ARTICLE

Making Automation the Standard: An Annex 1 Overview

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SUMMARY

The final version of the European Union (EU) good manufacturing practice (GMP) Annex 1 took effect in August 2023, advocating automated quality control (QC) technologies as a means of minimizing risk from microbial, particulate, and pyrogen contamination. Developers and makers of sterile pharmaceuticals can expect an array of new compliance challenges, not only in Europe but eventually in the United States.

INTRODUCTION

When a draft revision of the European Union (EU) good manufacturing practice (GMP) Annex 1 was published in early 2020, developers and makers of sterile pharmaceuticals were quick to notice that it posed wide-ranging compliance challenges only partially spelled out in the document. After publication of the final version in August 2022, companies worldwide looked ahead to its enactment in August 2023, knowing that it would affect not only European standards but also U.S. Food and Drug Administration (FDA) guidelines that will eventually incorporate many of the new principles and provisions.

Annex 1 is primarily concerned with manufacturing, but clearly points to automated quality control (QC) technologies as a means of minimizing risk from microbial, particulate, and pyrogen contamination. Section 2.1 of the Annex, for example, includes this passage identifying key areas for consideration by manufacturers of sterile products:

> i. Facility, equipment and process design should be optimized, qualified, and validated according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g., Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid microbial testing and monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and product.[1]

With the Annex 1 endorsement of automated quality control (QC) technologies, a critical next step for pharmaceutical firms is identifying a validated platform capable of accelerating compliance while minimizing risk. The fully validated Growth Direct® System is the most notable example, adopted by a majority of Top 20 biopharma manufacturers worldwide with a number of customers already verifying compliance to 21 CFR Part 11 in their own facilities. Consequently, companies hoping to gain an advantage by getting in early on a possible “automation rush” must be aware of Annex 1 developments.

REDUCING THE RISK OF MANUAL INTERVENTION

Longtime industry observer David Jones, Director of Technical Marketing and Industry Affairs at Rapid Micro Biosystems, says that Annex 1 will trigger significant changes in the future activities of pharma manufacturers and QC labs.

“At the top level,” Jones notes, “the Annex introduces the need for more risk assessments of processes to scientifically justify what is implemented, and to minimize human intervention in the manufacturing line as the key source of microbial contamination. On an operational level, this emphasis on minimizing human intervention also implies a greater need for automation and robotic handling systems.”

TABLE 1. *Significant microbial updates in Annex 1*[2]

Area Impacted	Updated Practices
MONITORING EQUIPMENT	Grade A zone should be monitored continuously (for particulates ≥ 0.5 and ≥ 5 µm) and with a suitable sample flow rate (at least 28 liters – 1 ft^3 – per minute) so all interventions, transient events, and system deterioration are captured. Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Recovery efficiency (ISO 14698/BS EN 17141) of the sampling methods chosen should be qualified. Size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified. Method of sampling used should be justified within the contamination control strategy and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.
USE OF RAPID MICROBIAL METHODS (RMM)	Limits are applied using colony forming units (CFU) throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU. Adoption of suitable rapid or automated monitoring systems should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methodology.

In fact, two sections in Annex 1 specifically suggest use of a rapid, automated microbial method:

> 9.28 The adoption of suitable rapid or automated monitoring systems should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methodology ….
>
> 10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the certification should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid monitoring systems.

As the Annex notes, these methods should only be used after they have been validated to be equivalent or superior to the established method. For this reason, it is important to look at the validation history and regulatory acceptance of rapid automated methods before implementing a new method at a facility.[3]

CONCLUSION

Annex 1's ten sections are broader in scope than earlier EU guidelines, going beyond medicinal products to a wide range of sterile product types, processes, and technologies.[4] Details are relatively sparse, but current industry practices would suggest that any regulatory admonition concerning quality control and risk management issues will ultimately mean big changes at every level of global supply chains.

Due to this broad impact, no single Annex 1 overview or resource can reasonably claim to be definitive. But many supplier companies have issued whitepapers and articles on Annex 1, reviewing potential effects on specific industries from either a manufacturing or microbial testing viewpoint. (See Table 2 below to find examples for further study.)

TABLE 2. *A sampler of Annex 1 perspectives*

Areas of Interest	Suggested Reading	Topline Summary
Microbiology impacts	EU GMP Annex 1 - The New Draft and the Implications for Sterile Products Manufacturers	Thorough overview of all Annex sections from a microbiologist's viewpoint
Risk analysis, product quality, contamination prevention	EU GMP Annex 1 Manufacture of Sterile Medicinal Products	Risk analysis implications from a QC consultancy
Data integrity, microbial enumeration and ID, quality investigations	Reducing Risk in Your Environmental Monitoring Program	Discusses automated colony counters and the need for viable colonies
Cleanroom compliance	FDA and EU GMP Annex 1 Differences in Cleanroom Specifications	Focus on particulates, microbial risk, and rapid microbial monitoring in air sampling
Cleanroom disinfection and cleaning	Annex 1: How New Draft Impacts Cleaning and Disinfection in Cleanrooms	Regulatory concerns about hidden effects from residues, as seen by disinfectant manufacturers
Isolator manufacturing	Understanding the Impact of Annex 1 on Isolator Operation	Robotics and automation systems figure to be key considerations for aseptic manufacturing in isolators
Air sampling	Insight into the New EU GMP Annex 1	Annex 1 could evolve into the backbone of quality assurance and documentation of contamination control
Microbial monitoring, air cleanliness, cGMP	Concerns Around Annex 1	Strong recommendation for RMM and closer regulatory alignment with industry best practices

In the meantime, a beneficial starting point for companies pondering future-ready automation technologies is Rapid Micro Biosystems, the only company currently automating critical compendial microbiology processes with a fully validated technology platform. Already possessing a substantial industry track record deploying its Growth Direct® System, Rapid Micro Biosystems has proven expertise evolving the traditional QC paradigm to meet today's complex regulatory and competitive pressures.

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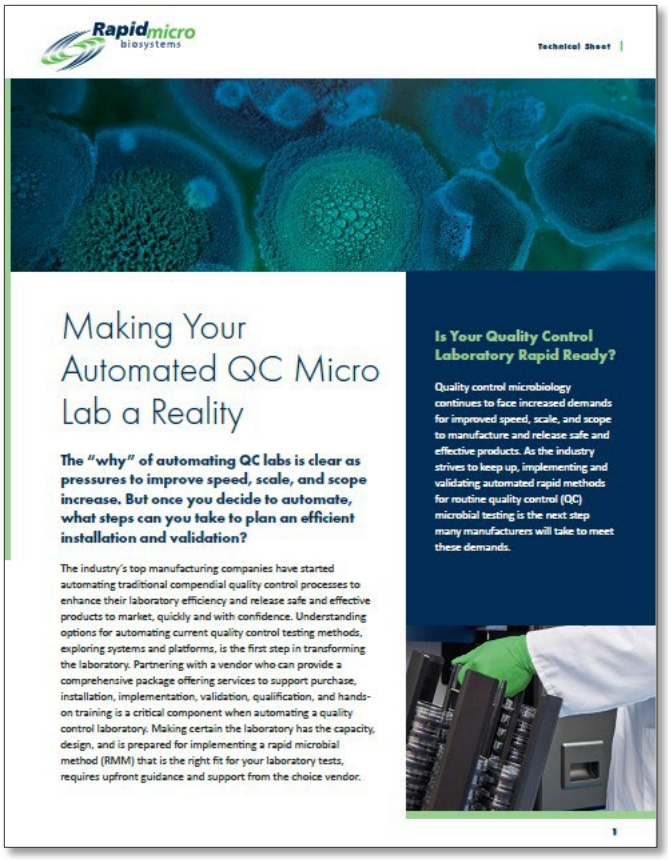

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