Managing the Expectations of Auditors for Microbial Data Collection

Abstract

Microbial environmental monitoring is a growing challenge for the pharmaceutical industry in an increasingly digitized industry, otherwise known as Industry 4.0. Manufacturers must be able to guarantee their blend of automated and operational processes are under statistical control while ensuring their data is secure and accurate. With the improvements made to other areas of production, there is a growing need for modern solutions to environmental monitoring and microbial data collection in critical areas.

A Changing Pharmaceutical Industry

The adoption of computers and automation in modern industries has dramatically increased the amount of data to be managed. Digitization, the fourth revolution of industrial manufacturing after steam power, mass production and computer automation, allows industries to manage this data systematically and efficiently.

Over time, pharmaceutical manufacturers have changed their processes to separate operators from products. Today, several already use robotic filling lines, further blurring the line between digital systems and operations. Information technology is a growing need as more companies adopt these solutions to manage so-called "big data". Environmental monitoring (EM) procedures could eventually be completely integrated into digital systems, preventing deviations and errors. For example, microbial data collection might be managed exclusively through digital means. The significant volume of data generated from EM should be managed in compliance with good manufacturing practice (GMP) guidelines to ensure reliability and integrity.

INDUSTRY 4.0 — THE DIGITIZATION OF MANUFACTURING PROCESSES

Statistical Control and Your Process

Though they are often used interchangeably, data integrity is not synonymous with data security. Data security makes data inaccessible to those who may use it in harmful or unintended ways. Data integrity is concerned with keeping information intact and accurate for the entirety of its existence. The meaning of data security is not broad enough to include the many processes necessary to maintain data integrity.

When thinking about data and its metadata components, first imagine a photo taken on a smartphone. The smartphone includes technical information concerning the photo itself, such as the size of the file and the date it was taken. The photo is the data, and the technical information about the photo is metadeta, which in turn helps the user to fully understand and effectively manage the photo. The full definition of data and metadata is described by MHRA.

For nearly any process, data represents figures, facts and statistics collected for reference or analysis. What should be managed is the original record or true copies of the original. A list of relevant guidelines concerning data management and data integrity can be found in the references section of this paper[2-9].

ALCOA

A well-known acronym, ALCOA, refers to the main priorities for maintaining data integrity: Attributable, Legible, Contemporaneous, Original, and Accurate. Metadata such as who collected the data and when it was logged are essential for demonstrating data fits within the ALCOA umbrella, and no changes to the data occurred.

Data management in relation to data integrity is a complex system of checks and balances. The International Society for Pharmaceutical Engineering (ISPE) Good Automatic Manufacturing Practices (GAMP) Guide and ICH Q9 emphasize the importance of first having the appropriate mindset and culture within a company in addition to critical thinking and scientific judgements. Training is recommended to ensure understanding of important principles across groups involved in implementing and operating data management systems. Auditors expect pharmaceutical manufacturers to have a future-oriented, consistent improvement mindset with regards to procedure management and process understanding, including a complete understanding of data flow.

FDA Inspections for Data Integrity

All cGMPs ask for actionable, proven method for ensuring data integrity, as decribed in 21 CFR Part 11. The term is widely described and discussed by pharmaceutical experts, and yet several failures in its application are still reported. From 2015 to 2018, more than 20% of FDA 483 warning letters were issued for data integrity failures[1]. Looking at only the top six citations issued to pharmaceutical companies, data integrity failures are frequently registered with a dramatic uptick in the number of citations issued by auditors, including those pertaining to data management and its related procedures.

A 483 was issued in December 2019 because inspectors found no procedures preserving data integrity after implementing data management software. The main takeaway is that databases should be designed to accomodate multiple user types, and all risks to the system should be accounted for. Even the best 21 CFR Part 11 compliant data management software cannot meet auditor data integrity expectations.

Microbial Monitoring

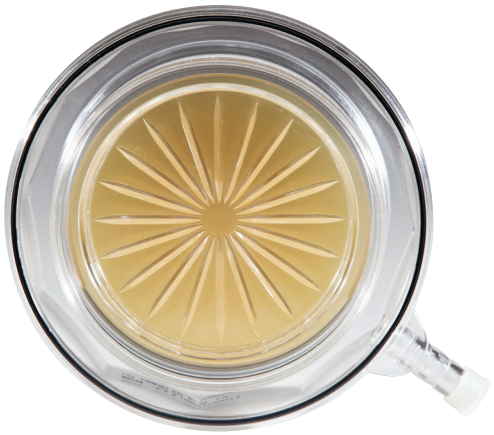
Auditors expect microbial EM management to be fully compliant with data integrity principles. With effective management of EM data, risky situations can be predicted and promptly rectified, avoiding deviations and the associated costs. Statistical tools suh as control charts can be used to detect drifts from specified acceptance limits. This data is used to better understand when, where and why the manufacturing environment is in a state of control, and also what increases the risk of drug contamination in aseptic areas.

A process can be considered in control when it is demonstrably stable with only random variation. Statistical data must show there is no risk of non-ordinary events and errors that influence quality assurance. As an example, consider a classified area with microbial EM data much lower than expected. This could be a sign of a problem in detectability rather than proof of greater control. A stable process that shows only one deviation could be out of control if the variability in out-of-specifications (OOSs) is much higher than expected. The efficacy of monitoring systems is just as important as the company's management of their quality procedures.

As stated by multiple guidelines, the risks pertaining to record-keeping may vary from systems to system. Inspectors request each company to define their own risks of data integrity failures within their process, considering all data flows. To do this, the Quality Risk Management (QRM) approach is a reliable tool to effectively identify and manage the risk of data integrity breaches for a specific data management system.

Sampling Devices and Industry 4.0

Performing microbial EM with traditional impactors leaves data collection tied to the impactor itself, as the data matrix is present only on the agar plate. This means that in the case of a positive result, the impactor cannot be used for the investigation of an OOS. Instead, other questions are considered, such as how the impactor was installed, and how the impactor was cleaned before sampling. Understanding all components involved in the sampling process is not possible if the impactor is missing from the investigation.

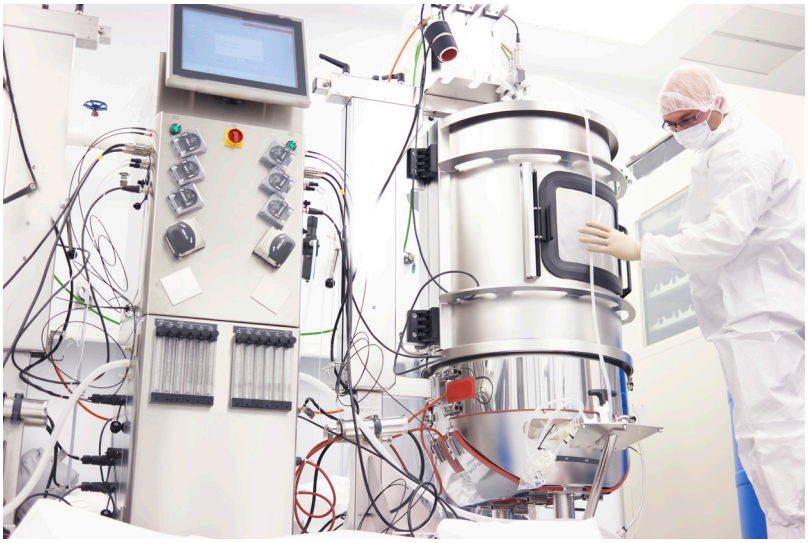


AN IMPACTOR FOR THE DIGITAL AGE—
THE BIOCAPT® SINGLE-USE

BioCapt Single-Use

The **BioCapt® Single-Use (BCSU) impactor** meets regulatory requirements for data integrity and Industry 4.0. In the BCSU, media and impactor are combined into one unit, eliminating the risk of false positives and reducing costs pertaining to investigations. It also allows the data matrix to include information pertaining to both the impactor and media, such as the media type, its sterilization, and expiration date. Costs for autoclaving and disinfection of reusable impactors are not present.

BCSU is validated for continous, two-hour sampling and includes a full validation report to facilitate its implementation. Each single use impactor is labeled with an unremovable QR code, in compliance of HDMA guidelines for bar coding in pharmaceutical supply chains. With its ease of use, BCSU can be seemlessly integrated with highly digitized, robotic systems and automated filling lines.



Conclusion

BioCapt Single-Use is the microbial EM solution that meets the requirements of an increasingly digital age. Traditional microbial monitoring such as the settle plate method do not promote thorough investigations, and ultimately hold back progress in understanding complex pharmaceutical processes.

Data management systems are integrating into automatic filling lines where robotics are increasingly used to replace operator tasks, reducing and ultimately eliminating human intervention. A pharmaceutical manufacturing plant set up according to Industry 4.0 principles primarily consists of machines with sensors to monitor all process flows, including the machines themselves.

References

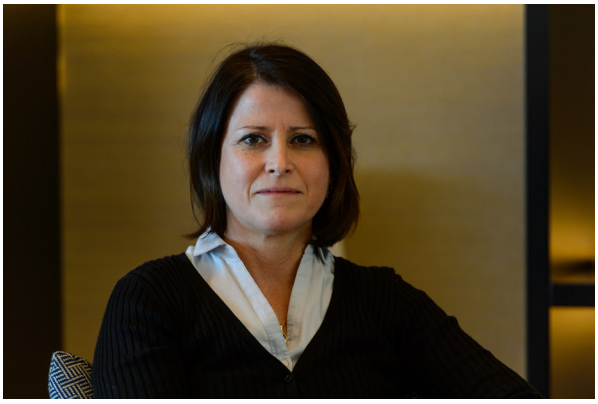
1. Unger, Barbara W. “Part 1: Analysis of CY2018 FDA Warning Letters That Cite Data Integrity Failures.” Govzilla, 9 Aug. 2019, govzilla.com/blog/2019/08/pharma-part-1-analysis-of-cy2018-fda-warning-letters-that-cite-data-integrity-failures/.
2. *Good practices for data management and integrity in regulated GMP/GDP environments*. PIC/S Guidance. Nov 2018.
3. *GMP Data Integrity Definition & Guidance*. MHRA. July 2016.
4. *Guidance on Good Data and Record Management*. WHO, TRS 966. 2016, under revision
5. *Guidance for Industry . Data Integrity and compliance with cGMP*. FDA. April 2016.
6. Documentation. EU-GMP, Vol. 4, Ch. 4. June 30th, 2011.
7. *Computerized systems*. EU-GMP, Vol. 4, Annex 11. June 30th, 2011.
8. *e-records, e-signatures*. FDA, 21 CFR Part 11. Aug 2003.
9. *Data integrity training and briefing is needed to ensure understanding and awareness across all groups involved in implementing and operating systems*. ISPE GAMP RDI Good Practice Guide: Data integrity. Manufacturing Records. 2019.

Authors

Paola Lazzeri
EMEA Sterility Assurance & Microbiology Product Specialist

Paola is currently part of the EMEA Sterility Assurance / Microbiology Product Specialist Team and the Advisory Team in Particle Measuring Systems. She is a subject matter expert in the field of cleaning and sanitization of Pharmaceutical Cleanrooms, with specific focus on microbiological hazard, setting rational cleaning and sanitization of cleanroom and pharmaceutical manufacturing plants. Paola participates as a speaker at national and international conferences.

Giulia Artalli
Global Product Line Manager



Dr. Artalli has a degree in biology from the University of Milan with over 20 years' experience in Microbiology, specifically for pharmaceutical applications. She has covered different roles acquiring knowledge on different topics useful for supporting customers in their needs. Now she serves as a Global Product Line Manager at Particle Manager Systems for the microbiology product line.

Editor: Briana Krueger, Technical Writer