Top 10 Revisions in the EC Annex 1 (2020): A Harmonization of Global Sterile Filling

WITH DALTON

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Company Vision

"To make the impossible possible, Dalton Pharma Services uses its scientific and pharmaceutical expertise to bring customer ideas to life. We develop their new drug products, optimize the synthesis of therapeutic candidates, and manufacture them at the highest level of quality."

Disclaimer

This technical report is intended to provide information to quality and regulatory correspondents on the 2020 revisions of *Annex 1: Manufacture of Sterile Medicinal Products*. This technical report should be read in conjunction with the relevant laws, regulations, and guidance's that apply to your situation.

FDA inspected, HC approved, & MRA with EMA

ANNEX 1 REVISION

A **full revision** of the current EU GMP Annex 1, Manufacture of Sterile Medicinal Products has been proposed and is currently under revision by the EMA Inspector Working Group. The intended goal is to organize and structure requirements into ten distinct sections as well as provide extra detail on many of the current requirements. The latest version of Annex 1 is one of the **most anticipated** regulatory guidance documents issued in the past several years.

REASONS FOR THE REVISION

- Since the initial edition was published in 1971, there have been multiple modifications with partial revisions made in 1996, 2003, and 2007 to align on cleanroom categorization, and provide recommendations on medium simulations, bioburden monitoring, and vial capping. However, the document was never fully revised, thus remained outdated.
- In December 2017, a first draft of the new *EU GMP Annex 1* was proposed to add clarity, introduce principles of Quality Risk Management (QRM) to allow for the inclusion of novel technology and innovative processes, and to change the structure to a more logical flow.
- The first targeted consultation opened in December 2017 to March 2018 and the second targeted consultation occurred from February 2020 to July 2020. Since then, around 6000 comments were submitted from 140 firms and organizations, such as PDA (Parenteral Drug Association) and ISPE (International Society for Pharmaceutical Engineering), demonstrating a substantial interest from all key stakeholders involved in sterile manufacturing.
- Substantial modifications have been introduced after each consultation. Currently, the annex is yet to be finalized by national and international experts MA, PIC/S, WHO, and even the US FDA which are all involved in the revision process.
- The key changes will be discussed in the next couple of pages.

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INCREASED SCOPE

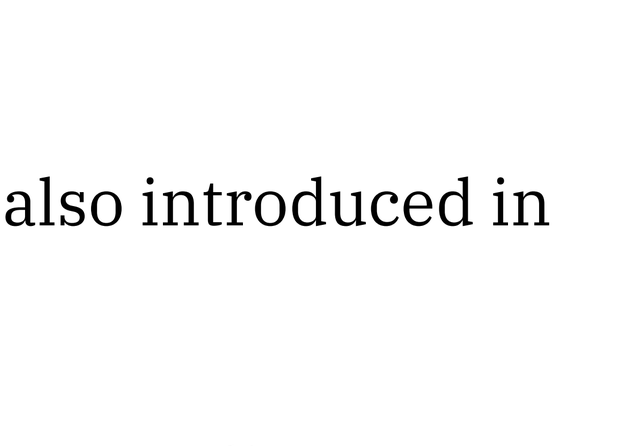
Section 1 & 2

The scope was expanded to include non-sterile products where contamination control principles could be applied. Specifically, contamination control strategies, room qualification, classification, monitoring, and owning may be used to support the production of non-sterile products (such as certain liquids, creams, ointments, and low bioburden biological intermediates) where microbial, particulate, and pyrogen contamination is a concern.

Contamination control principles should be used in conjugation with quality risk management (QRM) principles in a way that is tailored to these products. Section 2 provides greater detail.

More detailed personnel requirements are also introduced in section 1 and 2.

- Implementation of specific requirements regarding personnel, such as strong knowledge and expertise through adapted training, in conjunction with reinforced monitoring and gowning requirements.
- Sterile product manufacturing processes and monitoring systems must be designed, commissioned, qualified, and monitored by personnel with relevant process, engineering, and **microbiological** competence.



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INTRODUCTION OF CONTAMINATION CONTROL STRATEGY (CCS) & QUALITY RISK MANAGEMENT (QRM)

Section 1 & 2

- **CCS and QRM is the core element of the revised Annex 1.** Both CCS and QRM are not only based on good design for testing and monitoring, but also on good design for **equipment**, **facility**, and **processes**.

- QRM is in particular, a proactive means of preventing microbial, particulate, and pyrogen contamination associated with microbes. **It should be applied throughout the lifecycle of a medicinal product.** In conjugation with CCS, this means that each process and product should be evaluated to identify all critical control points, encompassing viable (microbial) and non-viable (pyrogen as well as other potential particulate matter such as glass, visible and subvisible) contamination concerns.

- The requirement for a CCS is expected to be the driver for the development of a documented strategy to contamination control that takes a holistic approach by taking into account the interaction of technical, organizational, and procedural contamination control measures. **Documentation should include modern methods**. In addition, the CCS is intended to be a dynamic process, and the amended draft mentions periodic reviews. A periodic review usually indicates an annual recurrence, meant to ensure that the strategy continues to work.

- NOTE: QRM adopts ICH Q8, Q9, and Q10 guidelines on pharmaceutical development, risk management, and pharmaceutical quality systems.

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INTRODUCTION TO PHARMACEUTICAL QUALITY SYSTEM (PQS)

Section 3

- PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that microbial, particulate and pyrogen contamination is minimized in sterile products

- Investigations should be performed when there are non-conformities, such as sterility test failures or environmental monitoring excursions or deviations from established procedures. Investigations should lean towards a specific focus regarding the potential impact to sterility. These investigation should also be performed to **not only the specific batch concerned but any other potentially impacted batch**.

DID YOU KNOW?

The highest number of observed inspection deficiencies are attributed to inadequacies of the PQS and documentation of events and investigations.

*At Dalton **quality control** and **contamination control** is our top priority to ensure strict regulatory standards for sterile and non-sterile pharmaceutical manufacturing are met. Contact us now for contract drug development and manufacturing services for early-stage clinical research/development through to commercializataion.*

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INTRODUCTION OF NOVEL TECHNOLOGY

Section 4

The use of novel barrier technologies, such as limited access barrier systems (RABS) and isolators, should be considered as part of the CCS.

TITLE CHANGE: CLEANING & DISINFECTION

Section 5

The word sanitization has been replaced with the word cleaning and disinfection.

UTILITY TREND ANALYSIS

Section 7

High risk utilities (i.e., water utilities) should be subject to **regular trend analysis**. For clarity, guidance documentation have been created for the production of water for injections.

NEW SECTIONS: FORM-FILL-SEAL, CLOSED SYSTEMS, & SINGLE-USE SYSTEMS (SUS)

Section 8

- For form fill seal operation, routine monitoring is required.
- For closed systems, manufacturers should ensure the system has been designed to minimise the number of manual interventions and that the system is able to maintain sterility.
- For SUS, companies need to ensure that if the sterilisation steps are being conducted by a 3rd party the controls and validation meet the manufacturers own sterilisation policies.

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DETAILED MEASURES AROUND ASEPTIC PROCESS SIMULATIONS (APS)

Section 9

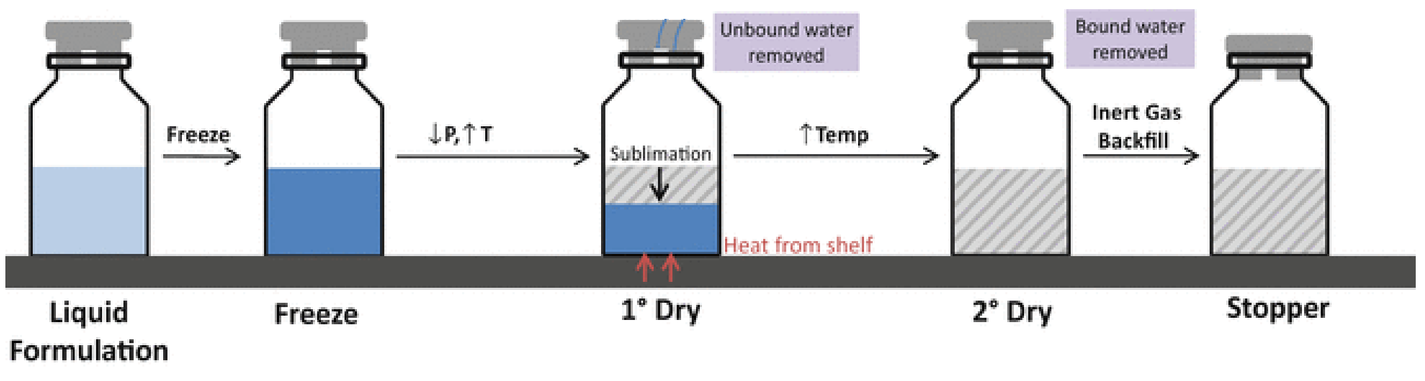
- The environmental and process monitoring program at the site is part of the overall contamination control strategy aimed at reducing the risk of microbiological and particle contamination. The following elements are usually included in this program:

  i. Environmental monitoring - nonviable
  ii. Environmental monitoring - viable
  iii. Aseptic process simulation (aseptically manufactured product only)

- Manufacturers must continue to reflect the worst-case operating conditions in APS; what's new is that the revision includes an element allowing for the use of surrogate materials – something that is not typically seen.

- Section 9 also provides more specific expectations for lyophilization evaluation. In particular, there is now more detail around loading, unloading, and requirements for chamber dwell time. Manufacturers are also now required to replicate the maximum time between sterilization and lyophilization, as well as the maximum hold times post-sterilization and lyophilization.

Lyophilization process:



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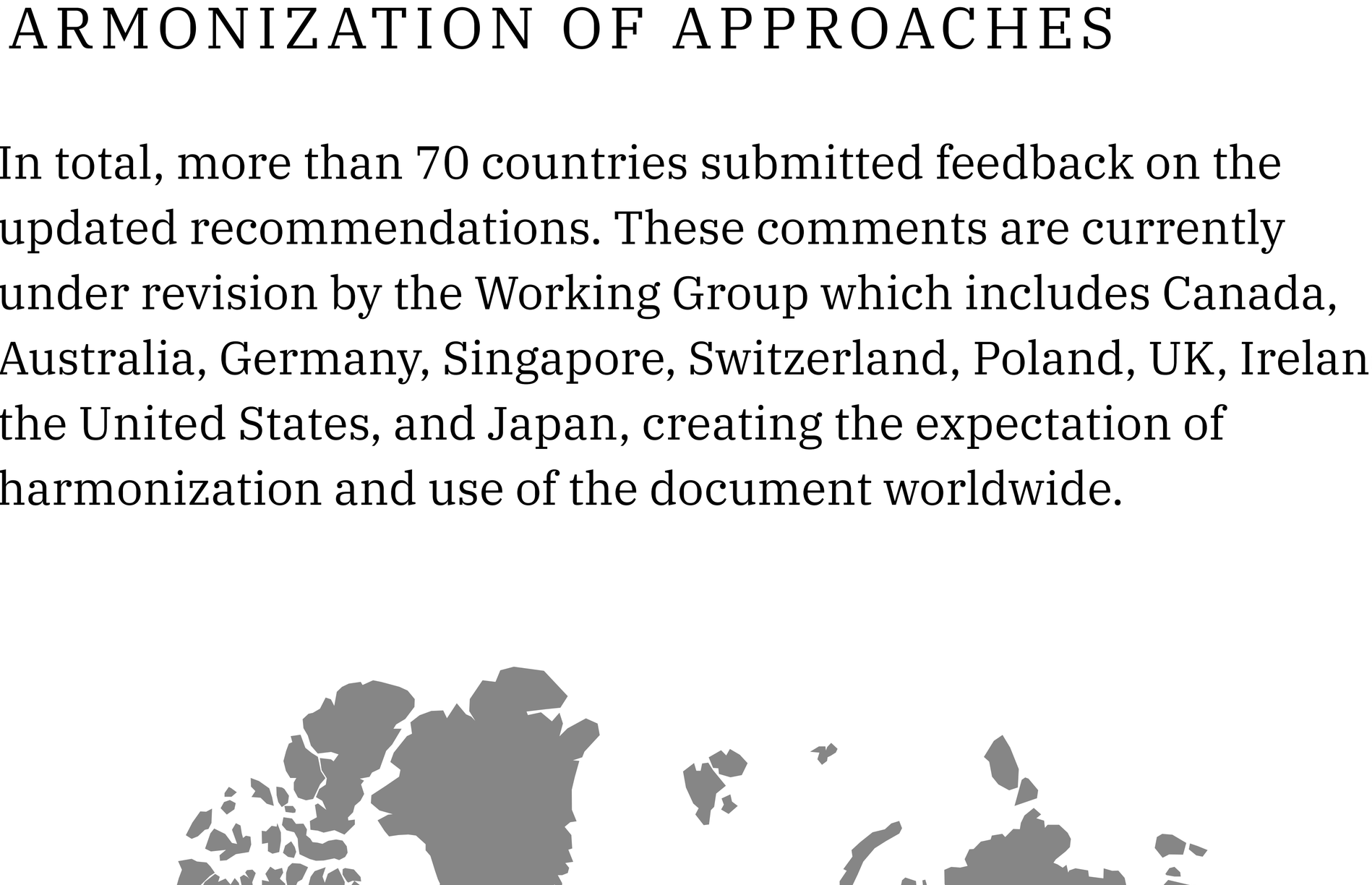
QUALITY CONTROL

Section 10

- The **sterility test** applied to the finished product should **only** be regarded **as the last in a series of control measures** by which sterility is assured. The test should be validated for the product(s) concerned.

HARMONIZATION OF APPROACHES

In total, more than 70 countries submitted feedback on the updated recommendations. These comments are currently under revision by the Working Group which includes Canada, Australia, Germany, Singapore, Switzerland, Poland, UK, Ireland, the United States, and Japan, creating the expectation of harmonization and use of the document worldwide.



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CHALLENGES

Although the draft Annex 1 is viewed as a significant step forward in providing a comprehensive set of detailed requirements for the manufacturing of sterile products, some of the new requirements proposed, offer substantial challenges to the industry and its ability to manufacture products. Key areas of concern are addressed below:

- The new CSS approach necessitates a periodic review of each risk assessment that was initially raised, as well as the execution of a new review of data and trends provided by essential systems or equipment in the CCS.
- New barrier technologies: we can observe that a high emphasis was placed on the use of new technologies to reduce the dangers of potential contamination. However, the technology to achieve such requirements does not yet exist.
- Due to the vast geographical scope of this guidance document, there is a need to clarify the intent of and harmonise the language in the Annex to mitigate potential misconceptions.
- Clarity on the use of prescriptive requirements versus examples is required. Examples may be misinterpreted by regulators as prescriptive requirements, which may limit or constrain present and future inventive approaches.

TIMELINE

The EMA has not provided an official date for the amended Annex's final publication. Although it is expected soon, it is important to note that the COVID-19 crisis has led to supply change disruptions and redeployment of focus, which may lead to longer waiting times for the final Annex 1 to be released. However, once released, it is expected that after the revision is published, EMA will communicate the planned implementation timelines. As of right now, the timeline for industry to come into compliance with the new requirements is anticipated to be within an implementation period of around 1-3 years. This implementation period reflects the time required to modify facilities/equipment, purchase/install equipment, develop and deliver training to ensure procedural control measures are followed, among others. To view the implementation timing proposed by PDA, click here.

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WHAT'S NEXT & QUESTIONS TO ASK

YOUR NEXT STEPS?

If you have not already done so, it is recommended you begin looking at the revised Annex 1 draft. While modifications between the draft and the final edition are to be expected, the draft provides valuable insight into the concepts and expectations being explored for the next version. **Keep in mind that the latest draft may change again following the seccond consultation period.**

In the meantime, you can ask yourself the following:

1 Are your current microbiological controls for your nonsterile products in line with proposed requirements?

2 Are you confident in your validation program for disinfection?

3 How many of your microbiologists are actively involved in the manufacturing process?

4 Are you planning to implement the modern methods for the most effective Contamination Control Strategy (CCS) in your facility?

5 Are you analyzing the trend of your utilities?

Dalton's Services

At Dalton, we offer both contract drug development and manufacturing services ranging from early-stage research and development through to developing material for both clinical trials and commercial production. As a CDMO, we enhance our customers production efforts through expertise from highly qualified chemists and researchers to accelerate the end-to-end process, while ensuring regulatory standards are met throughout. Given that Dalton is Health Canada approved and an FDA inspected facility, **quality control** and **contaminataion control** is essential to meeting these strict regulatory standards for pharmaceutical manufacturing.

We deliver fully integrated solutions with emphasis on speed, flexibility, and quality.

We are experts in:

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- Formulation Development
- API Process Development
- Sterile Filling Services
- Accelerated Stability

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References

EC. EU GMP Annex 1 Manufacture of Sterile Medicinal Products - Revision. (2008). European Commission. https://www.gmp-compliance.org/files/guidemgr/annex%2001[2008].pdf

EC. EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft). (2020). European Commission. https://www.gmp-compliance.org/files/guidemgr/2020_annex1ps_sterile_medicinal_products_en.pdf

Pharma Tech. (2020). Unlocking the Key Changes to Annex 1. https://www.pharmtech.com/view/unlocking-the-key-changes-to-annex-1

Pharma Tech. (2021). Considering Annex 1 Revisions: Expert Insights. https://www.pharmtech.com/view/considering-annex-1-revisions-expert-insights

PDA. Joint Letter RE: Annex 1 Revision: Manufacture of Sterile Medicinal Products. (2020a). Parenteral Drug Association. https://www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/regulatory-comments-resources/2020/pda-comments-to-ema-annex-1-revision---manufacture-of-sterile-medicinal-products-13-jul-2020.pdf?sfvrsn=56cb6281_8

PDA. ANNEX 1 Revision Task Force Update. (2020b). Parenteral Drug Association. https://www.pda.org/pda-letter-portal/home/full-article/annex-1-revision-task-force-update

PDA. Joint Letter RE: Implementation Timing of Annex 1 Revision. (2021a). Parenteral Drug Association. https://www.pda.org/docs/default-source/website-document-library/scientific-and-regulatory-affairs/annex1/letter-regarding-implementation-timing-of-annex-1-draft-14-march-2021.pdf

PDA. Joint Associations' Response Letter on EU Annex 1 Draft. (2021b). Parenteral Drug Association. https://www.pda.org/pda-letter-portal/home/full-article/joint-associations-response-letter-on-eu-annex-1-draft

PDA. Annex 1 and the New Revision — Setting New Expectations. (2021c). Parenteral Drug Association. https://www.pda.org/pda-letter-portal/home/full-article/annex-1-and-the-new-revision-setting-new-expectations

Lucia Ceresa, PhD, Senior European Product Specialist, Charles River. Understanding the EU GMP Annex 1 Revisions. https://www.criver.com/about-us/wbr-ms-understanding-eu-gmp-annex-1-revisions

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