It's Almost Here: August 25th, 2023
Are You Ready for EU GMP Annex 1?

Annex 1 "Manufacture of Sterile Medicinal Products" was first published in 1971, providing specific guidance on the minimum controls required to ensure sterility of medicinal products during manufacture. In December 2017, the initial draft of the first ever full revision of Annex 1 was published for public consultation, which ran from 20 December 2017 to 20 March 2018 and received 6200 lines of comments. Based on that overwhelming response, an updated draft was published in February 2020, followed by a second targeted consultation process, and the revised Annex 1 was finally published by the European Commission on 25 August 2022, its aim being 'to add clarity, introduce the principles of Quality Risk Management to allow for the inclusion of new technologies and innovative processes and to change the structure to a more logical flow.'[1]

Which Countries Are Affected by Annex 1?

Annex 1 covers manufacturing, packaging and distribution and applies to all sterile medicinal products manufactured in the European Union and the UK. It also applies to those manufactured in all other parts of the world, in the Unites States for example, that are intended for export into the EU and UK. The new Annex is the product of a truly international collaboration between the EC, EMA, WHO, and PIC/S. If your organisation is not in the EU/UK the revised Annex 1 to the PIC/S GMP Guide is published by PIC/S, which has over fifty regulators as part of the scheme.[2] The FDA has also been heavily involved and will train their inspectors on the revised Annex.[3] The Annex will not only be accepted by the EMA but by PIC/S too, of which the FDA is a member.

What Are the Core Requirements of Annex 1?

The revised Annex focuses strongly on the use of modern, pro-active quality risk management (QRM) through an extensive, holistic, facility-wide contamination control strategy (CCS) to 'establish and maintain a state of control'[4] and facilitate improvement: 'Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.'[5]

The new Annex requires that organisations involved in the manufacture, packaging and distribution of sterile medicinal products have a comprehensive, all-inclusive contamination control strategy in place that assesses the efficacy of measures employed throughout its processes and facilities, and that the CSS is actively updated

to drive ongoing improvement. Monitoring must take place throughout the manufacturing, packaging and distribution process, including the setup time, to minimise the risk of microbial, particulate and pyrogen contamination; rapid cubic metre sampling will no longer suffice. The Annex specifies that: 'A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety.'[6]

What Happens Next?

The new Annex 1 standards will enter into force on 25 August 2023 (except for Chapter 8.123 'Product transfer / loading/unloading areas for lyophilizers', which is postponed until 25 August 2024), and new provisions need to have been put in place and tested by that deadline. Obviously, the requirements of the new Annex will need to be incorporated into any new construction or process. An examination of all preexisting sites and processes will need to be undertaken, with remedies being put in place where necessary to render all parts of the organisation Annex 1 compliant. Acting sooner rather than later will enable your organisation to continue operating as usual while infrastructure and process updates takes place; failure to act may leave your organisation without the necessary time to make the required changes, impacting its ability to continue production or distribution. And don't forget that a core element of the CCS is ongoing improvement based on continuous monitoring; the CSS is not a one-time event.

Annex 1 compliance is a legal requirement for continued manufacture and distribution of sterile medicinal products from the 25 August 2023 deadline. Non-compliance will bring your organisation's operations to a costly and highly disruptive halt. If you have questions about the new Annex 1 requirements and what your organisation needs to do to be compliant, or you are concerned about how regulatory authorities may enforce the requirements, please get in touch. You can schedule a call through this link.

Notes:

[1] Health and Food Safety Directorate General, European Commission. *Second targeted stakeholders' consultation on the revision of Annex 1, on manufacturing of sterile medicinal products, of Eudralex volume 4*.
https://health.ec.europa.eu/consultations/second-targeted-stakeholders-consultation-revision-annex-1-manufacturing-sterile-medicinal-products_en

[2] The Pharmaceutical Inspection Co-operation Scheme (PIC/S) (2022). *Revised Annex 1 (Manufacture of Sterile Medicinal Products) to Guide to Good Manufacturing Practice for Medicinal Products*.

Website: https://picscheme.org/ Publication: https://picscheme.org/docview/4737

[3] The International Society for Pharmaceutical Engineering. *Regulatory Panel Discussions: Annex 1 Implementation from the Regulators' Point of View.* https://ispe.org/pharmaceutical-engineering/ispeak/regulatory-panel-discussions-annex-1-implementation-regulators

[4] European Medicines Agency and Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme., *Concept paper on the revision of annex 1 of the guidelines on good manufacturing practice – manufacture of sterile medicinal products.* https://www.ema.europa.eu/en/documents/scientific-guideline/concept-paper-revision-annex-1-guidelines-good-manufacturing-practice-manufacture-sterile-medicinal_en.pdf

[5] European Commission. *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. Annex 1: Manufacture of Sterile Medicinal Products. 2.2* https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf

[6] Ibid., *2.3*
