Introducing EU Annex 1:

UNDERSTANDING THE NEWEST REGULATORY REQUIREMENTS

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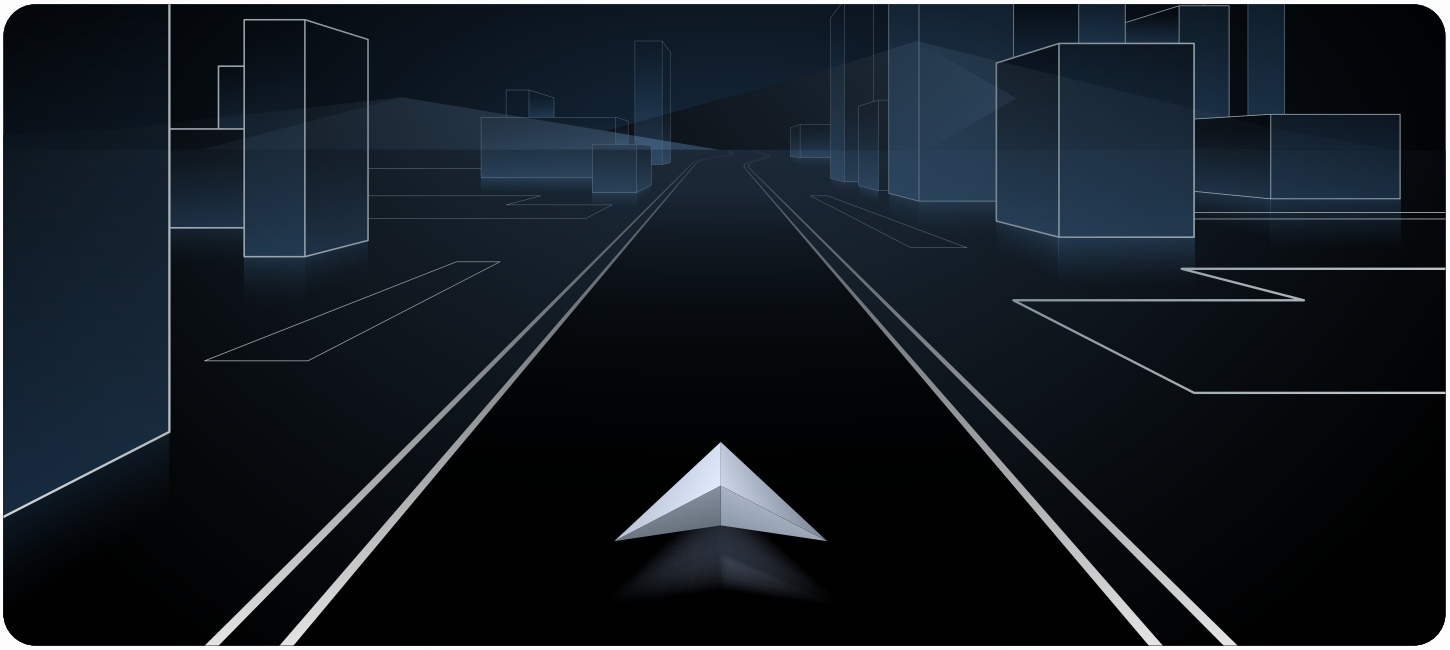
Table of Contents

Introduction

As its title implies, Annex 1 is the European guidance document for good manufacturing practices of medicinal products. As such, it serves as the road map for sterile drug manufacturers to follow in order to arrive at the pathway to the highest level of sterility, assuring that their medicinal drug products deploy operational best practices, are certifiable, and regulatorily safe.

The cumulative improvements and updates to the provisions of the recently published Annex 1 were derived from the evolution and development of medicines and technologies that have emerged over the last two decades. Cell and gene therapy, immunotherapy, and personalized medicines have revolutionized patient treatment options.

By the same token, novel bioprocess systems like rapid microbiological methods, restricted barrier access systems, isolators, and single use systems have gained industry and regulatory acceptance (2) as well as proven to reduce product cross contamination risk(1)(3)(4). The most pertinent changes in the Annex 1 guidance document are the management of these advances in pharmaceutical manufacturing, in connection with mitigating risks and supporting patient safety.



The Impact of the Publication

While published as a European document, the impact of the publication exceeds European boundaries.

The working group involved in the revision of Annex 1 is a multilateral forum of organizations such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the Food Drug Administration (FDA). These governing authorities engage in the implementation and harmonization of common core GMP standards.

The emphasis of regulatory harmonization is apparent from the start of the Annex 1 document as it references the application of the tools and guidelines outlined in the globally accepted International Council of Harmonization (ICH) documents, Quality Risk Management (ICHQ9), and Pharmaceutical Quality Systems (ICHQ10), the former of the two being fully embedded throughout the entirety of the document.

The Impact of Quality Risk Management (QRM)

While the concept of quality risk management (QRM) is not a new one, the emphasis is now more prominent and apparent than before.

Implementing the changes to meet the new requirements of Annex 1 text will provide numerous challenges for manufacturers. At a site level, manufacturers are formally required to have a contamination control strategy (CCS) document in place that provides a systematic description and overview of the sum of controls and measures in place to monitor, detect, assess, mitigate, and prevent risk to patients. This requires a process design that is inherent to the principles of QRM and well-understood.

A process is well-understood when all critical sources of variability are identified and explained. Variability is managed by the process, and product quality attributes can be accurately and reliably predicted (5). Equally, regulators face the challenge of determining when, if, or how new techniques and data should be incorporated into the regulatory science process (6). The deadline for coming into operation for the new Annex is August 25, 2023 , however there are specified grace periods for some elements of the text.

Balancing innovation without sacrificing safety to produce the most efficacious and reliable treatments for disease will require a good understanding and correct application of QRM tools.

Through research and customer experience the most impactful considerations for Pharmaceutical Quality Systems (PQS) are the embedment and proactive use of the QRM principles within the organization, creating, and operationalizing a CCS thoroughly investigating failures discrepancies. Annex's 1 commitment and emphasis on quality in pharmaceutical manufacturing empowers companies to implement a cross-functional integration of expertise in the manufacturing process whereby risks are reevaluated and reassessed on a continuous basis.

Principles, Guidance, and Justification

Some of the principles and guidance of the revised Annex 1 documentation may be used to support the manufacturing of products that are not intended to be sterile.

Pharmaceutical companies can expect regulatory bodies to look at how the company applies the principles and guidance of Annex 1 and good justification or rationale as to why or why not aspects of it have or have not been adopted and how they're implemented. A good example is the design of your premises, the justification of how the cleanroom classification is designed and selecting the gowning and cleaning regime that is applicable. Not only is that applicable to sterile manufacturing but to non-sterile manufacturing processes as well.

Quality by Design (QbD)

The concept of Quality by Design (QbD) and its principles are described in the ICH Q8 document. The ICH Q8 text guides pharmaceutical companies on how to interlink ICH Q9 and ICH Q10 by way of implementing the QbD fundamental practices.

The same considerations should be made for the equipment design size and location, personnel and material presence and flow, as well as product contact material and the frequency of interventions during business operations. There is a dedicated section for utility design and management in the updated Annex 1. These utilities include water, gas, heating, and vacuum systems which were not included in the previous version of Annex 1. The impact of utilities to the manufacturing process is determined by design, assessed based upon risks and is documented in the CCS.

Utilities feed into the classified environments where sterile drug product manufacturing activities occur. A well-designed Environmental Monitoring (EM) and quality control program is important in the evaluation of environmental controls and control of personnel-gowning performance and behavior as well as the effectiveness of the cleaning and disinfection programs.

Assessing the level of environmental control in cleanrooms can be difficult to determine for companies with legacy systems/processes as well as cleanrooms where biotechnology pharmaceutical processing takes place. The construction of a holistic risk-based approach framework that is suitable and sustainable is required to identify and filter risk for cleanroom, utility, and product testing.

Developing a GMP Compliant Culture

Investing in education and training programs is vital to support in the development of a GMP compliant culture.

Training procedures not only ensure that personnel have the knowledge to perform their essential job function, but they also create opportunities for feedback on compliance barriers, knowledge gaps, or misunderstandings about procedures. A blended training program of job-specific training, compliance, best practices, and refresher courses should be provided regularly. At a site level, the extent and frequency of such training will differ depending upon the level of participation in the pharmaceutical manufacturing industry.

The guidance set by Annex 1 is aimed principally at promoting and ensuring manufacturing processes are rigorously set and monitored.

Moving from Annex 2009 to Annex 2023: 7 Key Considerations

Support the collective knowledge management efforts to improve and update codified knowledge found in documents and databases.

A gap analysis of changes between different versions of the Annex 1 should be performed at a site level ensuring QRM is included in all aspects of the manufacturing process.

Sites with the current barrier technologies (Isolator and RABS) will require process improvements to meet new requirements.

Cleanroom process and practices, such as gowning, may require changes depending on the previous interpretation and implementation of the Annex 1 requirements.

Cleanroom operators should receive aseptic training, gowning qualifications, and assessment on the relevant manufacturing processes regularly. Additionally, all personnel entering cleanrooms should have access to training in hygiene, cleanroom best practices with summative assessments.

Evaluate the impact of the Annex 1 changes to the aspects of the CCS with an ongoing periodic review view of the PQS.

Assessment of cleanroom design, qualification, and validation as they relate the personnel and material flow to ensure current practices meet new requirements.

Conclusion

Beyond these key considerations, manufacturers will need to take a comprehensive and risk-based approach to evaluating their current processes and understanding what changes will need to be made to remain compliant with EU Annex 1.

This will likely require education, training, and a complete gap analysis of the current manufacturing processes. Determining what modifications are needed to keep the manufacturing processes compliant with EU Annex 1 while staying on top of other evolving regulations can be a challenge for most manufacturers – which is why many find it helpful to partner with an advisory & consulting firm that specializes in GMP compliance to help them navigate the ever-changing regulatory environment.

About the Author: Brandon Cuffee

Brandon Cuffee is a bio-pharmaceutical specialist with 10 years of experience in QualityControl (QC), GxP (GDP/GLP/GMP) manufacturing support and laboratory techniques/technologies in the field of microbiology.

He has vast experience in Environmental Monitoring, Utility Sampling, Aseptic Techniques, and Microbiology Assays. Brandon is a technical writer for risk assessment reports, protocols, marketing, regulatory affairs, teaching and education. Brandon is currently a Quality Control Consultant for Azzur Group.

About Azzur Group

From Discovery to Delivery™, Azzur Group provides the life science community full life-cycle solutions for all of their GxP needs.

From Azzur Cleanrooms on Demand™ facilities, to our labs, training centers, and consulting offices across the nation, Azzur Group helps organizations start, scale, and sustain their growing enterprises. With nearly four decades of service to the life science community, we have become a trusted partner to the world's leading pharmaceutical, biotechnology, medical device, and healthcare companies, as well as their supply chain.

For assistance in understanding what modifications will need to be made to keep manufacturing processes compliant with EU Annex 1, Azzur Group's nationwide network of engineers and consultants are available to provide advisory services specifically geared for the complexities of life science.

Learn more about Azzur's GxP Advisory and Consulting Services here.

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