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Blog Post

Optimizing Production and De-Risking the Aseptic Drug-Filling Process with Real-Time, Viable Environmental Monitoring

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In response to recent revisions to the European Commission's Annex 1 regulatory framework, many contract development and manufacturing organizations (CDMOs) are scrambling to retrofit their drug product fill lines with innovative technology that meets new environmental monitoring (EM) standards. In contrast, consider the benefit of partnering with a CDMO whose drug product fill lines were built to fulfill Annex 1 standards and reduce potential contamination risks from the start.

A manufacturer who leverages real time, viable EM aligned with contamination control strategies (CCS) that are supported by quality risk management (QRM) systems, will manufacture safe products and meet regulatory compliance. This article explores the importance of forming an end-to-end partnership with an Annex 1 compliant CDMO, where your biotherapeutic will be guided seamlessly from drug substance to drug product to finished goods manufacturing while making a long-term investment in high efficiency, quality, and product safety.

Prioritize Regulatory Compliance from Day 1

In August of 2022, the European Commission issued revisions to EU GMP Annex 1 regulatory framework on the "Manufacture of Sterile Medicinal Products" guidelines to account for change across the pharmaceutical manufacturing ecosystem. The Annex provides, "general guidance that should be used in the design and control of facilities, equipment, systems, and procedures used for the manufacture of all sterile products applying the principles of QRM to ensure that microbial, particulate, and endotoxin/pyrogen contamination is prevented in the final product."[1]

Class A isolator technology; real-time, viable EM; pre-use post-sterilization integrity testing (PUPSIT); no touch transfer (NTT); single use (SU); and robotics are all vital implementations to prevent contamination via human intervention and guarantee aseptic production and Annex 1 compliance. As a result, they are critical components of a successful CCS. Isolators are widely regarded as the safest way to manufacture aseptic drugs, prevent contamination of the filling environment, and help achieve sterility of the product. They establish a more effective barrier between personnel and the open primary containers than traditional restricted access barrier systems (RABS).

Partnering with a manufacturer that uses retrofitted facilities can add significant cost and time to your program. Retrofitting an existing fill line with the infrastructure and technology to meet Annex 1 specifications is difficult and time-consuming, often taking years to achieve, particularly for CDMOs that use older, open RABS, non-isolator technologies. To retrofit, CDMOs are forced to slow down production to update their facilities, impacting program timelines.

At FUJIFILM Diosynth Biotechnologies (FDB), our drug product multiuse filling line is being installed and qualified with a strong alignment to Annex 1. To prepare for Annex 1 specifications, FDB has conducted pre-operational meetings with health authorities, attended Annex 1 conferences and workshops, and collaborated as members of industry-leading groups. In concert, this carefully designed approach helps avoid or minimize potential impact to clients' timelines, costs, and contamination safety concerns while meeting regulatory requirements.

Build Safer Processes with Real-Time, Viable EM

Human interventions are viewed as the largest source of aseptic drug filling contamination; thus, it is critical to reduce the number of manual interventions via innovative EM technology. Traditional EM methods use conventional settle plates placed inside isolators to collect viable particles if present. To remove or change plates, a technician must halt the production process and manually remove them using glove ports, which creates potential for microparticle contamination. Once a settle plate is removed, it must be incubated. From there, it takes several days to determine whether a viable particle was present inside the isolator. As a result of this delay, manufacturers risk late-stage discovery of sterility failure, which results in non-conclusive root cause investigations, batch losses, and added costs.

Across the drug product space, real-time, viable EM is proving to be a critical innovation to optimize timelines via real-time results, alleviate the risks associated with traditional methods, and meet Annex 1 regulations. This technology uses a viable particle counter during drug product filling to determine continuously the presence of viable particles within an isolator. Probes at critical positions inside the isolator are connected to the particle counting instruments on the outside of the isolator. Air is sucked through probes to the particle counter and provides real-time readings on both viable and non-viable particle counts. It also includes a particle collection filter to collect particles for sampling and assessment to determine the identity of microorganisms.

This technology can be integrated with a monitoring system in which operation, data collection, alerts, and batch reports are automated. If a viable or non-viable particle is detected, an alarm stop will go off on the machine. From there, a technician steps in to segregate the impacted part of the batch, deal with any potential concerns, and continue production – potentially avoiding significant product loss and mitigating waste and downtime. Unlike the traditional settle plates, real-time, viable EM does not require repeated human intervention via glove ports, thereby reducing the associated contamination risk and improving overall risk profile. Furthermore, it eliminates the line stops associated with removing and replacing settle plates and the resource use for subsequent incubation and plate reading.

FDB is implementing real-time, viable EM on our lines in parallel with traditional plate monitoring to generate data sets that demonstrate the non-inferiority of real-time, viable EM as a precondition for switching off conventional EM. In addition to the safety benefits, real-time monitoring offers clients reduced microbiology costs and higher productivity as the need for EM plate changing is removed, decreasing the number of line stops.

Form a Partnership with Risk Management at the Center

Despite the apparent benefits of real-time, viable EM, its newness in the industry may give some drug developers pause. To help assuage any client anxiety associated with this novel technology, FDB has been collaborating with regulators and peers across the industry to structure an implementation approach aligned with industry best practices. Throughout FDB's implementation, regulators have provided feedback on our approach to real-time, viable EM.

Thorough QRM as the basis for CCS and manufacturing control strategy is vital to reduce risk in aseptic filling. At FDB, we have made these elements central to our aseptic filling process. With this approach, we ensure that our production activities are aligned with Annex 1 regulations. To maintain patient safety throughout, FDB is generating a holistic CCS for drug product in accordance with industry thought leadership and recommendations.

FDB's multiuse filling line is capable of filling vials (2-50R press-fits/conventional alucaps), syringes (0.5-10 mL), and cartridges (1-10 mL) made of glass or cyclic olefin homopolymer (COP)/cyclic olefin copolymer (COC). The filling, stoppering, and capping of drug product occurs within closed, state-of-the-art isolators. The line uses a single-use product path and no-touch transfer during handling of pre-sterilized, primary packaging material. Throughout the process, real time, viable EM occurs. The process is designed to avoid container-to-container contact throughout. Post-filling, a fully automated inspection is conducted. FDB is capable of manufacturing up to 150,000 units per batch and up to 28 million units annually.

That said, we continue to drive our technology forward towards what is best for our clients and their patients via partnerships with filling line suppliers and industry collaborations. Ultimately, our next filling line will only be safer and require less intervention thanks to increased robotics and automation.

Choose What's Best for Patients

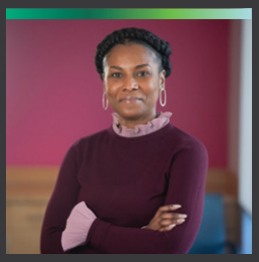
As technology evolves and standards are raised, drug product fill lines must continually be adapted to reach the highest quality and compliance standards for patients. CDMOs must rise to meet this challenge via collaboration with suppliers, drug developers, other manufacturers, and regulators to design new, tech-

centric approaches to aseptic drug filling. While you consider the best partner to meet your needs amid a sea of options, consider reliable, end-to-end CDMOs that have exceptional risk profiles, skilled teams, and proven track records to deliver safe, high-quality drugs to patients.

References

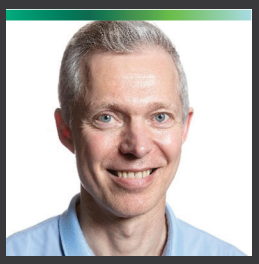
1. European Commission. (2022, August 22). The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Brussels.

About the Authors



Nadiyra Walker is the Head of Drug Product and Finished Goods Manufacturing at FDB in Holly Springs, NC. She holds a Bachelor of Science degree with double majors in Accounting/Finance and Business Administration from Wilson Community College and North Carolina Wesleyan University and she is currently pursuing an Executive MBA in Operational Organization and Process Improvement. She has 18 years of experience in the pharmaceutical and biopharmaceutical industry with the bulk of it being in large scale aseptic operations, including process improvement, lean transformation, and people leadership. Nadiyra also has leadership experience in supply chain and logistics as well as the manufacture of single use disposable assemblies. In addition to Drug Product and Finished Goods, Nadiyra is concurrently leading the Operational Readiness effort for Holly Springs, NC. Her focus is getting it right the first time.

Anders Magnusson is a Senior Engineer at FDB in Hillerød, Denmark. He holds a master's degree in chemical engineering from Lund University, LTH Faculty of Engineering in Sweden and has 35 years of experience in the pharmaceutical industry. Prior to joining FDB, he worked for AstraZeneca, NNE, Ferring Pharmaceuticals and Lundbeck A/S, holding various roles in drug and process development, clinical manufacturing, process engineering, conceptual design, and manufacturing support. He has extensive experience from previous employment working with a broad range of products from oral solid dose to liquid sterile products. At FDB, he is the subject matter expert in aseptic filling. He is currently one of the key figures in the company's implementation of its first commercial scale isolator filling line including the real-time EM systems.



Henrik Herrmann is Director of Manufacturing Sciences and Technology (MSAT) for Drug Product at FUJIFILM Diosynth Biotechnologies (FDB) in Denmark. He has been working in the Pharma Business for more than 20 years – starting at Novo Nordisk in 2002. Through his career his focus has been on drug product (DP) and finished goods (FG) manufacturing technologies and processes primarily at commercial scale. He joined Biogen manufacturing in 2015 in Denmark, after 3 years in China participating in bringing a new Novo Nordisk DP and FG facility into operation. In 2019 he transferred to FDB upon the company's acquisition of the Biogen facility, and he has the responsibility of building up the MSAT group for DP in addition to being part of DP technology choices and priorities going forward. He also leads the overall DP strategy for the company in terms of capabilities and capacities across manufacturing sites and scales. He has held several roles with progressive responsibilities such as SME, project manager and manager.

About FDB

FUJIFILM Diosynth Biotechnologies, a subsidiary of FUJIFILM Corporation, is a world-leading contract development and manufacturing organization partner for the development and manufacture of biologics, vaccines, cell and gene therapies, and oncolytic viruses. The company operates a global network with major locations in the United States of America, the United Kingdom and Denmark and it is building a new manufacturing site in Holly Springs, North Carolina, USA. FUJIFILM Diosynth Biotechnologies has over thirty years of experience in the development and manufacture of recombinant proteins, vaccines, monoclonal antibodies, among other large molecules, viral products and medical countermeasures expressed in a wide array of microbial, mammalian, and host/virus systems. We have drug product filling capabilities to support both clinical and commercial demands. Our Finished Good services, supported by more than 15 years of experience, can accommodate commercial products for more than 65 countries around the world. For more information, go to: www.fujifilmdiosynth.com.