eurofins | BioPharma Product Testing

Bio/Pharmaceutical NEWS

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Read more on pages 3 & 4, which highlight our innovative Cell & Gene Therapy capabilities, like this featured TEM, that help make the world healthier and safer.

In this Issue

The importance of a robust human factors engineering program in medical product development, particularly combination products

Liz Mauer, Senior Technical Director; Rachel Aronchick, Technical Director; Eurofins Human Factors MD

In early September, the FDA's Office of Combination Products finalized the guidance document, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* with a helpful Q&A document: *Application of Human Factors Engineering Principles for Combination Products: Questions and Answers.*

We at Eurofins Human Factors MD were glad to see that the FDA continues to emphasize the importance of a robust human factors engineering program in medical product development, particularly when it comes to combination products. Our key takeaway? A robust HFE program is clearly critical and not just a "nice to have."

Throughout the Q&A document, the existing 2016 final guidance (published by CDRH), *Applying Human Factors and Usability Engineering to Medical Devices*, was referenced several times and still serves as an important reference for combination product development. However, because unique aspects of combination products warrant nuanced considerations, the new Q&A guidance document offered clarity on a couple of valuable points for manufacturers:

• **Consider the combination product as parts, in addition to as a whole.** Combination products are comprised of two or more different types of products (i.e., a combination of a drug, device, and/or biological product with one another). As such, in the context of human factors, there may be use-related risks associated with the device only, use-related risks associated with the drug only, or use-related risks associated with the combination product that do not exist in the individual components. Therefore, it's important to consider the entire user interface, rather than considering the device and drug in a "siloed" manner, to ensure a thorough understanding of how the final finished combination product could affect users' interactions.

• **Develop a Use-Related Risk Analysis (URRA) that stands alone.** Attempting to incorporate use-related use issues in traditional engineering risk analysis (e.g., dFMEA, pFMEA, etc.) is not an appropriate approach given the expectations of the respective analyses. Ensure that the URRA exists separately from the full engineering risk analysis and focuses on use-related risks that could lead to harm or compromised medical care.

• **Identify *meaningful* critical tasks.** The document provides some clear examples of what would be considered non-critical vs. critical when it comes to identifying critical tasks. In general, if a use issue impacts dosing, administration, or could lead to actual harm (such as physical injury, adverse events, events that may need patient monitoring to confirm no harm, or events that may lead to hospitalization), it would be considered critical. However, if there is no urgency associated with task completion, if the issue is not likely to be repeated, or if the use issue is not linked to physical injury, it's unlikely that the task would be considered critical.

• **Consider your training approach and replicate it in your HF Validation study.** Participant training (or lack thereof) during an HF validation test has been a hot topic for years. The guidance comes closer to providing some clear expectations, but still leaves some room for considering training approaches on a case-by-case basis. In summary:

  o If training is part of your UI design requirements, validate your training during the HF validation test.

  o If training is not part of your UI design requirements, do not include training in the HF validation test.

  o If training is optional, may occur during actual use, or cannot be guaranteed upon commercialization, then the HF validation test may include both trained and untrained users. However, it seems there are still some instances where it may be acceptable to include only untrained users to assess a "highest risk scenario."

Of course, each combination product may have unique attributes that warrant special consideration. As such, we always recommend pre-submitting an HF validation protocol to the FDA for a pre-submission review to help de-risk the ultimate marketing submission.

If you have questions about how to apply this guidance to your product, ***CONTACT US*** to see how we can help.

Eurofins BPT grows Cell & Gene Therapy US Footprint

Loretta Sukhu, PhD, Senior Director of Operations, Bioassay, Cell & Gene Therapy, Biologics Raw Materials, EBPT Columbia; Stacie Fichthorn, Senior Manager, Biosafety Cell & Gene Therapy & Viral Clearance, EBPT Lancaster

Eurofins BioPharma Product Testing (EBPT) US is a pioneer in the analytical testing of Cell and Gene Therapy. Our first projects for Cell and Gene Therapy started in 2010 at our Eurofins BPT Lancaster, Pa, location. Over the past decade, Eurofins BPT has formulated a comprehensive business strategy that meets the analytical industry needs of Raw Materials, Cell Banks, Plasmids, and Viral Vectors (Lenti, Retro, Adeno, Adeno-associated), Genetically Modified Cells, CAR-T drug products and iPSCs. Eurofins BPT has continued to nurture the growth of Cell and Gene Therapy through various investments. This includes a focus on innovative technologies, such as droplet digital PCR (ddPCR), Analytical Ultracentrifugation (AUC), and Transmission Electron Microscope (TEM) testing. Investments also include dedicated space at several locations across the US.

In May 2023, the Lancaster site opened a 4,000 square foot laboratory space and hired staff dedicated to serving these specialized medicines. The ATMP lab is designed to accommodate many of the tests required to release viral vectors and cell therapies for use in cell and gene therapy applications. The space includes cell-based assay capabilities and instrumentation for a variety of endpoint analysis including qPCR, ddPCR, flow cytometry, and ELISA.

Eurofins BPT Lancaster is excited to feature Replication Competent test methods for Adeno (RCA), Retro (RCR), Lenti (RCL) and Adeno-associated (rcAAV) vectors. These methods are cell-based assays coupled with a vector-specific endpoint, fully validated and offered in a platform approach. As the methods were developed, turnaround times were optimized to deliver high quality results with the fastest means possible, while adhering to the expectations set forth by the regulatory agencies. These methods are another step toward our goal of a full service offering to Cell and Gene Therapy partners.

This year has also seen expansion at our Columbia, Missouri, site. This additional site extends the Cell and Gene laboratory services across two US Eurofins BPT locations, ensuring we are ready to accept these highly technical and complex programs. Eurofins BPT Columbia has state-of-the-art BSL-2 compliant Cell and Gene Therapy laboratories dedicated to viral testing, potency assessment, PCR, high throughput multiplex electro-chemiluminescence, flow cytometry and AUC. In addition to end point and quantitative PCR offerings, ddPCR supplies the ultrasensitive and absolute nucleic acid quantifications needed by Cell and Gene Therapy applications. Flow cytometry services are available to support clients who need to multiplex up to 13 individual targets in a single sample. Ultracentrifugation and SEC-MALS services are also offered for characterizing viral particles and other complex macromolecules. This comprehensive array of product characterization evaluations for Cell and Gene Therapy, including molecular weight determination, protein sequencing, peptide mapping, disulfide linkages and other post-translational modification analyses are available.

The Eurofins BPT Columbia and Eurofins BPT Lancaster teams offer complimentary services, which supply options and redundancy to manufacturers of specialized medicines. Both facilities have supported testing of raw materials, drug substances and drug products from early phases of development through post marketing commercial programs. Stay tuned for more exciting news about Eurofins BPT and Cell and Gene Therapy coming in 2024!

Cell and Gene Therapies – When Speed Matters

Tessa Patton, Manager, Bio/Pharmaceutical Microbiology; Chris Smith, Manager, Mycoplasma Services; Denise Kurtz, Group Leader, Bio/Pharmaceutical Microbiology

With the advent of Cell and Gene Therapies, specifically Autologous Cell Therapies (ACT), Eurofins has recognized that our clients with short shelf life products are in need of a solution to decrease the length of time it takes to obtain critical results to release life-saving therapies to patients. Eurofins BioPharma Product Testing (EBPT) offers a suite of services that allows us to be a one-stop-shop for your rapid and facility testing needs.

Rapid mycoplasma testing has been accepted in our industry as an alternative to the 28-day compendial-derived testing that has been available traditionally. Eurofins BPT offers two rapid mycoplasma detection methods to our services. MycoSEQ™ is a real-time qPCR assay using magnetic bead extraction and Power SYBR® Green dye. This method allows for standard results in five days, with the ability to support three-day prioritized results with preapproval. BioFire® is a single cartridge assay, performing both extraction and PCR within the cartridge that detects RNA from mycoplasma. This method allows for standard results in three days with the ability to produce prioritized results in less than 24 hours with preapproval. Comparability studies to show full equivalence for a product with either system are able to be performed as our lab also performs the traditional compendial methods and has live Mycoplasma onsite.

Eurofins BPT has also validated a method for a rapid contamination check. The method employs the use of the Biomerieux BACT/ALERT® 3D system. The method was validated in accordance with USP <1223> and was determined to be non-inferior to the USP <71> Sterility test. The method is able to provide a final result of positive or negative after seven days of incubation. In addition to the final result after seven days of incubation, the service offering provides a three-day interim read that is reported on a Quality Assurance approved Certificate of Analysis.

In order to provide a meaningful set of results for evaluation prior to dosing, Eurofins BPT has streamlined the process to execute the traditional Kinetic Chromogenic method for Bacterial Endotoxin Testing in order to provide a final result in three days.

In addition to rapid testing, ensuring that the facility meets the regulatory requirements for the manufacturing of safe and effective products, it is important to perform Environmental Monitoring Performance Qualifications and have a routine environmental monitoring plan in place. Eurofins BPT offers consultation to assist with designing a sampling plan and can also provide qualified analysts to perform the collections of non-viable air particulates, viable air, and surface samples utilizing state-of-the-art equipment. Eurofins BPT also provides analysts for on-site collection of purified water and compressed air/gases. All samples are transported back to Eurofins BPT and tested within 24 hours of collection with a turnaround time (TAT) of 14 days. Clients may also ship their samples directly to Eurofins BPT where we can provide the testing specific to the client's parameters with the same TAT of 14 days.

With this suite of services, our clients are guaranteed the shortest turnaround times available with the highest quality results for the tests needed to ensure their Cell and Gene Therapies are safe to be administered to patients.

TOX and CTM Manufacturing at Eurofins BPT

Rick Camp, President, Eurofins BioPharma Product Testing ENCO (Raleigh & Jacksonville); Joe Page, PhD, Business Unit Manager, Eurofins BioPharma Product Testing (San Diego)

Prior to becoming a commercial product, drugs must pass through a complex development, review and approval process to ensure patient safety and drug effectiveness. From the earliest steps of target identification to the identification of a new chemical entity (NCE), tens of thousands to potentially hundreds of thousands of compounds are screened prior to proceeding to preclinical phase. Preclinical pharmacology and toxicology are critical process steps in the drug development process and are critical to the translation of findings from the laboratory and the clinic.

Toxicology studies (TOX) examine the impacts of pharmaceuticals on biological tissues, then on living animal subjects. The studies are intended to match, as

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Eurofins BPT Lancaster earns Honorable Mention in Sustainable Laboratory Awards

The International Institute for Sustainable Laboratories (I2SL) recognized the Eurofins BioPharma Product Testing (EBPT) site in Lancaster, PA, with an Honorable Mention in its Sustainable Laboratory Awards program during its 2023 Annual Conference in Anaheim, California. The Eurofins BPT site's sustainability program that started as an employee led Green Team in 2009 was one of four Honorable Mention recipients in the Lab Programs or Initiatives category.

The I2SL Sustainable Laboratory Awards recognize projects, programs, and people that decrease greenhouse gas emissions, improve water and energy efficiency, divert waste from landfills, and promote sustainable best practices. Winners inspire, educate, and uplift others in the sustainable laboratory community with their dedication to advancing sustainable laboratories.

"This year's Sustainable Laboratory Award winners demonstrated a commitment to advancing both science and sustainability, and their efforts contribute to the overall goal of more efficient, safe, and decarbonized laboratories around the world," said Kathleen Brady, Executive Director of I2SL.

I2SL recognized the EBPT site in Lancaster, PA, for their sustainability program initiatives that have contributed to enhanced recycling practices, increased green commuting options for their employees, native habitat creation and biodiversity preservation on the campus and focused efforts to change behaviors in the laboratories to promote energy and water conservation and reduction of waste.

Christina Leslie, Eurofins Corporate Sustainability Senior Director, submitted the award application, and Sam Huber, Manager of Operations Support, accepted the award on behalf of the EBPT Lancaster, PA, site. Both Christina and Sam were founding members of the Green Team at the site in 2009 and have supported the expansion and growth of the sustainability program since then.

Chrissy Leslie, Senior Director, Corporate Sustainability, Equality Ambassador

I2SL is a nonprofit organization dedicated to the sustainable design, engineering, and operation of laboratories and decarbonizing laboratories worldwide. Since 2006, I2SL has supported information sharing and education among the various global stakeholders interested in improving efficiency and reducing the environmental impact of laboratories.

Helium Usage Management – Preparing for a Sustainable Future

Heidi Wojno, Director Method Development and Validation, Heather Bridwell, Director Pharmaceutical Product Testing, and Terry Schuck, Senior Manager Pharmaceutical Raw Materials

Helium is utilized as the primary carrier gas for GC chromatography testing, since inception of the technology. Currently, helium is still preferred due to its inertness, separation efficiency, and consistent performance.

Helium is a finite, non-renewable, resource, and in recent years, supply chain issues have created increased cost and availability concerns. Helium usage has a negative impact on the environment. Helium is extracted from natural gas. Natural gas mining processes contribute to greenhouse gas emissions with high methane content.

The Eurofins Lancaster BioPharmaceutical Chemistry teams assess testing alternatives and take actions to reduce helium usage in the laboratory. Future efforts will continue to reduce helium use as a GC consumable, losses from use as an inert purge supply for mobile phase, plus potential leakage loss from a massive in-house gas supply infrastructure.

Where helium is the preferred or the only allowable carrier gas in GC applications, conservation efforts are implemented to include the following:

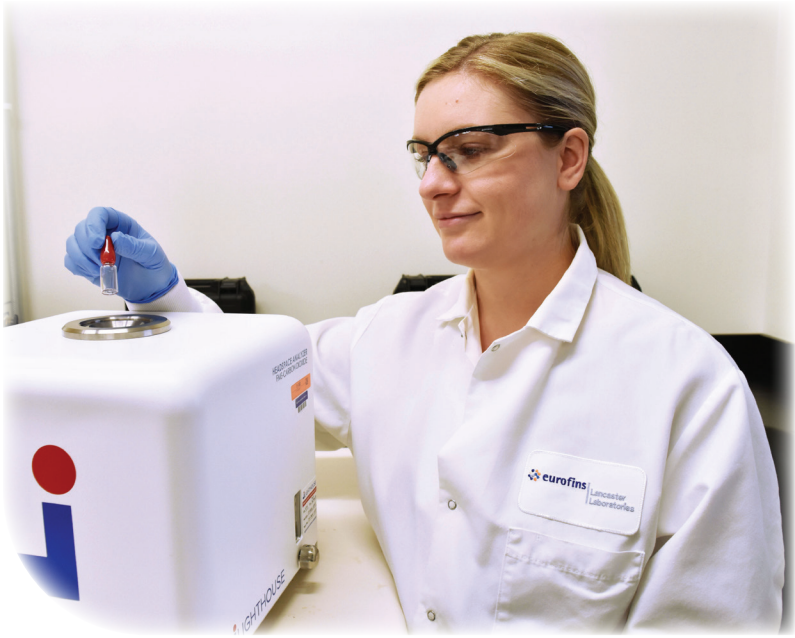
- Gas chromatography methods with an excessive split flow are being evaluated to use the instrument gas saver mode, which reduces split flow after a programmed time within the injection.
- Facility staff remove unused valves and check hundreds of helium lines for leaks during periodic room audits.
- Per vendor recommendation, GC instruments do not "idle" between analytical runs. Immediately after analysis completion, the column is removed and the helium flows turned off until the instrument's next use.

Where options exist to modify gas type for existing analytical methods, laboratories have begun transitioning methods and developing alternative parameters. Optimizing nitrogen use for pressurization/carrier gases for GC analysis is preferred. However, nitrogen has a lower optimal linear velocity than helium. This can lead to broadening peaks, causing increased analysis times and potential resolution issues when compared to helium-based analyses. Substituting nitrogen for helium for use as a GC carrier gas needs to be evaluated per method. Nitrogen has been evaluated as an alternative for USP <467> Residual Solvent testing with acceptable results in many cases. Hydrogen is a secondary alternative but poses an increased safety concern. Both nitrogen and hydrogen can be sourced from generators in an ultrapure state. Already, some existing GC methods established for clients have been modified and re-validated by customer request, using nitrogen or hydrogen as the carrier gas.

Helium may be the only option for use in purging/creating inert atmosphere for Mobile Phase for analyses like Ion Chromatography. Where an alternative is not acceptable for use, assuring sealed containers and limited loss of gas is a key action taken.

Fluctuations in helium production impacts prices and supply. Developing strategies to conserve or eliminate helium usage is critical for our Industry. Eurofins will continue efforts to achieve this as it pertains to reduced helium reliance and consumption.

Determining the best approach for your Container Closure Integrity Testing needs



Lenn Harris, Manager of Chemistry and Container Testing, Eurofins Medical Device Testing

Container-Closure Integrity (CCI) is critical to ensuring that the quality and safety of marketed drug products are stable throughout the shelf life of the material.

Per the USP, "It is not practical to require that packages be absolutely leak-free. Rather, it is the significance of the leakage in relation to product quality that needs to be considered." Basically, this means the container-closure system needs to contain the drug product and stop ingress of harmful materials such as microorganisms, contaminants and possibly gases from manufacture to the end use of the product.

In 2016, the USP issued guidance that deterministic methods should be examined in place of older probabilistic methods such as dye ingress or microbial ingress.

Deterministic methods can detect smaller defects more effectively and reliably in the container closure system than the older probabilistic methods.

The choice of an appropriate deterministic method is critical to the success in measurement of CCI in a system. Each technique has its advantages and disadvantages that must be considered as a method is chosen. Multiple technologies are mentioned in the USP for testing CCI.

While the USP does list technologies that can be used, there is no specific method in the USP <1207> monograph. There is no single method/technology that can be used for all testing.

Each product/closure system configuration needs to go through the process of proving that a specific technique can detect leaks at an appropriate level.

The Eurofins team is able to help you determine the best approach for your CCI testing and execute the development and validation of appropriate methods.

Eurofins BPT in Lancaster wins Ethics in Business Award

Eurofins BioPharma Product Testing in Lancaster, PA, is honored to have earned the prestigious 2023 Ethics in Business Award by the Samaritan Center of Lancaster.

Kudos to Daniel Peckman, Director of Scientific BioPharma Biologics and Chief Ethics Officer, for his outstanding representation of our company during the award vetting process. "This recognition underscores our commitment to maintaining the highest ethical standards in all aspects of our business operations and is a testament to the hard work and dedication of our entire team," Dan said.

Dr. Marian McKee, Dan Peckman, and Dr. Jon Kauffman accept the Ethics in Business Award.

Employing more than 2,000 people at its laboratory campus in Lancaster, Eurofins BPT has established decades-long brand recognition in the biopharmaceutical space for being an ethical laboratory testing partner.

Since the 1960s, leaders in Lancaster have cultivated a culture of integrity. Employees are empowered to be part of an investigative process, testing biopharmaceuticals and providing reliable and accurate results to the world's largest biopharmaceutical and medical device companies that contribute to the health and safety of our world.

The Ethics in Business Award recognizes companies in the Lancaster region of Pennsylvania that:

- **Firmly adhere to an ethical code**
- **Conduct business in a way that improves quality of life**
- **Treat employees and other stakeholders justly and with respect**
- **Are transparent in their communications and dealings**

People Are our Chemistry

At Eurofins BioPharma Product Testing, we believe that our people provide our strength. Their dedication to quality, team work, and customer satisfaction are the key elements in the company's success.

In this regular feature, we introduce you to some of the people who have helped make Eurofins an industry leader and the world healthier and safer.

Eric Shaver and his wife, Shiloh, volunteering at "Rake up Boise."

Eric Shaver, PhD, has been with Eurofins Human Factors MD for nine years, serving in the capacity of a senior leader and as a key technical contributor. He has over 20 years of experience in the field of human factors and brings a unique perspective to all his work given his experience in safety and litigation.

He truly understands what it means to claim a product is "safe and effective." He champions this perspective in all his programs, meaning that human factors integration in the product development process is not just a checkbox but is critical to ensure a product can be used safely and effectively by the intended users in the intended use environments.

Eric is also a solid citizen who gives back to his community of Boise, ID, in his spare time. On Veteran's Day, he and his wife Shiloh, volunteered their time to help rake leaves from the yards of veteran, disabled, and senior neighbors who needed assistance as part of "Rake Up Boise."

How did you get into the field of human factors?

I transferred into Psychology during my sophomore year of college and my advisor taught graduate-level human factors courses. I started assisting him with research and the rest is history.

What did you do before you came to Eurofins?

I was head of human factors for FUJIFILM Sonosite, a manufacturer of Point of Care Ultrasound Systems (POCUS).

What are your favorite types of programs to work on?

A complex combination product that is used by patients and caregivers.

What has changed the most over your time in the field?

A greater emphasis on the importance of the discipline in biopharmaceutical and medical device companies due to the influence of the FDA.

What was the most rewarding program you ever worked on?

Assisting a client develop a new method for continuous delivery of medication for Parkinson's patients.

Why should clients trust us with their projects?

Our senior-level staff average more than 20 years of experience designing, developing, and testing medical technology. We've seen just about everything; so we're able to help our clients with anything.

When you aren't working in human factors, what do you do to give back to the community or for fun?

I participate in local service organizations that help people in our community and protect public lands. Also, I enjoy spending time hiking in the mountains of Idaho with my wife and dog.

Contact us

For information on services, literature requests or address changes, please contact: Bio/Pharmaceutical Business Development, 717-656-2300, pha@eurofinsus.com, or visit *www.eurofinsus.com/bpt*

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TOX and CTM Manufacturing at Eurofins BPT

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closely as possible, the route or mode of administration to the anticipated human exposure. From a regulatory perspective, TOX materials are prepared under guidance from Good Laboratory Practices (GLPs), as outlined in 21 CFR Part 58. Prepared supplies are tested and released using qualified methods with oversight by both Quality Assurance and a Principal Investigator. Similar systems are employed for clinical trial materials (CTMs), often with added design assurances for aseptic products. Once a product reaches clinical phases, Good Manufacturing Practices (GMPs), 21 CFR Part 210/211, are utilized, from starting material manufacture to the use of validated analytical methods.

Eurofins BPT supports both TOX and CTM requirements at our Jacksonville, FL, facility by preparing scaled down batches, utilizing the same formulations and processes as closely as possible to those that will be utilized for finished products. TOX and CTMs can be provided in a variety of container closure systems, from sealed polyethylene ampoules, dropper bottles, to sterile vial systems. The use of single-use technologies for in-process materials and preparation reduces the overhead and expense of cleaning validation.

Eurofins BPT fills sterile CTM in our state-of-the-art fill-finish facility in San Diego, CA. Our gloveless, robotic isolator (Cytiva/Vanrx Microcell) with vapor phase hydrogen peroxide decontamination provides the greatest assurance of sterility compared to any RABS, open isolator or cleanroom currently available. Onboard sensors provide real-time data on the temperature, humidity, and 0.5 and 5.0 micron particles. Viables are monitored throughout the filling process with a TSB collecting bottle. This gloveless, robotic isolator removes the operator from the critical zone, the greatest source of contamination. The efficient design of this system, minimizes line loss to extremely low levels, delivering optimum results to clients and safe products to patients.