Making Automation the Standard: An Annex 1 Preview

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SUMMARY

A final version of the European Union (EU) good manufacturing practice (GMP) Annex 1 is expected to be released in late 2021, with potential to advocate automated quality control (QC) technologies as a means of minimizing risk from microbial, particulate, and pyrogen contamination. Developers and makers of sterile pharmaceuticals are keeping a watchful eye on Annex 1 developments for a wide-ranging array of possible compliance challenges, not only in Europe but eventually in the United States.

INTRODUCTION

When a new draft 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. Consequently, companies worldwide are looking ahead to the release of a final version later this year, knowing that it is likely to affect not only European standards but also U.S. Food and Drug Administration (FDA) guidelines that could 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]

If automated quality control (QC) technologies are endorsed as expected, a critical next step for pharmaceutical firms will be 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 a competitive advantage by getting in early on a possible “automation rush” are keeping a close eye on Annex 1 developments.

REDUCED MANUAL INTERVENTION, INCREASED TEST VOLUME

Longtime industry observer David Jones, Director of Technical Marketing and Industry Affairs at Rapid Micro Biosystems, expects the Annex to 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."

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 rightly 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.[2]

Another possible consequence could be a dramatic increase in the number of QC tests that must be performed by manufacturers of sterile pharmaceuticals. To raise just one example, environmental monitoring demands might become not only more numerous, but continuous:

> Manufacturers of sterile products will have to devise environmental monitoring programs and procedures based on QRM [Quality Risk Management] to ensure that microbial, particulate and pyrogen contamination is prevented in the final product. QRM should cover the entire chain, from the facility's design to its equipment and processes, then on to the implementation of suitable procedures, and finally to monitoring systems ….
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> Annex 1 also states that viable air monitoring in a Grade A zone should be undertaken continuously (e.g. by air sampling or settle plates) over the course of critical processing, including aseptic equipment assembly and filling operations. What does continuous monitoring mean in practical terms? According to the definition in the PDA Technical Report No. 13.2 (2020) "that a state of control is maintained during processing and that any aberrant events are detected. Frequency of monitoring is determined by a risk assessment." Depending on the risk assessment, the monitoring frequency can by quite high which, in turn, calls for care that more frequent manual handling activities do not themselves lead to greater contamination risks.[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 1 below to find examples for further study.)

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.

TABLE 1. *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 Medical 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

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4. Ibid.

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