Annex 1 and the new revision

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GDP/GMP/ATMP - keskustelutilaisuus

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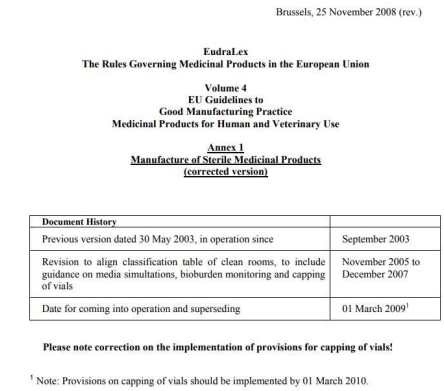


Brussels, 25 November 2008 (rev.)

EudraLex
The Rules Governing Medicinal Products in the European Union

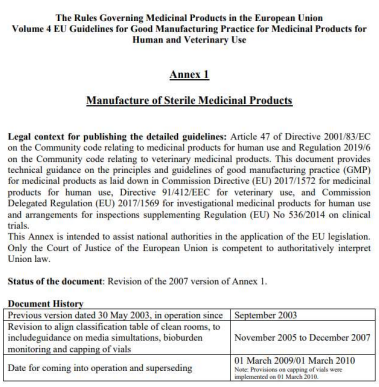
Volume 4
EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Annex 1
Manufacture of Sterile Medicinal Products
(corrected version)

Document History	
Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to include guidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009[1]

Please note correction on the implementation of provisions for capping of vials!

[1] Note: Provisions on capping of vials should be implemented by 01 March 2010.



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

Legal context for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation 2019/6 on the Community code relating to veterinary medicinal products. This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Commission Directive (EU) 2017/1572 for medicinal products for human use, Directive 91/412/EEC for veterinary use, and Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products for human use and arrangements for inspections supplementing Regulation (EU) No 536/2014 on clinical trials.
This Annex is intended to assist national authorities in the application of the EU legislation. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Status of the document: Revision of the 2007 version of Annex 1.

Document History

Previous version dated 30 May 2003, in operation since	September 2003
Revision to align classification table of clean rooms, to includeguidance on media simultations, bioburden monitoring and capping of vials	November 2005 to December 2007
Date for coming into operation and superseding	01 March 2009/01 March 2010 Note: Provisions on capping of vials were implemented on 01 March 2010.

Reason for revision

- The original version (1992) was partially revised in 1996, 2003 and 2007
- No complete review of the document since it was originally issued
- Changes in technologies
- Significant changes in GMP following the adoption of the ICH Q9 (QRM) and Q10 (PQS) guidelines
- Contains historical inaccuracies and areas of ambiguity

- ➢ To facilitate implementation of the principles of the ICH guidelines
- ➢ To extend the underlying concepts to include new areas of technology/innovative processes and processing not previously covered
- ➢ To clarify areas that have been highlighted as ambiguous due to the age of the document

Annex 1 timeline

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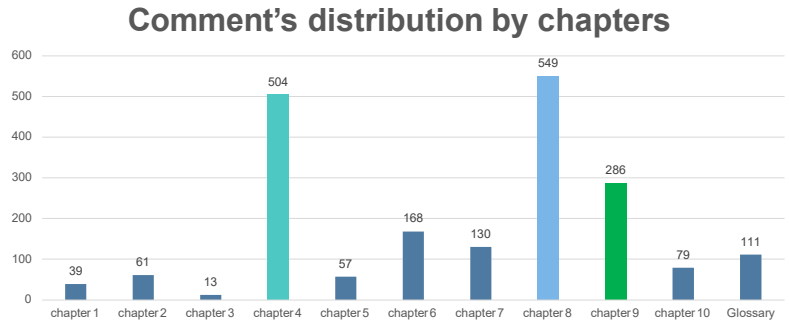
Comments received on the draft (2020)



1. Scope
2. Principle
3. Pharmaceutical Quality System
4. **Premises**
5. Equipment
6. Utilities
7. Personnel
8. **Production and specific technologies**
9. **Environmental and process monitoring**
10. Quality control
11. Glossary

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Changes between 2020 (draft) and 2022

- Basic structure of Annex 1 has remained unchanged:
  - scope, principles, PQS, premises, equipment, utilities, personnel, production and specific technologies, environmental and process monitoring (instead of viable and non-viable environmental and process monitoring), QC, glossary
- More comprehensive, the number of pages from 52 to 58 (current 16 pages)
- The subchapter ”Barrier technologies” in the chapter ”Premises” more detailed
- The topics of background environment, gloves and decontamination methods have been dealt with separately for isolators and RABS
- The subchapter ”Form-Fill-Seal” and ”Blow-Fill-Seal” in the chapter ”Production and Specific Technologies” more detailed
- In addition, there are furher deletions, summaries and new insertions in many chapters as well as rewordings

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Implementation

- The final version of the revised Annex 1 was published on August 25, 2022, seven years after the revision process started
- 1 year implementation (25 August 2023), except for 2 years (25 August 2024) for Chapter 8.123:

  Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS
- Adopted also by PIC/S and WHO

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Annex 1 – the new revision – some highlights

- Restructured to give more logical flow
- Added detail to several sections to provide further clarity
- Risk management principles added: why certain premises/equipment/process/ environmental controls have been chosen
  - Some keywords demonstrated the increased usage of certain terms, like ”risk” can be found 124 times compared to 20 times before
  - Microbial now present 67 times compares to 12 counts previously
- New manufacturing technologies – RABS, FFS, BFS, lyophilization, SUS
- Process and personnel separated (barrier technologies)
  - Personnel – training, capability and gowning
- Contamination Control Strategy

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Section 1: Scope

- General guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products
  - ➢ To ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product
- QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs
- Some of the principles and guidance may be used to support the manufacture of other products that are not intended to be sterile such as
  - Certain liquids, creams, ointments and low bioburden biological intermediates
    - ➢ where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important

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Section 2: Principles

- Minimize risks of microbial, particulate and endotoxin contamination
- Key areas:
  - Facility, equipment, process
  - Personnel
  - Raw materials and packaging materials
  - Contamination Control Strategy (CCS)

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Section 3: PQS

General attributes described in chapter 1 of Eudralex volume 4 Part 1

- Highlights the specific requirements of the PQS when applied to sterile products
- To ensure that all activities are effectively controlled, resulting in reduced contamination in sterile products

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Section 4: Premises

- RABS and isolators encouraged
  - Other options can be used as long as justified within the CCS
  - More details are given in the “Barrier Technologies” section on RABS, isolators and gloves
- Unidirectional process for the transfer of materials, equipment and components into the grade A/B areas
- Items which cannot be sterilised – effective and validated disinfection and transfer process + protection of recontamination
- The use of separate change rooms for entering and leaving the grade B area is desirable
- Air visualization studies clarified
  - Requirement to record the studies (video)
- More detail regarding clean room qualification tests (in line with ISO 14644)
  - CCS and historical data for decision for monitoring ≥ 5 µm particles
- Requirements regarding the disinfection of premises
  - Need to establish a cleaning and disinfection written program (and to monitor its effectiveness) and the need to validate the disinfection process
  - Disinfection should include periodic use of a sporicidal agent
  - Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS

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Section 5: Equipment

- General guidance on the design, qualification, cleaning and operation of equipment
- For aseptic processes, direct (e.g. filling needles or pumps) and indirect (e.g. stopper bowl) product contact parts to be sterilised
- Particle counter, sampling tube specification

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Section 6: Utilities

- Special requirements of utilities e.g.
  - qualification
  - trend analysis for critical parameters and critical quality attributes of high risk utilities
- Sub-chapters for water, steam, gases and vacuum systems
  - Includes WFI generated from reverse osmosis and discusses minimizing biofilms
  - Gases in aseptic process to be filtered, filter integrity test, microbial monitoring periodically at the point of use

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Section 7: Personnel

- Requirements for specific training, knowledge and skills
- Guidance to the qualification and disqualification of personnel
- Compliance with aseptic gowning procedures to be assessed at least annually
- Special requirements for gowning and cleanroom clothing e.g.
  - Visual integrity check at entry/exit
  - Sterilization checks for garments and goggles
  - Dedicated undergarments (under sterile suit)
  - Sterile eye coverings (e.g. goggles)
  - Folded for optimal gowning – no contact with outer surface and the floor
  - Undergarments with long sleeves and legs (facility socks) – grade C and D
  - Maximum wearing period to be defined as part of garment qualification
  - Garment qualification to include a maximum number of laundry and sterilisation cycles
- Only clean room approved electronic devices (designed to permit cleaning & disinfection)

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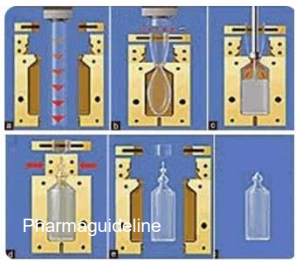
Section 8: Production and specific technologies

- Terminally sterilised products
- Aseptic preparation and processing
- Finishing of sterile products
- Sterilisation – heat, moist heat, dry heat, radiation, ethylene oxide, sterile filtration
- Form-Fill Seal (FFS)
- Lyophilization
- Blow-Fill-Seal (BFS)
- Closed systems
- Single use systems (SUS)



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Section 9: Environmental & process monitoring

- Design of the EM program specified
  - Total particle
  - Viable particle (environment & personnel)
  - Temperture & humidity
  - APS
  - Trending
- Maximum total particle and viable action limits specified, but more stringent action limits may be applied
  - Alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data
  - Limits (viable) for grade A monitoring: ”no growth”
- Monitoring of personnel assessed by risk assessment
- Guidance on the requirements of APS
  - Factors to be considered when developing the APS plan
  - Used filling volume per container justified, use of air, incubation start asap, local isolates

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Section 10: QC

- Gives guidance on some of the specific QC requirements relating to sterile products
- Appropriate training and knowledge to support design and manufacture
- Media - Growth promotion test
  - suitably representative isolates (environmental monitoring & APS)
  - by end user

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Contamination Control Strategy, CCS

- Like a Site Master File (SMF), which provides an overview of the facility, the CCS document should
  - ➢ provide an overview of the totality of contamination control measures and their linkage to an overall strategy
- The development of the CCS requires thorough technical and process knowledge:
  - All potential sources of contamination should be identified
  - Critical control points should be acknowledged (robust risk assessments)
- The effectivness of the implemented controls (design, procedural, technical and organizational) should be monitored, assessed, investigated and trended
- The CCS should be periodically reviewed and updated as appropriate in order to drive continuous improvement

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CCS – periodic review

The frequency of a periodic CCS review depends on several variables that the manufacturers have to identify, for example:

- Change in the process; the change control should trigger the review of the existing risk assessments where necessary
- Deviations that may conclude that the contamination program in place is lacking and trigger the review of existing risk assessments where necessary
- Introduction of new equipment, a new product that would lead to the creation or review of existing risk assessments
- Results from routine data trending and analysis that indicate a potential gap in the CCS

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CCS- Proposed elements to consider

i. Design of both the plant and processes including the associated documentation
ii. Premises and equipment
iii. Personnel
iv. Utilities
v. Raw material controls
vi. Product containers and closures
vii. Vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers
viii. Management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services
ix. Process risk management

x. Process validation
ix. Validation of sterilisation processes
xii. Preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination
xiii. Cleaning and disinfection
xiv. Monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination
xv. Prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools
xvi. Continuous improvement based on information derived from the above

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CCS

The CCS document to contain or referred to e.g.:

- Risk Assessments / Risk Analyses
- Qualification and Validation reports
- Maintenance/calibration programs
- Monitoring and control plans (e.g., IPC, QC release instructions)
- SOPs / policies / working instructions, etc.
- Master batch records, specifications
- Trending results and reports
- Complaint management and complaints related to potential contamination during manufacturing, e.g., foreign particulates

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Summary

The entirety of measures to achieve the intent of Annex 1 can be summarized as the

Contamination Control Strategy

"*Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.*"

Manufacturers should design their production facilities, equipment, and processes and implement Quality Risk Management (QRM) to ensure appropriate contamination control to minimize or detect contamination

Intent of Annex 1 can be understood as the adequate approach to ensure

- Sterility Assurance
- Bioburden control / low bioburden
- Pyrogen / endotoxin control
- Control of foreign particulate matter

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Kysymyksiä:

Missä määrin Annex 1 on noudatettava non-sterile valmistuksessa?

Annex 1 uudet pukeutumisohjeet: Voiko steriilin B-tilan haalarin pukea C-tilan haalarin päälle? Jos henkilöliikenne kulkee C-tilasta B-tilan henkilösulkuun ilman erillistä pukuhuonetta, jossa C-tilan haalari ensin riisuttaisiin, olisi C-tilan haalarin päälle laitettava steriili B-tilan haalari.

Miten toimitaan sopimusvalmistajien kanssa, jos he eivät pysty implementoimaan Annex 1 uusia vaatimuksia annetuissa aikatauluissa. Suomen QP varmistaa erän sertifioinnissa, että valmistus on tehty EU GMP guiden mukaan. Voidaanko riskiarviointia käyttää ao. tapauksissa, kun ei olla täysin Annex 1 komplianssissa ?

Odotettavissa olevia asioita Annex 1 myötä

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Kiitos!

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