Assis. “In order to reduce variability and dosage accuracy issues during the continuous manufacturing process, it is crucial to have a highly stable and controlled feed rate. With an all-in-one coprocessed excipient, rather than five feeders for the API, binder, filler, disintegrant, lubricant, only two are required for the API and the all-in-one coprocessed material, affording a more straightforward process,” he explains.

In addition, because coprocessed excipients reduce blend variability, they can contribute to reduced sampling and analytical errors for continuous processes monitored using inline/on-line/at line sensors, according to Assis. “Process analytical technology is increasingly being used during formulation development as well as in manufacturing. Coprocessed excipients have been shown to be less sensitive to shear, and due to their coprocessed multicomponent nature, the blend has lower intrinsic variability. In effect, this leads to more accurate and robust PAT [process analytical technology] models that do not require extensive model maintenance and updates,” he observes.

**Regulatory hurdles present biggest challenges**

Beyond demonstrating that individual ingredients in coprocessed excipients have not undergone any chemical changes, there are a few other challenges to developing new coprocessed solutions. One, according to Zhang, is that coprocessed excipients have fixed ratios of the various ingredients and as a result they may not be as broadly applicable as simple blends of excipients. “The current solution for this challenge is to design the coprocessed excipient in a way so that it meets the majority of needs,” she says. They are also designed as fit-for-use.

Manufacturing coprocessed excipients that are truly highly functional is not easy either, Muley adds. “A deep understanding of the problem or issue that will be addressed by the coprocessed excipient and proper research and development efforts are both required to ensure that new coprocessed excipients are highly functional and produced using a robust manufacturing process,” he comments.

It is important, for instance, to understand and control the variability of the excipient’s material attributes, according to Dejan Lamešić, head of formulation and process development, Softgel and Oral Technologies with Catalent. “Doing so further supports pharmaceutical users in determining the potential impact of an excipient on a final drug product,” he says.

The higher cost of coprocessed excipients can be an issue as well,

Contin. on page 49
Focusing on the Patient in Drug Development

Felicity Thomas

Putting the patient at the forefront of drug development is essential, particularly to ensure medication compliance is optimized.

A major component in the success of a therapeutic product is whether the patient actually takes the medicine—an aspect that is particularly pressing in patients with chronic and long-term illnesses. It has been well reported that non-adherence to medication regimens is significantly burdensome on healthcare systems and, ultimately, countries’ economies.

One way to improve patient adherence to medication is by ensuring the dosage form is patient-centric or user-friendly. “Patient centricity is gaining more focus and importance in drug development,” confirms Anil Kane, PhD, MBA, senior director, global technical scientific affairs, pharma services, Thermo Fisher Scientific. “Problems related to polypharmacy and patient non-adherence is critical to healthcare. Patient-centric pharmaceutical drug product is increasingly important to gain patient adherence in pediatrics, adults, and geriatric patients.”

Patient-focused thinking

Ideally, a dosage form should incorporate multiple facets to be patient-friendly, notes Anita Solanki, lead—White Papers, Formulation R&D (Pharma and Nutra), ACG Group. “The ideal, patient-friendly, dosage form is one that is easier to swallow, non-invasive, with no taste or odor, has quicker brand recall and is easier to handle and carry, with suitable packaging materials,” she says. “So, throughout the process—right from dosage form selection, through to excipient selection, appearance, packaging, and material selection—every step needs to be considered with the patient in mind.”

Cornell Stamoran, PhD, vice president of Strategy and co-chair of the Catalent Applied Drug Delivery Institute, also agrees that key decisions made during drug development, such as molecule design, formulation, dose form, device selection, and packaging, can have an impact on how successful the therapy will be for patients. Stamoran confirms that through discussions with physicians and payors that were performed at Catalent’s Applied Drug Delivery Institute there is a belief “that those companies that more effectively incorporate patient-focused thinking into drug product design, and provide evidence from the resulting clinical trials, will increasingly have a significant advantage in the market, and ultimately this will benefit patients.”

In terms of dosage form, Thomas B. “Brad” Gold, PhD, vice president, Pharmaceutical Development, Metrics, specifies that oral solid dosage (OSD) forms are preferred by both patients and payers. As such, OSD forms are dominant within drug development and payer schedules. However, despite the fact that OSD forms are preferred there are still issues with compliance, he continues.

“Depending on the formulation and treatment course, orally administering a drug to patients can become problematic and contribute to poor health outcomes,” Gold adds. “Individual dose size, as well as dose frequency all have an impact on the patient centricity of an oral drug. Fortunately, formulation and manufacturing techniques like amorphous solid dispersions, multiple unit particle systems, mini-tablets and other systems are helping to make OSDs more patient centric than ever.”

Kane concurs that OSD forms continue to be market-leading, not least because of the preference by patients, but also due to cost savings and efficiencies afforded by the dosage form in the small molecule market. “Strategies for improving adherence need to consider the characteristics of the individual therapeutic regimens according to the needs of the patients. In particular, geriatric, and pediatric populations have special needs/preferences that should be considered when designing drug products,” Kane continues. “Introducing patient centricity into drug product design offers the opportunity to meet the needs and preferences of patients.”
Providing some examples, Kane explains that through employing taste-masking to create palatable dosage forms will allow for improved patient compliance in geriatric patients with dysphagia, which is a difficulty in swallowing. Other considerations to improve patient centricity of a dosage form for the pediatric segment of the population include the size of the dose, ease of administration, volume of fluid required to be administered, and dosing frequency or frequency of administration, he confirms.

“Innovative ideas and formulation strategies including fixed-dose combinations, modified release dosage forms, orodispersible formulations, multi-particulates, and minitablets in capsules or tablets will support patient-centric drug products,” Kane states.

For Ali Rajabi-Siahboomi, vice president—chief innovation officer, Colorcon, another factor to consider is the potential differentiation between tablets, which is being sought by regulators and marketers. “Unique designs are important because they help make medicines memorable to patients, caregivers, and pharmacists, and may also make a tablet easier to take. From an anti-counterfeiting perspective, unique designs also make products more difficult to copy,” he says. “There are production benefits as well. A unique design offers differentiation on the packaging line, making it easier to visually spot a mix-up and prevent product recalls before it even happens.”

Furthermore, Rajabi-Siahboomi reports that the FDA has also acknowledged the advantages of better design, a fact that is apparent through its guidance documents—“Safety Considerations for Product Design to Minimize Medication Errors and Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules (1,2).” “In essence, too many products and dosages look the same and there’s a risk dispensers may distribute the wrong product, or people taking more than one medicine (increasingly common in our aging population) will get their pills mixed up,” he explains. “Regulators now expect companies to consider aspects such as size, shape, color, and differentiation between dosage strengths before marketing. Similar-looking dosages, especially plain white tablets, may not get through the regulatory process. Your tablet needs to be different.”

Adding to these thoughts, Hans-Christian Mahler, CEO of ten23 health agrees that regulatory focus on patient-centricity will further increase, albeit to ensure the therapeutic product is being used adequately and to understand potential liabilities when products are used incorrectly. “Additionally, connectivity (to e.g., smartphones) and sustainability are in my view key topics in relation to patient-centricity for drug/device combination products,” he says.

In concurrence, Rajabi-Siahboomi also points out that the connection with smartphones or smart medicines can provide a significant opportunity with on-dose authentication technology. “Imagine a patient scanning their pill with a smartphone that not only confirms the identity of the medicine but also connects the patient directly to support materials, such as the product leaflet, information that explains the benefits of the medicine, the importance of adherence, what to do if there are side effects, and even the ability to opt into reminders to take the medicine at the right time,” he states.

Final thoughts
As was specified earlier, poor adherence to a therapeutic regimen not only impacts the effectiveness of a drug but also has a financial impact on healthcare systems, economies, and patients. “Prescription drug medication adherence is a growing concern for public health, and poor adherence to therapy has been associated with poor health outcomes and higher costs for patients,” notes Kane.

Solanki believes that the influence of patient-centricity on the pharma industry will continue to grow and is leading to a big shift in priorities during the development of most dosage forms. “The patient centricity trend is fueling the focus on developing patient-friendly dosage forms. This trend has to be accomplished whilst maintaining optimum therapeutic efficacy and safety,” she says. “Concept transformation has led to the integration of patient-centricity into all aspects of R&D—including formulation design and dosage form development.”

However, there is more work to be done, according to Stamoran. “Through Catalent’s Applied Drug Delivery Institute, we have been advocating for an intentional, patient-focused approach to these areas for the last 10 years. There are important signs of progress, but there remains substantial opportunity to improve patient usability of both new and existing treatments,” he states.

Mahler hopes that patient-centricity and product usability remain priorities for the pharma industry and even that they grow in relevance. “After all, patient-centric drug development all about the patient and to enable them to have an effective and safe treatment,” he concludes.

References
1. FDA, Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, Guidance for Industry, fda.gov (June 2013).
Coming Together to Enable Cell and Gene Therapy Manufacturing

Jennifer Markarian

Precompetitive consortiums seek solutions to industry-wide challenges.

Precompetitive consortiums create a space for both manufacturers and equipment and technology suppliers to find solutions to manufacturing challenges that affect the whole industry. By working together, they seek to create standardized tools—including software, hardware, and analytical methods—and to harmonize the technical language around these tools. One of the desired results is that vendors can then create products that all manufacturers can use, rather than designing bespoke solutions. Another way consortiums boost technology adoption is by bringing together different perspectives to identify industry challenges, broaden and clarify the definition of specific problems, and propose “roadmaps” that companies can then use in their own journeys.

Jennifer Markarian is manufacturing reporter for Pharmaceutical Technology.

Consortiums are especially crucial for emerging therapy areas as [they] move through development.

“[Cell and gene therapies] are incredibly complex by historical biopharma industry standards,” says Tim Charlebois, NIIMBL Senior Fellow. “While we have seen great promise with the early successes, there is still a lot we don’t understand about them—how to make them, how to analyze them, [and] how to ensure they can be produced with a reliability and quality that meet the standards that patients expect and deserve. At the same time, there is great urgency to develop products rapidly, because many of the therapies are intended to address acute unmet medical needs.”

Charlebois explains that one challenge is understanding the relationship of critical quality attributes to fundamental process and analytical technology. Other challenges involve workforce needs and manufacturing capacity, complexity, and cost. “Overall, these challenges are tied to the tremendous novelty and diversity of the candidate technologies and therapeutic approaches being undertaken,” he concludes.
Facilitating technology development

BioPhorum’s Cell and Gene Therapy Phorum, formed in 2018, aims to facilitate development of CGTs and smooth the way to commercialization of CGT products (1). For example, detailed process maps for the manufacture of cell therapies (2) and gene therapies (3) explain the different modalities. A “toolkit” released by BioPhorum in April 2022 (4) defines and describes the complex ecosystems of CGT manufacturing and supplies to “provide a common language and framework for collaboration,” (5) which is important for supply partnerships and, in particular, for developing information technology (IT) systems. BioPhorum says that the models, which map out six common types of CGTs, can be expanded to new modalities as needed. According to BioPhorum, “If IT solutions built today can support multiple therapy modalities, then future therapies can be brought to market more quickly and supported more easily” (6).

Best practices for single-use technologies

The Bio-Process Systems Alliance (BPSA), an industry association that facilitates biopharmaceutical manufacturing using single-use technologies (SUT), has a technical committee dedicated to CGT chaired by Brendan Lucey, who is also Cross Unit director of Marketing Strategy at Entegris.

“Due to the broad nature of our membership, we are able to understand what is going on across the industry and address the pain points that we are seeing globally,” says Lucey. He says that a key advantage of addressing these issues through the BPSA consortium is having input from both the end users (i.e., drug manufacturers) and the SUT suppliers to find solutions that will work for everyone. Having broad solutions, rather than a custom solution that works for just one user, has been crucial to meet production needs during times of tight global supply chains, such as those the industry has been experiencing in the past couple years.

The common goal is to bring solutions—quickly and cost-effectively—to patients.

Increasing the industry’s capacity to make and supply viral vectors has been of high importance, as demand for these starting materials in cell and gene therapy production has outpaced supply. The BPSA CGT Committee has been working on a technical guide for viral vector manufacturing, which is due to be published in June 2022.

“This paper was an 18-month project led by more than a dozen subject matter experts [who have] insights into the challenges and benefits of scalable cell and gene therapy processes,” says Kevin Ott, executive director of BPSA.

The report will discuss how SUT can meet both present and future challenges in viral vector manufacturing. It will address topics including scalability, standardization, change management, system robustness and integrity, and quality. The paper will also show how a completely closed system is designed to keep out any potential contaminants, says Lucey.

The committee has previously published technical guides detailing best practices for SUT in CGT manufacturing (7) and considerations for extractables and leachables (E&L) in CGT development (8).

“Each emerging biotherapeutic class comes with potentially unique process, regulatory, and commercial requirements that must be taken into account,” says Lucey. For example, E&L concerns in CGT differ from the historical concerns of other types of bioprocessing. “[The BPSA report on CGT E&L considerations] helps end users assess their risk and think about regulatory concerns before having that first meeting with regulatory agencies. It enables end users to make smart choices early in the process that reduce any E&L concerns,” he explains.

Advancing innovation in the US and globally

NIIMBL, a public-private partnership funded by the US federal government and consortium members, works to advance biopharmaceutical manufac-

Catalyzing new technologies

Alongside the precompetitive consortiums finding solutions to industry-wide problems are organizations that bring together academic researchers, investors, and infrastructure to demonstrate technologies or provide resources to start-up companies.

The United Kingdom’s Cell and Gene Therapy Catapult (CGT Catapult) collaborates with companies at its Manufacturing Innovation Centre located in Stevenage, United Kingdom. For example, in March 2022, the CGT Catapult, contract manufacturing organization Symbiosis, and clinical-stage biotechnology company Freeline Therapeutics together completed a project to demonstrate a lean manufacturing method for the sterile filling of Freeline’s viral vector (1).

“This reduction in the time taken between consecutive stages in the UK’s [advanced therapy medicinal products] drug development manufacturing supply chain not only exceeds the project’s original target to reduce the timeline by over 25%, but underlines how progressive collaborative strategic approaches can create opportunities for our shared clients to add value to their pharmaceutical assets by accelerating their development through clinical trial and, ultimately, bring life-changing therapies to patients more quickly,” said Symbiosis CEO Colin MacKay, in the press release (1).

Reference

turing in the US through activities such as developing standards and workforce training. In the CGT area, NIIMBL is focusing on viral vector manufacturing and analytics.

“Limited availability of viral vectors, such as adeno-associated virus (AAV) and lentivirus, represent a major bottleneck, which is constraining the growth and successful development of both gene and cell therapies,” says Charlebois. “Enormous investments in facilities, equipment, technology, and staff have recently been undertaken, but there is a long way to go to meet the overall needs of the cell and gene therapy community. We are bringing together thought leaders and technical experts across industry to develop a program of collaborative, precompetitive work that can both advance and improve access to the critical process and analytical technologies in this space. We are also developing and supporting workforce programs to help address the rapidly growing need for expertise in technical development, manufacturing, quality, and regulatory disciplines for viral vector manufacturing.”

In one project, the United States Pharmacopeia and the US Department of Commerce’s National Institute of Standards and Technology are performing an interlaboratory study to measure critical quality attributes for AAV products, which can be used to deliver gene therapies, and NIIMBL is providing the collaborative platform (9).

In a project funded through the American Rescue Plan (10), Caring Cross is working with NIIMBL to develop open-source platform technologies and materials for AAV and lentivirus. “The intent is to make these broadly available for research purposes and enhance the ability of investigators and smaller, less-well funded entities to pursue therapies dependent on viral vectors,” explains Charlebois.

NIIMBL is also partnering with the international advocacy group Alliance for Regenerative Medicine (ARM). NIIMBL and ARM’s Project A-Gene is a case study-based approach to integrating quality-by-design (QbD) principles in gene therapy chemistry, manufacturing, and controls programs (11). The project brought together more than 50 industry experts from 20 therapeutic developers, as well as experts from FDA and the Standards Coordinating Body for Gene, Cell, and Regenerative Medicines and Cell-Based Drug Discovery to identify best practices for the manufacture of a viral vector for use in gene therapy. The results of the four-year project were shared in a report (12) and in a webinar series that will culminate with a workshop in June 2022. The project leaders hope that the study will help developers overcome barriers to moving from clinical trials to commercial production, similarly to how a 2009 case study on applying QbD to monoclonal antibody production lowered barriers in that area (11).

Having broad solutions, rather than a custom solution that works for just one user, has been crucial to meet production needs during times of tight global supply chains.

“The case study represents current thinking around best practices in advancing small-batch clinical trial manufacturing to commercial-scale production,” explains Gene Schaefer, NIIMBL Senior Fellow. “The output document is a valuable reference for both organizations that participated as well as other organizations working in this area. [The document] is not meant to be prescriptive, but rather a starting point for discussions and decisions within an organization about the best approach that aligns with an organization’s capabilities and priorities.”

Later in 2022, ARM and NIIMBL will be releasing project A-Cell, which takes a similar approach of applying QbD principles to the manufacture of a cell-based therapy.

Benefits of consortia

Companies should get involved in consortia that are relevant to them, both to benefit themselves and the industry as a whole. “Progress is being made to advance the field, and that progress benefits from as broad a cross-section of stakeholders being engaged as possible,” concludes Yochim. “Organizations that actively engage in meetings, on project teams, in the governance of the institute, and in other ways generally have very deep and lasting interactions that provide technical and workforce-related benefits back to the member.”

References

Considerations for Cleaning Lipid Nanoparticles

Dijana Hadziselimovic, Si Myra Tyson, and Paul Lopolito

This article explores the concerns with cleaning pharmaceutical products utilizing LNP delivery vehicles and provides a general cleaning recommendation based on laboratory and field testing.

In the past several decades, advances have been made in the drug delivery vehicle for hydrophilic and lipophilic pharmaceutical actives (1). Drug delivery vehicles progressed from basic liposomes and emulsions to lipid nanoparticles (LNPs) and more advanced nanostructured lipid carriers (NLCs), which improved the therapeutic effect, reduced degradation, improved stability, controlled dosing, and minimized adverse toxicological effects of the target active (2,3). The particle size of these encapsulated LNPs and NLCs can range from 50–1000 nm and incorporate components such as lipids, surfactants, emulsifiers, co-surfactants, charge modifiers, preservatives, cryoprotectants, and others (Table I and Figure 1) (4).

Depending on the components and manufacturing process, the drug active may be within the core, lipid bilayers, surface, or combined locations (5). LNPs and NLCs delivery vehicles have been used for oral, pulmonary, nasal, topical, ocular, intravenous, and intramuscular drugs. Most recently, these LNPs and NLCs have been used in a wide range of vaccines, including hepatitis A, influenza, shingles, and the COVID-19 messenger RNA (mRNA) vaccines by Moderna/National Institute of Allergy and Infectious Disease (NIAID) and Pfizer/BioNTech (3).

The poor solubility and complexity of the LNPs with the active ingredient create cleaning challenges when cleaning with water, sodium hydroxide in water, or alcohol (Table II). Solubility of the LNP is improved with alcohol; however, this creates flammability, storage, handling, and disposal concerns. The investigation and design of a cleaning process using laboratory coupon studies incorporating the drug components, LNP or NLC delivery vehicle, manufacturing process conditions, and surface material align with testing a process’s life cycle design phase. Critical parameters to investigate may include different components, process conditions, surface materials, cleaning agent, temperature, time, mechanical action, water quality, and rinse parameters. The overall goal of a cleaning study is to design a repeatable cleaning procedure and maintain process equipment.

This article explores the use of laboratory studies to recommend a cleaning process for COVID-19 mRNA vaccines. It provides a technique to easily design the cleaning process for other LNP and NLC delivery vehicles. The article also includes lab study results and a case study for cleaning LNPs currently used for the COVID-19 mRNA vaccine.

Materials and methods
Developing a cleaning procedure for LNPs is the first step in a validation process to minimize or eliminate product contamination and ensure product reproducibility. The nature of the sample, processing time and temperature, dirty-hold-time (DHT), water quality, available temperature range, cleaning method capability, and preferred detergent of use are considered during the cleaning study (6). Studies are performed at a lab-scale using 304 stainless-steel coupons with a 2B finish to duplicate a large 316-L stainless-steel vessel used in production. The final product or components of the final blend are coated onto the surface and air-dried at ambient temperature for 24–72 hours, depending on the individual DHT requirement (Figure 2). At the end of the DHT, the coated cou-
pon is placed in a prepared cleaning solution at the minimal temperature available using agitated immersion. Once the cleaning parameters are determined by agitated immersion, the same cleaning parameters are tested using spray wash, cascading flow, or manual scrub/wipe followed by rinse water. The cleaning parameters were evaluated by visual cleanliness, a gravimetric weight check of the pre-cleaned and post-cleaned stainless-steel surface, and a water break-free test.

In review of the manufacturing process, the cleaning and compatibility of various substrates should be considered and possibly evaluated when designing a cleaning procedure. In one example, platinum-cured silicon was tested for substrate compatibility (Table III). At a minimum, this process requires the substrate to be exposed to the recommended detergent at a specific concentration for a designated period. If no significant changes are observed to the substrate, it is usually considered compatible.

**Results**

Based on the processing conditions and DHT, the cleaning recommendations ranged from a solution of 1–5% v/v formulated alkaline detergent at 45 °C–80 °C for a contact cleaning time of 15–45 minutes per agitated cleaning, spray wash cleaning, and cascading flow cleaning. These test conditions were successful as reported in Table IV, based on visually clean, water-break free, and gravimetric analysis (6). In comparison, a solution of 1N sodium hydroxide (NaOH) at 60 °C, cleaned for 60 minutes, was not effective in completely removing the LNP residue.

**Case study**

Progress in mRNA technologies and LNP-based delivery systems has allowed the development of mRNA COVID-19 vaccines at unprecedented speed, demonstrating the clinical potential of LNP–mRNA formulations and providing a powerful tool against the coronavirus pandemic (1). Along with the mRNA vaccine development, the goal was to develop optimum cleaning parameters, so production was safe and reproducible.

A large pharmaceutical company that developed a mRNA vaccine sent their new product to the laboratory for
testing. All coupons were coated and baked at 35 °C for two and 16 hours to simulate manufacturing DHT conditions. Cleaning parameters (time, temperature, action, and concentration) were identified through testing by agitated immersion. A 1% volume-by-volume (v/v) cleaning solution of potassium hydroxide formulated detergent at 45 °C for 15 minutes was able to clean the residue. Results were confirmed by spray wash, cascading flow, and manual cleaning. Sodium hydroxide, however, was unable to achieve acceptable results.

After the successful cleaning trial with potassium hydroxide formulated detergent, the entire manufacturing area, including filling and packaging lines, adopted the same cleaning regimen.

**Conclusion**

Modifying the delivery vehicle of hydrophilic or lipophilic drugs from basic liposomes to complex LNPs and NLCs has improved these drugs’ therapeutic effect, stability, and toxicological profile.

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**Table II. Lipid nanoparticle components, examples, and solubility in water.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Lipids</th>
<th>Surfactants/ co-surfactants</th>
<th>Surfactants/ emulsifiers</th>
<th>Charge modifiers</th>
<th>Preservative</th>
<th>Cryoprotectant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
<td>Cholesterol, Steric acid, Caprylic triglyceride, Cetyl palmitate, Glycerol stearate, Glycerol trilaurate, Glycerol tripalmitate</td>
<td>Sodium dodecyl sulphate, Tyloxapol, Sodium oleate, Taurocholate sodium salt, Sodium glycocholate, Butanol</td>
<td>Phosphatidyl choline, Soy lecithin, Egg lecithin, Poloxamine, Polysorbate 80</td>
<td>Dipalmitoyl phosphatidyl choline, Stearylamine, Dimyristoyl phosphatidyl glycerol Polyethylene glycol (PEG)</td>
<td>Thimerosal</td>
<td>Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinylpyrrolidone (PVP), Polyvinyl alcohol (PVA)</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Insoluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Practically insoluble</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
</tbody>
</table>

**Figure 2.** L–R: (a) Lipid mixture, (b) messenger RNA (mRNA)–encapsulated lipid nanoparticles in ethanol/citrate buffer, (c) mRNA encapsulated lipid nanoparticles in 10% trehalose, and (d) clean coupon. All residues (a–c) were applied to 304 stainless-steel surfaces and baked at 50 °C for 48 hours to simulate the process condition, followed by dirty hold time (DHT) conditioning at 30 °C for 48 hours. This residue was slightly corrosive to 304 stainless-steel coupons with the development of a small micro-pit on the surface. The process should be repeated with passivated 316-L stainless steel coupons to simulate the effect on production equipment. Early warning signs of corrosivity of process conditions within cleaning studies can be investigated using a predictive model to define a preventative maintenance plan or justify the inclusion of routine maintenance steps with a formulated acid detergent (8). Stainless-steel maintenance studies performed early in the cleaning design phase can greatly reduce unscheduled maintenance events and investigations.
Water-insoluble lipids, practically insoluble charge modifiers, and hydrophilic or lipophilic active ingredients create difficulties with water or caustic (hydroxide in water) cleaning processes. Using flammable solvents, such as ethanol and isopropyl alcohol, improves lipids’ solubility and creates storage, handling, and disposal hazards, due to the volatile carbon emissions and flammability. Early investigations into the cleaning process of LNP delivery vehicles with small molecule drugs, and recently with mRNA vaccines, have demonstrated that a formulated alkaline cleaning agent can successfully clean both the active ingredient and the LNP or NLC delivery vehicle to an acceptable limit.

Table III. Compatibility of platinum-cured silicone in water for injection (WFI) in comparison to formulated alkaline detergent after 24 hours of submersion at 70 °C. The temperature was maintained throughout the testing cycle.

<table>
<thead>
<tr>
<th>Test conditions</th>
<th>Concentration</th>
<th>Pre-visual observation</th>
<th>Hardness (Type A, N/mm²)</th>
<th>Post-visual observation</th>
<th>Hardness (Type A, N/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient temperature (untreated control)</td>
<td>N/A*</td>
<td>Opaque no visible damage</td>
<td>65</td>
<td>No visible change compared to control</td>
<td>65</td>
</tr>
<tr>
<td>WFI</td>
<td>N/A</td>
<td>Opaque no visible damage</td>
<td>67</td>
<td>No visible change compared to control</td>
<td>66</td>
</tr>
<tr>
<td>WFI</td>
<td>N/A</td>
<td>Opaque no visible damage</td>
<td>68</td>
<td>No visible change compared to control</td>
<td>66</td>
</tr>
<tr>
<td>Formulated alkaline detergent</td>
<td>1% v/v</td>
<td>Opaque no visible damage</td>
<td>66</td>
<td>No visible change compared to control</td>
<td>66</td>
</tr>
<tr>
<td>Formulated alkaline detergent</td>
<td>1% v/v</td>
<td>Opaque no visible damage</td>
<td>68</td>
<td>No visible change compared to control</td>
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<tr>
<td>Formulated alkaline detergent</td>
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<td>No visible change compared to control</td>
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</tr>
<tr>
<td>Formulated acid detergent</td>
<td>1% v/v</td>
<td>Opaque no visible damage</td>
<td>70</td>
<td>No visible change compared to control</td>
<td>68</td>
</tr>
<tr>
<td>Formulated acid detergent</td>
<td>1% v/v</td>
<td>Opaque no visible damage</td>
<td>68</td>
<td>No visible change compared to control</td>
<td>66</td>
</tr>
</tbody>
</table>

(*) N/A = not applicable

Table IV. Dirty hold time (DHT) and cleaning parameters for cleaning lipid nanoparticles (LNPs). NaOH is sodium hydroxide.

<table>
<thead>
<tr>
<th>DHT (hours)</th>
<th>Cleaning method (*)</th>
<th>Cleaning solution</th>
<th>Concentration</th>
<th>Temperature (°C)</th>
<th>Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Agitated immersion</td>
<td>1N NaOH</td>
<td>1N</td>
<td>60</td>
<td>Slight residue after 60</td>
</tr>
<tr>
<td>24</td>
<td>Agitated immersion</td>
<td>Formulated alkaline detergent</td>
<td>3% v/v</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>Spray wash</td>
<td>Formulated alkaline detergent</td>
<td>3% v/v</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>24</td>
<td>Cascading flow</td>
<td>Formulated alkaline detergent</td>
<td>3% v/v</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>48</td>
<td>Agitated immersion</td>
<td>Formulated alkaline detergent</td>
<td>5% v/v</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>Agitated immersion</td>
<td>Formulated alkaline detergent</td>
<td>5% v/v</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>48</td>
<td>Agitated immersion</td>
<td>Formulated alkaline detergent</td>
<td>1% v/v</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>Spray wash</td>
<td>Formulated alkaline detergent</td>
<td>1% v/v</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>48</td>
<td>Cascading flow</td>
<td>Formulated alkaline detergent</td>
<td>1% v/v</td>
<td>80</td>
<td>30</td>
</tr>
</tbody>
</table>

(*) Agitated immersion—a coated coupon was immersed in a beaker filled with the cleaning solution and the solution was agitated at a fixed speed using a magnetic stirrer. Spray wash—a coated coupon was positioned vertically so that the spray hits the coated area of the coupon. Cascading flow—a coated coupon was positioned vertically so that the wash or rinse solution cascades evenly down the coated area of the coupon. The spray wash and cascading flow cleaning parameters were programmed into the microprocessor, and the cycle was started.

Water-insoluble lipids, practically insoluble charge modifiers, and hydrophilic or lipophilic active ingredients create difficulties with water or caustic (hydroxide in water) cleaning processes. Using flammable solvents, such as ethanol and isopropyl alcohol, improves lipids’ solubility and creates storage, handling, and disposal hazards, due to the volatile carbon emissions and flammability. Early investigations into the cleaning process of LNP delivery vehicles with small molecule drugs, and recently with mRNA vaccines, have demonstrated that a formulated alkaline cleaning agent can successfully clean both the active ingredient and the LNP or NLC delivery vehicle to an acceptable limit.

References
Topical drug products are widely used in treating a variety of human skin diseases; however, the development of topical generics lags far behind other pharmaceutical product categories (1). One key issue is the lack of standardization in bioequivalence (BE) studies and statistical data analysis, unlike in the development of generic oral drugs. The in-vitro permeation test (IVPT) is most widely used to evaluate the cutaneous pharmacokinetic (CPK) parameters (i.e., the rate and extent of drug permeation through the skin). This in-vitro approach has been proven to be appropriate for the demonstration of bioequivalence of locally-acting topical drug products (2), thus facilitating the regulatory approval of affordable generic versions for patients. FDA and the European Medicines Agency both recognize IVPT as a regulatory approach to determine BE of many generic topical drugs (3–4). A vertical diffusion cell system (also known as a static diffusion system) and a flow-through cell system are typical apparatuses used to perform an IVPT study. During an IVPT study, the product tested is dosed uniformly on the topical surface of a skin section mounted on a diffusion cell, with the opposite skin surface placed in contact with the isotonic receptor solution. The test (T) and reference (R) products are tested in parallel. By analyzing the drug concentrations in receptor solutions collected at different sampling time points during the study, the permeation rate profile (flux versus time) and cumulative amount profile (cumulative amount permeated versus time) can be plotted.

The maximum flux (Jmax) at the peak of the flux profile should be compared for the test and reference products. This is analogous to the comparison of the Cmax for T and R products in the case of plasma pharmacokinetics. Similarly, the total cumulative amount of drug permeated (denoted as AMT) across the entire study duration should be compared for the T and R products. This is analogous to the area under the curve (AUC) of plasma pharmacokinetics.

The statistical approach introduced in FDA’s Draft Guidance on Acyclovir, which is modified from the BE statistics for plasma pharmacokinetics (5), as well as FDA’s Draft Guidance on Progesterone are being most widely adopted for BE evaluation for topical drugs (6). Statistical analysis software (SAS)
codes for progesterone plasma BE analysis cannot be directly used for the IVPT study, and necessary modifications should be made. There is so far no article introducing the step-by-step BE analysis of CPK data (I_{\text{max}} and AMT data), not to mention any conventional approach that can easily be implemented without professional statisticians or software.

The present work introduces IVPT-Stat, an MS Excel file, to perform the BE analysis of IVPT data as per FDA recommended statistics for acyclovir cream. IVPT-Stat utilizes a set of user-defined formulas and macro codes as well as some MS Excel functions to complete the statistical analysis. It can help industry practitioners analyze BE data of topical generic versus reference drugs or BE data of products before and after formulation/process changes.

IVPT experiment steps

Data collecting. The determined values of drug concentrations were used to calculate, as per Equation 1, the cumulative amounts of drug permeated at all the time points. The Flux during a time interval between two contiguous time points was calculated as per Equation 2. For a skin section, the maximum one among all flux values of time intervals is defined as the I_{\text{max}}. Another cutaneous pharmacokinetic parameter, AMT, is defined as the total cumulative amount permeated by the last time point.

\[
Q_n = \frac{C_n V_c + V_s \sum_{i=1}^{n} C_{i-1}}{A}
\]

[Eq. 1]

where \( Q_n \) is the cumulative amount permeated by the \( n^{\text{th}} \) sampling time point (\( \mu g/cm^2 \)); \( C_n \) is the drug concentration in the receptor solution at \( n^{\text{th}} \) sampling time point (\( \mu g/mL \)); \( V_s \) is the volume of receptor solution in a diffusion cell (mL); \( V_r \) is the volume of aliquot sampled at each sampling time point (mL); and \( A \) is the area of diffusion (cm\(^2\)).

\[
\text{Flux}_n = \frac{Q_n - Q_{n-1}}{T_n - T_{n-1}}
\]

[Eq. 2]

where \( \text{Flux}_n \) is the drug permeation rate during a time interval between the \( n^{\text{th}} \) and \((n-1)^{\text{th}}\) sampling time points (\( \mu g/cm^2/h \)); \( Q_n \) is the cumulative amount permeated by the \( n^{\text{th}} \) sampling time point (\( \mu g/cm^2 \)); and \( T_n \) is the time of the \( n^{\text{th}} \) sampling (hour).

Data natural log transformation

The values of natural log-transformed \( I_{\text{max}} \) and AMT are used for BE statistical analysis.

Dataset. Figure 1 illustrates the layout of balanced and unbalanced datasets. It is recommended that a balanced design be used, which has the same number of skin-section replicates per donor per treatment group (T or R), as this design/dataset will give a higher statistic power. To keep a design/dataset balanced, skin sections (diffusion cells) that are discontinued due to documented deviations from the study, based upon criteria specified in the study protocol, may be discontinued.
replaced with new skin sections from the same donor, and the data recollected. In certain situations, discontinued skin sections could not be replaced, leading to some replicate values being dropped, but not uniformly per donor per treatment, which then resulted in an unbalanced dataset.

For a balanced dataset, each of the $n$ donors has $r$ replicates in the test product group and $r$ replicates in the reference group, where $r$ is ≥ 4, as required by FDA; each group has $r \times n$ $J_{\text{max}}$ (or AMT) values. For an unbalanced dataset, within any donor, the two product groups may have different numbers of replicates with one another; the numbers of replicates across all donors may also be different; the test and reference product groups have $r^t_1 + r^t_2 + \ldots + r^t_n$ and $r^R_1 + r^R_2 + \ldots + r^R_n$ replicates, respectively.

When any value of $J_{\text{max}}$ or AMT happens to be 0, it could be replaced with half the lower limit of quantification value of the analytical method for receptor solution. This is to ensure the successful natural log transformation from a statistical perspective, respecting an α level.

**FDA statistics**

**Calculation of $S_{WR}$**

FDA statistics have a mixed criterion for BE analysis, which uses $S_{WR}$, the within-donor standard deviation of data of the reference product group, as a cutoff point. The value of $S_{WR}$ can be calculated as per Equation 3: As shown in Figure 2 and Table I, when $S_{WR}$ is ≤ 0.294, average bioequivalence (ABE) criteria should be used; when $S_{WR}$ is > 0.294, a modified scaled average bioequivalence (SABE) criteria should be used. The detailed criteria for ABE and SABE are listed in Table I.

\[
S_{WR} = \sqrt{\frac{\sum_{i=1}^{n} \sum_{j=1}^{r} (R_{ij} - R_{ij}^*)^2}{r \cdot n - \bar{x}^2}} \tag{3}
\]

where $R_i = \text{the CPK value of the } i^{th} \text{ one of the } r^i \text{ replicates of the } j^{th} \text{ donor in the reference product group; } \pi^* = \frac{1}{r^i} \sum_{j=1}^{r^i} R_{ij}, \text{ the average of all the } r^i \text{ replicates' CPK values of the } j^{th} \text{ donor in the reference product group; } r = r^t_1 + r^t_2 + \ldots + r^t_n \text{ is the total number of replicates in the reference product group; } n = \text{the number of donors; } i = \text{the } j^{th} \text{ one of the } r^i \text{ replicates of the } j^{th} \text{ donor in the reference product group; } j = \text{the } j^{th} \text{ one of the } n \text{ donors in the reference product group.}

When $S_{WR}$ ≤ 0.294 (ABE). When $S_{WR}$ ≤ 0.294, the T and R products can be declared bioequivalent if the inverse natural log-transformed values of the means of the two one-sided 100(1−2α)% confidence interval (CI) (90% CI when α = 0.05) for point estimate $\mu_T - \mu_R$, $\bar{T} \pm t_{1−α, df} \times SE(\bar{T})$ (see Equation 4), are within [0.80, 1.25].

\[
\bar{T} \pm t_{1−α, df} \times SE(\bar{T}) \tag{4}
\]

where $\bar{T} = \mu_T - \mu_R$ and $\mu_T$ and $\mu_R$ are the population means of the natural log-transformed CPK values of the T and R product groups, respectively; $SE(\bar{T})$ is the standard error of $\mu_T - \mu_R$; $t_{1−α, df} = (1-2α) × 100^{th}$ percentile of the student’s t distribution with df degrees of freedom, where α = 0.05 (regulatory level).

Although FDA’s guidance for acyclovir cream gives a simple arithmetic formula of $\bar{T} \pm t_{1−α, df} \times SE(\bar{T})$ using inter-donor variability $S^2_d$ to calculate the confidence interval (5), it is not applicable to an unbalanced dataset. A better approach to calculating the $\bar{T}$, $df$, and $SE(\bar{T})$ for both balanced and unbalanced datasets is to run a multiple linear regression with the CPK ($J_{\text{max}}$ or AMT) values as the dependent response, while the donor code and treatment code are run as independent factors (as demonstrated in a later section of this paper). This multiple linear regression generates the values of lower and upper bounds of 90% CI of point estimate, as can be performed by the below SAS codes (7–8):

```
proc mixed data=IVPT.data;
class DONOR TRT;
model J_max = DONOR TRT/; estimate ’ln(J_max) Test-Ref’ TRT -1 1/ cl alpha=0.1; run;
```
When \( S_{WR} > 0.294 \) (SABE). When \( S_{WR} > 0.294 \), the test and reference products can be declared bioequivalent if the below two criteria are both met:

- The inverse natural log-transformed value of \( \mu_T - \mu_R \) is within [0.80, 1.25]
- The critical bound, the upper bound of \((1 - \alpha) \times 100\%\) (95%) when \( \alpha = 0.05 \) CI for \( \left( \mu_T - \mu_R \right)^2 - \theta \times S^2_{WR}, \) is \( \leq 0, \) where \( \theta = \frac{(\ln(n_m))^2}{(\ln(n_0))^2} \), with \( n_m \) being the regulatory BE limit 1.25; and \( S^2_{WR} \) is the square of \( S_{WR} \).

The critical bound can be calculated by Equation 5 (6):

\[
\text{critbound} = (x + y) + \sqrt{\text{boundx} - x} + (\text{boundy} - y)^2
\]

[Eq. 5]

and the variables in Equation 5 can be calculated as shown in Table II.

### IVPT-Stat

**Calculation mechanism.** IVPT-Stat, a user-friendly MS Excel-based tool utilizing the above mathematics, has been developed to analyze IVPT data. It consists of an MS Excel file containing two worksheets: data & analysis and supporting layout.

The data & analysis sheet has several cell blocks with a yellow background color where the users can enter the raw CPK data (i.e., \( I_{\max} \) (µg/cm²/h) or AMT (µg/cm²) values). The natural log-transformed values of these raw CPK data can be calculated automatically and shown in the nearby cells. Clicking the button titled “click to run IVPT-Stat” will run a custom-defined program, which rearranges this natural log-transformed dataset into a matrix (filled with binary codes 1 and 0) that is suitable for MS Excel’s multiple linear regression function LINEST(), as shown in the supporting layout sheet. The function LINEST() in cells B1 and B2 of the supporting layout sheet uses CPK data in column E as the dependent parameter while donor and treatment codes in columns F and thereafter are treated as independent parameters; cells B1 and B2 return the results of the point estimate and StdErr, respectively. The cells from C4-C26 in the data & analysis sheet then calculate \( S_{WR} \) and other variables (as can be seen in the formula of such cells) and makes a final BE conclusion of either “BE” or “Not BE”.

**User manual.** A user can complete the BE analysis by sequentially implementing the below steps in the data & analysis sheet:

- Enter the raw CPK data into the yellow-background cells
- Click the button titled “click to run IVPT-Stat”
- Read the \( S_{WR} \) value in cell B1
- Read the lower and upper CI in cells C4 and C5 (in case \( S_{WR} \leq 0.294 \)), or read the critical bound and inverse natural log-transformed point estimate in cells C14 and C15 (in case \( S_{WR} > 0.294 \))

**Example 1**

**Experimental data.** Example 1 demonstrates how IVPT-Stat performs BE analysis of IVPT data (a balanced dataset). The IVPT experiment used 60 skin sections dermatomed from six donors (10 replicates per donor). The skin sections were uniformly assigned to the T product group and the R product group (five replicates per donor per product group). During the experiment duration, each skin section (diffusion cell) generated a series of flux values and Q (permeation amount) values at different time points (as illustrated in Table III), of which the maximum flux value is the \( I_{\max} \) of this skin section while the Q value at the last time point is the AMT of this skin section (as illustrated in Figure 3). Table IV lists all the 30 \( I_{\max} \) values of the T product group and 30 \( I_{\max} \) values of the R product group.

| **Table II. The mathematic formula and Microsoft Excel formula for calculation of the critical bound.** |
|-------------------|-------------------|
| **Mathematic formula** | **Excel formula** |
| critical bound = \((x + y) + (\sqrt{\text{boundx} - x}) + (\sqrt{\text{boundy} - y})^2\) | critical bound = \((x + y) + \text{SQRT(} |\text{boundx} - x|\times |\text{boundy} - y|\times 2\times \text{boundx} - x\times \text{boundy} - y)^2\) |
| \( x = \text{point estimate}^2 - \text{StdErr}^2 \) | \( \text{point estimate}^2 - \text{StdErr}^2 \) |
| \( y = -\theta \times \text{n_m} \) | \( \text{n_m} \times \text{PSWR}^2 \) |
| \( \text{boundx} = (\text{max}(\text{LowerCL}, \text{UperCL}))^2 \) | \( \text{boundx} = (\text{max}(\text{LowerCL}, \text{UpperCL}))^2 \) |
| \( \text{boundy} = \frac{y \times dfb}{\text{CHISQ.INV}(1 - \alpha, dfb)} \) | \( \text{boundy} = \frac{y \times dfb}{\text{CHISQ.INV}(1 - \alpha, dfb)} \) |
| \( \text{dfb} = n_m - n \) | \( \text{dfb} = n_m - n \) |
| \( \theta = \text{ln(MLT)}^2 \) | \( \theta = \text{ln(MLT)}^2 \) |

**LowerCL = point estimate - \( t_{\alpha/2, n_m - n} \times \text{StdErr} \) | **UpperCL = point estimate + \( t_{\alpha/2, n_m - n} \times \text{StdErr} \) |

- \( \alpha = 0.05 \)
- \( LMT = 1.25 \), the regulatory BE limit
- \( n_m \) = the number of donors
- \( m_T = \) the total number of replicates in the test product group
- \( m_R = \) the total number of replicates in the reference product group
- \( S^2_{WR} = \) the squared value of \( S_{WR} \)

The values of below three variables can be obtained from the multiple linear regression output table:

- **point estimate = \( I_{\max} - \mu_T - \mu_R \), where \( \mu_T \) and \( \mu_R \) are the population means of the test and reference products, respectively**
- **StdErr = SE_\text{R}, the standard error of point estimate**

**Calculation of \( S_{WR} \):** Once the raw data have been entered into the yellow cells of the data & analysis sheet, the natural log-transformed values will be immediately displayed in the nearby cells and are used for statistical analysis. Using the data of the R product group in the data & analysis sheet, \( S_{WR} \) is calculated according to Equation 3. The calculated \( S_{WR} \), as shown in cell B1, is rounded to 0.156, which is \( \leq 0.294 \); consequently, ABE should be used for analysis.

**BE summary.** After clicking the button titled “click to run IVPT-Stat” in the data & analysis sheet, the supporting layout sheet lists all the natural log-transformed CPK data in column E, as sorted by “donor” code and “T or R” code in columns C and D, respectively (shown in Figure 4). The other six columns F–K show the matrix of the donor and treatment codes (1 or
Table II. The exemplary series of flux and Q values of a skin section. **Author: what does AMT bio-equivalence. SABE is scaled average bio-equivalence. CI is confidence interval.**

![Figure 3. The J_max (maximum flux) and AMT (total cumulative amount at last time point) of a skin section (diffusion cell) identified from the flux and cumulative amount profiles, respectively.](image)

![Figure 4. The matrix of J_max (maximum flux) data with "Donor" code and "T/R" (T is test product while R is reference product) code.](image)

Table III. The exemplary series of flux and Q values of a skin section.

<table>
<thead>
<tr>
<th>T_n (h)</th>
<th>initial</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q_n (µg/cm²)</td>
<td>0</td>
<td>0.2</td>
<td>0.8</td>
<td>12.8</td>
<td>48.8</td>
<td>96.8</td>
<td>150.8</td>
<td>202.8</td>
<td>246.8</td>
<td>280.8</td>
<td>304.8</td>
<td>322.8</td>
<td>333.6</td>
</tr>
<tr>
<td>Q_n – Q_{n-1} (µg/cm²)</td>
<td>0</td>
<td>0.2</td>
<td>0.6</td>
<td>12</td>
<td>36</td>
<td>48</td>
<td>54</td>
<td>52</td>
<td>44</td>
<td>34</td>
<td>24</td>
<td>18</td>
<td>10.8</td>
</tr>
<tr>
<td>T_n – T_{n-1} (h)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flux_n (µg/cm²/h)</td>
<td>0</td>
<td>0.1</td>
<td>0.3</td>
<td>3</td>
<td>9</td>
<td>12</td>
<td>13</td>
<td>5</td>
<td>13</td>
<td>11</td>
<td>8.5</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 1, 2, 3, …12; n – 1=0 means the initial zero point.

As summarized in Table V, the 90% CI bounds of J_{max} are 0.90 and 1.04, respectively, which are within the regulatory BE limit [0.80, 1.25]. In the same way, the AMT data are also analyzed (raw data not shown). Only when both J_{max} and AMT CIs are within [0.80, 1.25], the T and R products can be declared bioequivalent. For this example, both J_{max} and AMT CIs are within [0.80, 1.25], so the T and R products are bioequivalent.

Example 2

**Experimental data.** An unbalanced dataset, shown in Table VI, is used as an example. This highly variable dataset includes some extreme values.

**Calculation of S_{WS}.** The S_{WS} was calculated, as described in the example 1 section, to be 0.426, which is larger than 0.294, therefore SABE should be used.

**BE summary.** For SABE, the point estimate and the lower and upper bounds of J_{max} were calculated in the same way with ABE (as shown in the example 1 section). The other BE parameters were calculated by formulas in cells C16–C26 of the data & analysis sheet.
Table IV. The raw data and natural log-transformed values of the 30 $J_{\text{max}}$ values of the test (T) and 30 $J_{\text{max}}$ values of the reference (R) product groups across the six donors.

<table>
<thead>
<tr>
<th>Data type</th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Donor 4</th>
<th>Donor 5</th>
<th>Donor 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>J_{\text{max}} values (µg/cm²/h)</td>
<td>T</td>
<td>R</td>
<td>T</td>
<td>R</td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Raw data</td>
<td>10.5</td>
<td>12.75</td>
<td>9</td>
<td>10.5</td>
<td>11.7</td>
<td>13.05</td>
</tr>
<tr>
<td>Natural log-transformed data</td>
<td>2.351</td>
<td>2.546</td>
<td>2.197</td>
<td>2.351</td>
<td>2.460</td>
<td>2.569</td>
</tr>
</tbody>
</table>

Table V. The bioequivalence (BE) comparison of test and reference products. IVPT is *in-vitro* permeation test. PK is pharmacokinetic. ABE is average bio-equivalence. SABE is scaled average bio-equivalence. CI is confidence interval.

<table>
<thead>
<tr>
<th>IVPT PK endpoint</th>
<th>BE Criteria</th>
<th>Maximum Flux $J_{\text{max}}$</th>
<th>Total amount permeated (AMT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_{\text{inf}}$</td>
<td>--</td>
<td>0.156</td>
<td>0.109</td>
</tr>
<tr>
<td>ABE</td>
<td>90% CI [0.8, 1.25]</td>
<td>0.90 - 1.04</td>
<td>0.92 - 1.10</td>
</tr>
<tr>
<td>SABE</td>
<td>Point estimate [0.8, 1.25]</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>95% upper confidence bound [≤ 0]</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Passing BE criteria</td>
<td>--</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Both $J_{\text{max}}$ and AMT passing BE criteria</td>
<td>Bioequivalent</td>
<td></td>
</tr>
</tbody>
</table>

Table VI. The 42 $J_{\text{max}}$ raw data (20 test [T] data and 22 reference [R] data) and natural log-transformed values for the test and reference groups across all five donors.

<table>
<thead>
<tr>
<th>Data type</th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Donor 4</th>
<th>Donor 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>J_{\text{max}} values (µg/cm²/h)</td>
<td>T</td>
<td>R</td>
<td>T</td>
<td>R</td>
<td>T</td>
</tr>
<tr>
<td>Raw data</td>
<td>10.5</td>
<td>12.75</td>
<td>9</td>
<td>10.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Natural log-transformed data</td>
<td>2.351</td>
<td>2.546</td>
<td>2.197</td>
<td>2.351</td>
<td>2.460</td>
</tr>
</tbody>
</table>

The analysis sheet according to the mathematics described in the section “When $S_{\text{inf}} > 0.294$ (SABE),” as shown in cell C15, the inverse natural log-transformed point estimate is 1.12 (rounded), which is within [0.8, 1.25]. The other BE parameter, the upper bound of 95% CI ($\alpha = 0.05$) for $(\mu_T - \mu_R)^2 \cdot 2 \cdot \text{var}_{S_{\text{inf}}}$, was calculated as per Equation 5, where:

$$\text{critbound} = (x + y) + \sqrt{(\text{bound} x - x)^2 + (\text{bound} y - y)^2}$$
Validation of IVPT-Stat

The IVPT-Stat was validated by comparing the output results generated by IVPT-Stat with those generated by SAS programs using the \( J_{\text{max}} \) data from example 1 and example 2. The results, as listed in Table VIII, show that the two programs generate the same values. Therefore, it is demonstrated that the two programs are equivalent, and IVPT-Stat can be used for BE analysis of IVPT data. For SABE, the validation of the calculation of additional statistical parameters (other than those listed in Table VIII) was done by authors’ step-by-step checking the correctness of MS Excel formulas as per the statistic mathematics.

Conclusion

The IVPT data processing procedures and BE statistics are introduced. The developed IVPT-Stat can be used by industry practitioners to perform BE analysis of IVPT data as per FDA’s statistics described in its Draft Guidance on Acyclovir (5). IVPT-Stat has been validated as a tool to implement the complex BE analysis. As no official standard procedures for IVPT study statistical analysis of BE have been established so far, it is essential that users validate IVPT-Stat before use in an updated regulated environment. With this tool, the users can obtain the BE parameters and make a BE/Not BE conclusion by simply entering the raw data of \( J_{\text{max}} \) or AMT. IVPT-Stat could be a helpful tool for topical drug product developers. The IVPT-Stat file and its user manual video can be downloaded for free from IVPT-Stat@163.com.

Access to tool. The open-source IVPT-Stat file can be freely downloaded from IVPT-Stat@163.com.

Acknowledgement

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References

5. FDA, Draft Guidance on Acyclovir (CDER, December 2016).

Lei Lei, PhD, ryan.lei@cutiatx.com, is the vice-president R&D of Cutia Therapeutics, Shanghai, China, and Ashvin Patel, PhD, is the director of Analytical Research & Business Development, Teledyne Hanson Research, New York, USA.

To whom all correspondence should be addressed.
Ensuring Patient Safety Through Elemental Impurity Analysis

Felicity Thomas

Analyzing elemental impurities in drug products is—much like other analytical testing—primarily aimed at ensuring patient safety.

Patient safety is paramount

PharmTech: Why is the analysis of elemental impurities so important in bio/pharma?

Cross (RSSL): Any analytical testing performed on pharmaceutical and biopharmaceutical materials is primarily to ensure that patient safety is maintained. This is performed either by confirmation that the correct dose of the correct drug substance is being administered or that the dose has no physical or chemical contaminants that may cause harm, or if there are contaminants, that they are below a defined acceptable exposure level. Elemental impurities are no different from any other contaminant, but until recently, the control of these potentially harmful species has been somewhat lacking.

The current elemental testing requirements came into force in 2018 in both the European and United States pharmacopeias following the ICH Q3D document on elemental impurities. This document defined permissible daily exposure (PDE) limits for 24 elements based on robust medical data, which considered the toxicity of the elements and route of administration, and it is written as such to allow for consistent evolution of potential elemental impurity contamination across all pharmaceutical and biopharmaceutical products. This approach has greatly improved patient safety, as it allows for a common approach to controlling elemental impurities based on health risks. Prior to this, elemental testing and limits were often based on the analytical capabilities of the instrumentation or reliance on a colorimetric ‘Heavy Metals’ test, which was insensitive, unspecific, and prone to poor recoveries (500 parts per million [ppm] of mercury in a sample could still give a passing result).

Suggested techniques and best practices

PharmTech: What analytical techniques are commonly employed to measure elemental impurities in bio/pharmaceutical products?

Cross (RSSL): Although ICH guidelines do not include any specific recommendations on instrumental methods, the following analytical procedures are suggested in United States Pharmacopeia (USP) <233> dependent on the expected concentration of the elemental impurity in the product or component: inductively coupled plasma–mass spectroscopy (ICP–MS)—parts-per-billion (ppb) concentrations; and inductively coupled plasma–optical emission spectroscopy (ICP–OES)—ppm concentrations. The chapter also sets out recommended analytic procedures for measuring elemental impurities to these methods.

Both techniques are ideally suited to elemental impurity analysis, as they are able to measure multiple elements simultaneously. Therefore, if a full analysis of the 24 elements is required, these techniques are ideal. Both ICP–MS and ICP–OES also allow for a simple screen...
to take place whereby samples are analyzed against a simplified calibration. This can be powerful in performing risk assessments on samples, as described in the ICH Q3D guideline in which 30% of PDE can be set on a product. If three lots of in-production or six lots of development product tested by the screening method and are shown to be below this level, then further testing may not be required.

“...until recently, the control of the potentially harmful [elemental impurities] has been somewhat lacking.”

—Alan Cross, RSSL

As the regulations insist that methods are validated prior to use, this allows flexibility for alternative methods to be used. These methods may be considered based on existing capability, specific chemistry of samples, or simplification of analysis if only one or two elements require testing. Examples might include, atomic absorption spectroscopy (AAS), typically a flame AAS would struggle to achieve the required levels of detection for elemental impurities control but for some elements other forms of AAS can be used which will provide the required detection limits. Vapor generation AAS is sensitive to ppb levels for elements such as arsenic and mercury, and graphite furnace AAS is easily applied to detect lead and cadmium at low levels.

Other techniques that may be employed might be microwave plasma atomic emission spectroscopy, a relatively new technique to the market which uses nitrogen as a plasma gas so has relatively low running costs, when compared to ICP-OES which uses expensive argon as a plasma gas.

Specific mercury analyzers utilize the volatile nature of mercury to allow untreated whole samples as solids or liquids to be analyzed directly by heating and measuring the mercury gas evolved, this simplifies testing and reduces analysis time and preparation costs.

**PharmTech:** Could you share any best practices in terms of analyzing elemental impurities in development?

**Cross (RSSL):** Preparation of the samples is as important as the analysis itself. Understanding the behavior of the analytes and the sample matrix will allow for robust methods to be developed.

**Technique limitations and advantages**

**PharmTech:** Are there any limitations with current analytical techniques for the analysis of elemental impurities?

**Cross (RSSL):** Traditionally, the main issue with elemental analysis, particularly in ICP–MS with chemical interferences affecting the accuracy of the results, is that over time many modifications to the basic ICP–MS system have allowed for better resolution—with systems such as collision cells and kinetic energy discrimination to remove interferences from the samples. These methods are now also commonly being combined into triple quadrupole systems, which allow for even greater discrimination and reduction in detection limits.

All analytical techniques, with the exception of graphite furnace AAS, use solution volumes in excess of 1 mL for analysis. This is not problematic if there is a large amount of sample, but it can cause issues when the amount of drug product or substance produced is very small, which is becoming more typical in the burgeoning biologics and biosimilars field. This means that novel preparation techniques need to be employed that can work with small sample amounts and final volumes to maintain the required detection limits, as well as further use of sample introduction systems that can work with small volumes, which are currently employed in some instrumental set-ups.

**PharmTech:** How about the advantages of the current techniques? Could you run through some of those?

**Cross (RSSL):** The advantage of the key analytical techniques, such as ICP–MS, ICP–OES, and AAS, is that they are truly multi-elemental techniques. These systems can analyze, either simultaneously or sequentially, the majority of the periodic table. The instrumentation manufacturers are constantly working towards lower detection limits and better resolution, as well as interference control.

“Understanding the behavior of the analytes and the sample matrix will allow for robust methods to be developed.”

—Alan Cross, RSSL

**An interest in speciation**

**PharmTech:** What trends do you foresee impacting elemental impurity analysis in the future?

**Cross (RSSL):** The food industry has had a particular interest in the speciation of certain elements, such as arsenic and mercury, where the form (organic or inorganic) has a big impact on the toxicity, and this consideration is also included in the USP/EP/ICH guidance. If a drug product is found to have levels of arsenic or mercury exceeding the PDE levels, speciation could be used to discriminate between toxic and less toxic forms to demonstrate compliance with the regulations.

**References**

1. ICH, Q3D(R1) Guideline for Elemental Impurities (ICH, March 22, 2019).
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When Is It Appropriate to Outsource Bioanalysis Work to a CRO?

Amy Lavelle and Laura Brunner

As a drug moves through the development and regulatory pipeline to approval, a sponsor may choose to outsource some or all of its bioanalytical work for a variety of reasons. Some biopharma companies may be virtual and need to outsource everything. Others may have the capabilities to do the work in house but choose to outsource for financial or other strategic reasons. When a sponsor chooses a contract research organization (CRO), it may be looking for a partnership, while others may simply be in need of a service and the relationship is strictly transactional. Whatever the situation, a sponsor should consider its own needs, capabilities, expectations, and limitations when choosing a bioanalytical CRO.

Not all CROs are the same. There are the niche or specialty CROs and the “one-stop-shop” CROs. CROs may cover a wide range of offerings outside of bioanalytical such as clinical trial management, central lab activities, manufacturing, etc. There are also CROs that solely provide bioanalytical services. Some may specialize in certain therapeutic areas or have special equipment to perform specific types of assays. Others will be best suited for pre-clinical development studies and some for long-term, high-volume clinical trials. Small CROs may not have the capacity to accommodate several large-scale studies and also support other clients, while some larger CROs may hesitate to commit to smaller studies that could interfere with their commitments to large studies. In this case, the choice of CRO is then narrowed. The bioanalytical laboratory location and cost of services also may be limiting factors in the decision to choose a CRO.

Throughout drug development, a number of labs may be required for various stages (see Figure 1 for examples.) Pre-clinical studies are necessary to support investigational new drug (IND) filings and clinical trial design. Bioanalytical good laboratory practice (GLP) studies are expected to be conducted with the proper quality systems in place to ensure the integrity and reliability of the data. Early development work also may include exploratory biomarker assay determination, to be narrowed down for eventual clinical endpoints and companion diagnostics to be co-developed with a therapeutic. Given the need for rapid data turnaround for decision-making purposes, factors to consider when choosing a CRO for early development studies may include the capacity to meet critical timelines, as well as the future prospects of entering into a partnership for clinical studies.

Clinical development includes first-in-human (FIH) through Phase III studies. Bioanalytical programs become more complex with good clinical practice (GCP) regulations and often utilize a central laboratory for sample processing. Bioanalytical strategies include pharmacokinetic/pharmacodynamic (PK/PD), anti-drug antibody (ADA) and biomarker assessments, as well as the use of a cell culture lab for neutralizing antibody (NAb) assays.

Regulatory considerations for clinical development include safety and efficacy data for regulatory agency filings and medical device application data for companion diagnostics (if applicable).

Clinical programs can last many years, be very large, and include studies in different populations as well as genotoxicity, reproductive toxicity, and carcinogenicity studies. Not only are there considerations for bioanalytical assay development, validation, and sample analysis, but other items for consideration include long-term sample storage and assay lifecycle maintenance for critical reagents. Choosing a CRO with the capacity for developing, validating, and analyzing high-through-
Throughout drug development there are put studies per regulatory guidance and the stability to accommodate the needs of a longitudinal study are factors to consider for clinical studies.

Post-marketing requirements (PMRs) and post-marketing commitments (PMCs) are part of a post-marketing study that may be requested by regulatory authorities at the time of approval or after approval if new safety information becomes available. These studies may be observational and meta-data driven or may require additional clinical trials needing bioanalytical support for safety and efficacy data in different populations, as well as long-term studies for vaccines and cell and gene therapies. Agency-required studies are often timebound. Failure to comply with post-marketing requirements could lead to regulatory agency actions. The choice of CRO for these studies may be based on current relationships, because utilizing the same CRO that performed the previous clinical studies would be most appropriate, given their experience with the study(ies) and lifecycle maintenance of the assay methods and reagents. For special indications, a CRO that has specific expertise in a certain therapeutic area or in a specific patient population might be required. The choice may come down to which CRO has the capability and capacity and can commit to meet critical timelines.

Outsourcing by data need
Throughout drug development there are many different opportunities for bioanalytical data acquisition. Drug concentrations, drug target, anti-drug antibodies, biomarkers, drug activity assays, drug metabolites, biomarker metabolites, genetic markers, and genetic mutations all represent the variety of data needs for a therapeutic to reach the market. All or some may be of interest and/or required for a sponsor to fully understand the effects of their drug. Large molecule, ligand binding PK and ADA assays are common in practice across industry and don’t necessarily require special equipment. However, some may require instrumentation that not all CROs have access to. For example, some biomarkers require high sensitivity that must have specific specialized instrumentation to assess at pico- or even femtogram levels. Mass spectroscopy, cell labs, and molecular biology labs are not a given at all bioanalytical CROs. The needs for these assessments may be a consideration when choosing a CRO, if the preference is to outsource to multiple CROs versus one that offers a variety of analysis platforms.

With the number of therapeutics coming to market, industry is seeing increasingly complicated modalities and compounds. This requires not only regulatory and analytical expertise but scientific expertise to ensure accurate method development and analytical oversight for a program. As the complexity of biotherapeutics increases so does the need for innovative technologies and platforms to address the bioanalytical needs of getting a drug to market. Particularly for long-term programs that are not technically standard, scientific oversight of method performance will be necessary. While the sponsor will have ultimate responsibility of the final data reported, scientists at a CRO will be responsible for the initial assay development and optimization and act as the first line in identifying trending changes, technical assay challenges, and can assist in risk mitigation if needed. Scientific experience and knowledge in a CRO are imperative to a successful clinical trial.

The CRO will likely follow specific regulatory requirements and guidelines for assay validation, data management and reporting, sample handling, and equipment and IT systems validations and maintenance support, depending on their laboratory specifications. Some examples of common documents include:

- FDA, Bioanalytical Method Validation Guidelines
- FDA, Guidance for Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products
- European Medicines Agency (EMA), Guideline on Bioanalytical Method Validation
- Guideline on Immunogenicity assessment of therapeutic proteins
- US, Code of Federal Regulations Title 21

In addition, CROs may be certified by the College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments of 1988 (CLIA) or follow GxP regulations and be regularly inspected by the FDA, the Brazilian Health Regulatory Agency (ANVISA) or other similar regulatory bodies. When considering the bioanalytical needs of a program, it is not only important to have expertise, instrumentation, and capabilities, but the infrastructure of the organization and the security of processes to ensure the integrity and safety of data.

Choosing the right CRO is an important decision and can be instrumental in a successful drug development program. Capacity needs, expertise, regulatory knowledge, or timelines may drive decisions. Whether it’s a one-stop shop or a specialty CRO, all CROs should adhere to best practices, standard operating procedures, and regulatory guidance to assure quality and integrity of the data.
Is AI a panacea for pharma’s productivity gap?

Artificial intelligence (AI) is a disruptive force and promises to help speed up drug identification; improve patient selection; create digital twins; improve manufacturing; tailor marketing material; enhance customer engagement; predict chronic diseases; and support health equity (1). However, there are some disadvantages with AI that need to be taken into consideration.

The following article discusses AI in the bio/pharmaceutical industry and its effect on who, what, when, and why its adoption is of interest.

Who: winners and losers

- In 2021, AI start-ups attracted $66.8 billion in investment (+108% year-on-year) and healthcare AI accounted for nearly 20% of total funding (2). Healthcare AI company Deep Mind (a Google Health company) was in pole position followed by IBM Watson Health and Oncora Medical. However, many companies such as Babylon Health and Caption Health are waiting to jump on the podium (3).
- Investment in AI has stimulated growth in start-ups, specialized products, initial public offering (IPOs), and acquisitions. Exscientia, one of the first companies to evaluate AI-designed drugs in Phase I clinical trials listed on the NASDAQ with a valuation of US$3 billion in October 2021 (4). In December 2021, Benevolent AI signed an agreement with the SPAC, Odyssey Acquisition to accelerate its AI-enabled clinical pipeline and reached unicorn status with a pre-money valuation of €1.1 billion (US$1.24 billion) and a post-valuation of up to €1.5 billion (US$1.69 billion) (5).
- Not surprisingly, AI start-ups have attracted a lot of attention from biopharma with Pfizer, Takeda, and AstraZeneca leading the way in terms of deals, followed by Novartis, Bristol Myers Squibb (BMS), Roche, Janssen, Merck KGaA, Boehringer Ingelheim, Bayer, GlaxoSmithKline (GSK), and Sanofi (6). A number of partnerships have already been announced in 2022 between AstraZeneca/Benevolent AI (7), Sanofi/Exscientia (8), Shinogi/Elix (9), Shinogi/NEC Corporation (10), Astrogen (11), Ono Pharmaceutical (12), and Teijin Pharma with Iktos (13).
- However, all is not rosy in the AI garden. Concerns have been raised regarding the accuracy of AI-supported software used to diagnose and guide treatment (14, 15), highlighting the importance of high-quality training data to prevent AI bias and, in some cases, AI-enabled systems may be more beneficial to augment human decisions rather than as standalone tools (14, 16). In addition, the ethical implications of using AI analytics and the wider issues associated with healthcare data storage and data security continues to be debated, emphasizing the need for strict regulatory oversight in this area (17).

What: leading innovators

- Although many biopharma companies have established their own in-house AI capabilities, some still rely on partnerships with AI vendors—Atomwise, BenevolentAI, ConcertAI, Exscientia, Google Quantum AI, Iktos, Insilico Medicine, MicroSoft, Recursion Pharma, and Sensyne Health—to support their drug discovery programs and identify novel drug targets, biomarkers, and new chemical entities for clinical valuation (18, 19).

When: new arrivals

- According to market research (2021), the global AI in pharma market is expected to grow from...
Weighing Up Big Pharma

US$935 million in 2021 to US$1236 million in 2022 at a compound annual growth rate of 32.3% driven by the launch of new start-ups and new services (20). Pharma is looking at leveraging AI beyond drug discovery and development to transform the way they perform clinical trials and interact and communicate with stakeholders. This has fuelled a new breed of AI start-ups—AiCure, Avaya, Deep Lens, Owkin, UNlearn.AI, and VeriSIM Life—to US$935 million in 2021 to US$1236 million in 2022 at a compound annual growth rate of 32.3%. Aran Maree, chief medical officer, The Janssen Pharmaceutical Companies (J&J) posted on LinkedIn that, “Single cell datasets are transforming the field of drug discovery. By leveraging AI and Machine learning, we’re able to analyse individual cells, identify specific genes involved in disease progression—and then identify potential ways to better treat these diseases...my company announced that we are joining a new pre-competitive consortium, led by Rancho BioSciences, that will help us leverage the power of single cell datasets to drive the discovery and development of innovative medicines. The mission of the consortium is to find a common industry standard around how single cell datasets are created and formatted. This is an exciting example of how we can use the power of data science to advance precision medicine and shape the future of healthcare to benefit patients everywhere” (24). Expect to see and hear more partnership announcements as the bio/pharmaceutical industry feels its way forward.

Why: pluses and minuses

• Overall, AI is being adopted on a large scale by pharma and healthcare companies due to its capacity to bring intelligence to repetitive tasks. It is well-suited to managing substantial amounts of healthcare data and can be deployed quickly, cheaply, and flexibly across the supply chain to problem-solve and tailor solutions to meet business requirements and market demands. For instance, in a review article Paul Debleena et al. (2021) stated, “AI can also be implemented for the regulation of in-line manufacturing processes to achieve the desired standard of the product. Artificial Neural Network (ANN) based monitoring of the freeze-drying process is used, which applies a combination of self-adaptive evolution along with local search and backpropagation algorithms. This can be used to predict the temperature and desiccated-cake thickness at a future time point (t + Δt) for a particular set of operating conditions, eventually helping to keep a check on the final product quality” (23).

• Nevertheless, an AI-driven approach requires a different business mind-set and culture, one where management must buy-in to AI-generated insights to drive the decision-making process. AI relies on leveraging historical data to train the algorithms, so the adage ‘junk in, junk out’ is very apt and the use of high-quality data alongside robust governance processes and human oversight will be essential to instil trust and increase accountability. The buck stops with humans/the CEO and not machine.

Food for thought

Many experts argue that if pharma does not invest in AI it will fall behind because a rule-based AI model can help analyze large quantities of data to support decision-making, drive efficiencies, and increase profitability. Aran Maree, chief medical officer, The Janssen Pharmaceutical Companies (J&J) posted on LinkedIn that, “Single cell datasets are transforming the field of drug discovery. By leveraging AI and Machine learning, we’re able to analyse individual cells, identify specific genes involved in disease progression—and then identify potential ways to better treat these diseases...my company announced that we are joining a new pre-competitive consortium, led by Rancho BioSciences, that will help us leverage the power of single cell datasets to drive the discovery and development of innovative medicines. The mission of the consortium is to find a common industry standard around how single cell datasets are created and formatted. This is an exciting example of how we can use the power of data science to advance precision medicine and shape the future of healthcare to benefit patients everywhere” (24). Expect to see and hear more partnership announcements as the bio/pharmaceutical industry feels its way forward.

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Lamešić notes. “Coprocessed excipients must demonstrate sufficient manufacturing process efficiency for customers,” he says. The uniqueness of coprocessed excipients, meanwhile, can be a concern for drug formulators from a security-of-supply perspective. “The excipients are usually only available from one supplier, which can increase supply risk and impact an innovator’s supply chain strategy,” Lamešić explains.

The biggest challenge to the adoption of coprocessed excipients, however, is a regulatory one. “Despite the significant positive feedback we have received about coprocessed excipients, there is a reluctance on the part of drug formulators to use these ‘novel’ excipients because of the higher risk they represent with respect to the regulatory approval process,” says Zhang.

The fact that many coprocessed excipients do not have an official monograph available is one of the major obstacles to their wider adoption in drug products, agrees Lamešić. “Although there have been developments in recent years, including the ongoing development of a general monograph on coprocessed excipients and guidance from the International Pharmaceutical Excipients Council on these products, there are still regulatory hurdles that need to be resolved,” he observes.

One of the fears surrounding the use of coprocessed excipients for formulators has been that regulatory agencies may request additional data to support the safety and efficacy of these materials, adds Joshi. He does note, however, that lately pharma companies have realized they cannot develop the drugs of tomorrow using traditional excipients that were developed decades ago.

In addition, Joshi points out that excipient manufacturers have put into place robust manufacturing and quality control mechanisms to ensure reproducible manufacture of high quality, coprocessed excipients. There is also significant regulatory support provided with Type IV drug master file (DMF) filings and well-documented analytical procedures. He also notes that FDA’s new pilot program to evaluate and approve new excipients before they are used in a drug filing is a significant positive step. “All these factors have significantly increased the acceptance and use of coprocessed excipients by the pharma industry, leading to their increasing use in FDA-approved formulations,” he concludes.

**Continued growth with improved robustness**

Despite these regulatory hurdles, the drive to reduce the time and cost for new drug development will continue to make coprocessed excipients attractive and lead to their growing use, according to Muley. The ability of these materials to help drug makers produce more robust oral solid dosage forms by overcoming manufacturing process challenges and reducing variabilities will also keep interest levels high, adds Assis. Growth will increase at an even greater rate if a regulatory pathway for coprocessed excipient approval is established, Zhang notes.
Productive Client-CDMO Relationships

Susan J. Schniepp, distinguished fellow at Regulatory Compliance Associates, discusses the basics for maintaining an acceptable working relationship between a client and their CDMO.

Q. I work for a small company with a few products in the development phase. I am reviewing several contract development and manufacturing organizations (CDMOs) to determine which one best fits our needs. Can you give me some general guidance on what I should look for when choosing an appropriate partner?

A. Contract manufacturing continues to be one of the fastest growing segments of the pharmaceutical industry. There are many small companies with products in development who do not own manufacturing facilities and must utilize CDMOs to handle their development and manufacturing needs from clinical to commercial product. It is important for both parties to be invested and respectful in the relationship because it is a long-term commitment.

The first step in this relationship is to establish a quality agreement (1–3). If we view the relationship between the two parties as an equation it would be:

\[ A + B + C + D = E \]

where A represents the CDMOs needs, B represents the client needs, C represents the compliance requirements, D represents the regulatory commitments for both parties, while E represents the quality agreement/quality relationship between the two organizations.

Breaking the equation down a bit more, variable: A should take into account the needs of the CDMO including auditing, testing, material sourcing, and any special client needs required to successfully manufacture the product. When defining the audit responsibilities, the CDMO should consider determining the amount of involvement of the client(s) for all audit types.

Variable B represents the client needs and should take into account requirements that might be influenced by development data, regulatory registration commitments, specific sourcing strategies, or any cooperative partnership with other companies. The client should also inform the CDMO of any additional quality agreements that are associated with the manufacturing of the product.

At one point in my career, I worked for a small start-up company which had three quality agreements associated with one product in clinical trials. The three agreements were for three different contract organizations. One CDMO organization was manufacturing the material, another was performing the release testing, and the final one was performing the product labeling. These complicated relationships should be disclosed to all involved parties so communication between organizations can be optimized, particularly when issues arise.

Variable C represents compliance requirements of the CDMO, which is influenced by multiple customers, regulatory agencies, and standard-setting organizations. Company standard operation procedures (SOPs) (4–6), client SOPs, audit observations, and compendial requirements define this element of our equation. Clients should be aware that CDMOs are usually global in nature and may have obligations to meet compendial requirements of the United States Pharmacopeia–National Formulary (USP–NF), The European Pharmacopoeia (Ph.Eur.), and the Japanese Pharmacopoeia (JP) (7). In my opinion, this would be the optimal section to include the communication expectations for regulatory audits conducted either at the CDMO or the client’s business locations. The need for the CDMO to communicate with the client when a regulatory audit is being performed at their facility is evident, but it is equally important that the client communicate with the CDMO when the positions are reversed. This two-way communication is crucial because each organization could be vulnerable based on the audit outcome regardless of where the audit was conducted.

The final variable in this equation is variable D. Variable D considers the regulatory commitments of the client and/or the CDMO. Regulatory commitments are the evolving body of knowledge made up of new or impending regulations or guidelines that may require changes in operations in order to meet the expectations of the new requirements. A CDMO must communicate changes and commitments affecting their quality system to their client and vice versa because these changes may affect regulatory filings.

Finally, the solution to the equation is variable E, which represents the robust quality agreement. The quality agreement should be a living, breathing document that is reviewed and revised as often as needed to clarify both party’s responsibilities and avoid conflict of responsibilities to ensure a successful partnership.

The relationship between the client and the CDMO is important and complex. Both parties need to be knowledgeable on the application and interpretations of the regulations, and they need to work through any opposing opinions to reach an interpretation that works for both parties. A cooperative working relationship can be achieved if each party clearly identifies and communicates their needs through an effective quality agreement.

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Presenter
Katie Falcone
Scientific Support Manager
Datwyler

Moderator
Chris Spivey
Editorial Director
Pharmaceutical Technology

The Role of Parenteral Drug Packaging in Patient Safety

Event Overview
When it comes to drug delivery, patient safety is of the utmost importance. In order to ensure life-saving drug products are delivered both safely and effectively, drug developers and their packaging suppliers must ensure that specific product requirements are met and patient and healthcare provider use are taken into account.

In this webinar, common challenges for packaging a safe and effective drug product will be discussed, as well as how packaging suppliers can help mitigate these risks. Case studies and examples will be introduced to explore real-world scenarios and implications for patients and their providers. The audience will leave this webinar with an understanding of the importance of patient-centric delivery and how to prepare for future challenges that may arise.

Key Learning Objectives
• Recognize the challenges and concerns regarding safe and effective drug delivery
• Understand case studies and examples of how parenteral packaging suppliers mitigate patient risk
• Learn ways to engage in a patient-centric drug development process

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

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

For questions email JdelaBandera@mjhlifesciences.com
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