Microbial Contamination and Control Conference

Aseptic Processing - A Standards Update

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Today's Presentation

- **Main Topic: ISO 13408-1:2023**
  - What it is and its related standards (brief overview)
  - Previous editions
  - Development of this (2023) standard
  - Key points
- **Other aseptic processing standards**
  - Comparisons on key points?

Aseptic processing

- "Handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials, equipment and personnel are regulated to maintain sterility." (ISO 11139:2018)

- "The handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials, equipment and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination." (EU GMP Annex 1)

Genesis of ISO 13408-1

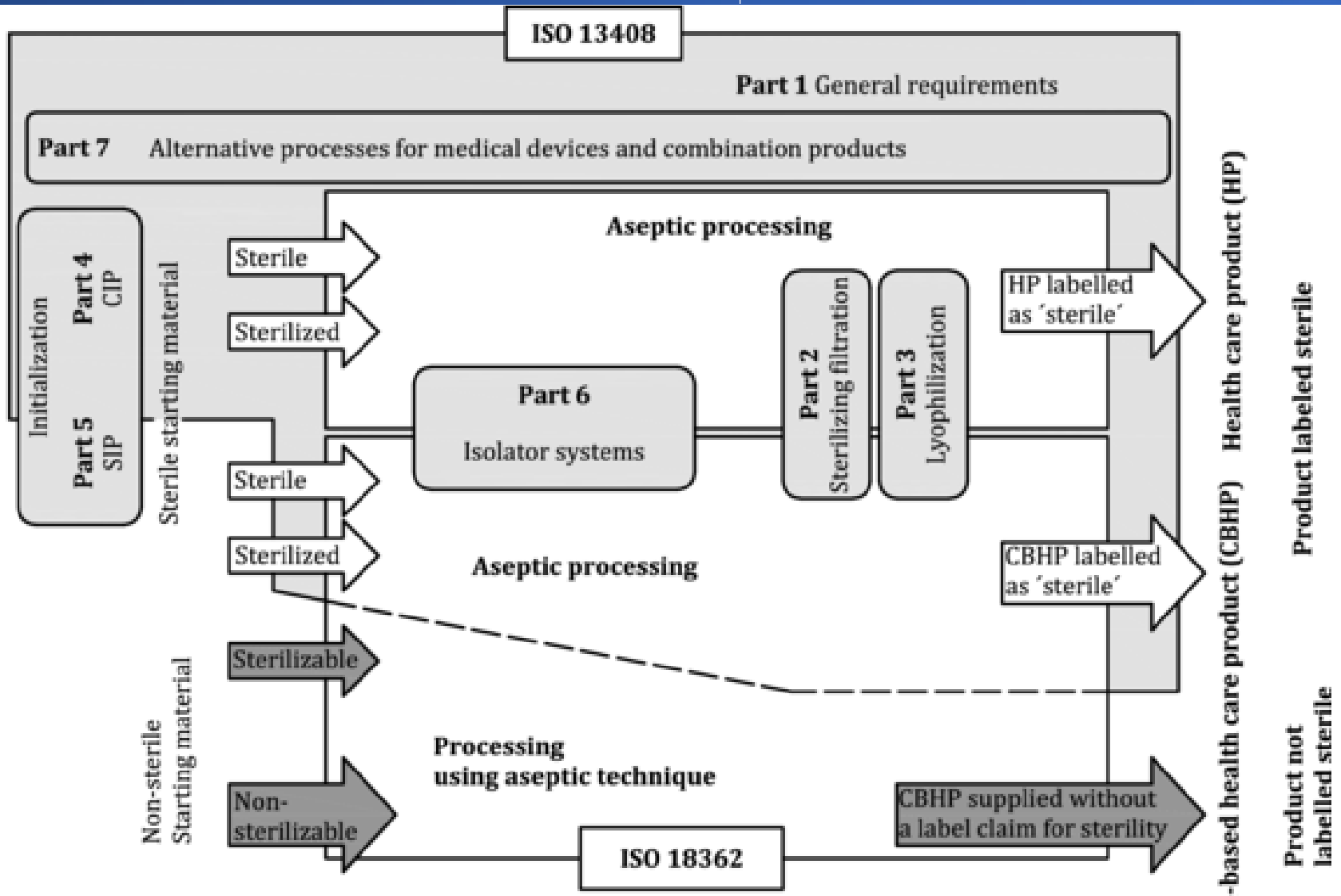
- ISO/TC 198 – Sterilization of health care products
- WG 9 – Aseptic processing
- First edition published in 1998
- Second edition: 2008
- Third edition: 2023
- Full title: *Aseptic processing of health care products – Part 1: General requirements*

ISO Technical Committee 198

- Sterilization of health care products
  - Scope: Standardization of processes and equipment for sterilization of health care products.
- Develops international voluntary consensus standards that specify requirements for:
  - Cleaning, disinfecting, sterilizing and aseptic processing of health care products (HCPs)
  - Associated equipment and ancillary products used in ensuring effective application of these processes
- Published 67 standards/technical specifications (15 under development):
  - Applicable to industrial and health care facility processes
- 34 'P' (participating) members
- 21 'O' (observer) members

Standards by ISO/TC 198 WG9 – Aseptic Processing

- ISO 13408-1:2023 – General Requirements
- ISO 13408-2:2018 – Sterilizing Filtration
- ISO 13408-3:2006 – Lyophilization
- ISO 13408-4:2005 – Clean-in-place technologies
- ISO 13408-5:2006 – Sterilization in place
- ISO 13408-6:2021 – Isolator systems
- ISO 13408-7:2012 – Alternative processes for medical devices and combination products
- ISO 18362:2016 - Manufacture of cell-based health care products — Control of microbial risks during processing


ISO 13408
Part 1 General requirements
Part 7 Alternative processes for medical devices and combination products
Initialization
Part 4 CIP
Part 5 SIP
Sterile starting material
Aseptic processing
Sterile
Sterilized
Part 6
Isolator systems
Part 2 Sterilizing filtration
Part 3 Lyophilization
HP labelled as ´sterile´
Health care product (HP)
Product labeled sterile
Sterile
Sterilized
Aseptic processing
CBHP labelled as ´sterile´
Cell-based health care product (CBHP)
Sterilizable
Non-sterile Starting material
Processing using aseptic technique
Non-sterilizable
CBHP supplied without a label claim for sterility
Product not labelled sterile
ISO 18362

Standards development timeline

- ISO 13408-1:2008 underwent Systematic Review in 2012
  - Passed, but revision suggested
    - Amendment; comments submitted
- US Sub-TAG (AAMI Sterilization Standards Committee WG9) started review in Q4 2012
  - Focused on Clauses
    - 5.2 – Risk Management
    - 6 – Manufacturing Environment
    - 10 – Process Simulation
- Initial discussion with ISO WG9 in January 2013 (virtual) but presented in May 2013 (Vienna)

Revision of ISO 13408-1

KEY OBJECTIVES

- Inclusion of science and risk-based approaches and new technological advances in aseptic processing
- Adoption of an integrated quality systems orientation throughout the product life cycle
- Alignment with current industry guidance, e.g.:
  - ICH Q8 Pharmaceutical Development
  - ICH Q9 Quality Risk Management
  - ICH Q10 Pharmaceutical Quality System
  - WHO, Annex 7
  - EMA, Guideline on Process Validation
  - FDA, Guidance to Industry - Process Validation: General Principles and Practices
  - FDA, Pharmaceutical CGMPs for the 21st Century – A Risk Based Approach

(not PDA Technical Reports No. 17, 22, 24, 44 or EU GMP Annex1)

Section 5.2 (Quality) Risk Management

5.2.1 General CURRENT VERSION

5.2.1.1 A risk management process shall be carried out, applying ISO 14971 and/or ICH Q9

Risks associated with the aseptic process

Shall be identified, assessed and controlled in order to establish acceptance criteria for all elements of the aseptic process definition.

Compliance with the requirements as defined in Clause 6 *et seq.* and/or regulatory documents can be used to demonstrate acceptability of the implemented risk control.

NOTE While this part of ISO 13408 is primarily concerned with microbiological contamination issues, there are other contamination risks that are relevant (e.g., endotoxin, particulate and chemical contamination)

5.2.1 General DRAFT

Due to the nature of aseptic processes, sterile products produced aseptically present a higher risk to the patient than terminally sterilized products. Because of the **high level of risk**, an **effective quality risk management program** shall be established that is integrated into the **product life cycle** and existing aseptic processing operations to minimize the risk of microbial contamination. (Reference ISO 14971 and ICH Q9?)

Risk-based approaches and tools shall address process and product design, validation and the impact of change, including design of process simulation; environmental control and monitoring; and personnel requirements in order to understand the sources of microbial contamination, establish acceptance criteria for all stages of the aseptic process, and prevent microbial contamination through appropriate risk reduction measures.

QRM shall include systematic processes designed to coordinate, facilitate and improve **science-based decision making with respect to the risks of microbial contamination of sterile product**.

Section 5.2 (Quality) Risk Management

5.2.1 General (repeated) CURRENT REVISION

5.2.1.1 A risk management process shall be carried out, applying ISO 14971 and/or ICH Q9

Risks associated with the aseptic process

Shall be identified, assessed and controlled in order to establish acceptance criteria for all elements of the aseptic process definition.

Compliance with the requirements as defined in Clause 6 *et seq.* and/or regulatory documents can be used to demonstrate acceptability of the implemented risk control.

NOTE While this part of ISO 13408 is primarily concerned with microbiological contamination issues, there are other contamination risks that are relevant (e.g., endotoxin, particulate and chemical contamination)

5.2.1 General (continued) DRAFT

Reference risk management tools (Annex describing each or reference ICH Q9):

- Basic risk management facilitation methods (flowcharts, check sheets)
- FMEA / FMECA
- FTA
- HACCP
- HAZOP
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering

NOTES:

The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk

While this part of ISO 13408 is primarily focused on microbiological contamination issues, there are other contamination risks that are relevant, e.g., endotoxin, particulate, and chemical cross contamination.

Clause 6: Manufacturing Environment

Steps to revision process

- Review and evaluate collated comments
    - Also included with Clause 6 are Annex D and Annex F.
- Review latest guidance documents, such as EU GMP and ISO 14644 series, to ensure Clause 6 is updated to current practices
    - **Potential roadblock**: ISO 14644-1 and ISO 14644-2 are delayed in their revision process. The revised standards will not be published until last half of 2014.
- Review requirements of non-conventional cleanrooms and update Clause 6 to include newer technologies

Clause 10: Process Simulation

- Steps to revision process
  - Incorporate previous comments received during 2012
  - Review Clause 10 of 13408-7 to identify areas which should be covered in Part 1:
    - Discussion of risk assessment applicability in process simulation
    - “Life Cycle” approach to aseptic processing – from initial clinical batches to large scale manufacturing
    - More detail on use of a surrogate product
    - Inclusion of similar flow chart (Figure 1) from Part 7, including scale-up concepts
  - Review US FDA / EU aseptic processing guidance and ICH Q8 for applicable concepts – ensure good harmonization

Standards development timeline

- May 2013 decision - US only to work on drafting the initial revision
- April 2014 (Sydney) – update on process
  - 1st draft presented; "approval" received
  - Not elevated as a new work item because of current project load (ISO 13408-2 revision and writing of ISO 18362)
- February 2015 (Berlin) – another update
  - Task Group created (lead by myself) to work in the background
    - Previous standards plus revision of 13408-6 had started
- December 2015 (Berlin) – First TG working draft reviewed
- Several TG working drafts exchanged through emails and virtual meetings

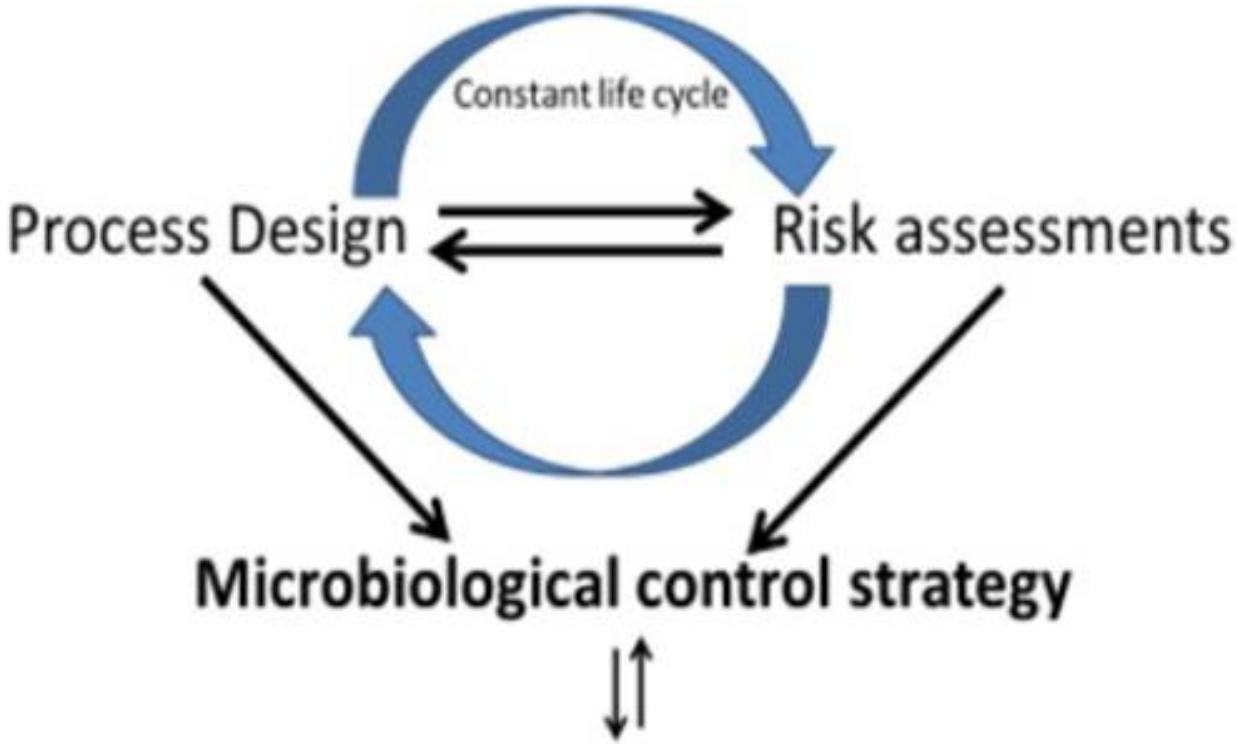
Standards development timeline

- Another systematic review (October 2016 – March 2017)
  - Confirmed again
- April 2017 (Minneapolis) – TG 5th working draft reviewed
  - Discussion to prepare NWIP, but did not progress
- October 2017 (Berlin) – TG 6th working draft reviewed
- February 2018 (Berlin) – Discussed 1st commenting period of Annex 1
  - WG submitted comments and concerns with Annex 1
  - Idea of total re-write of 13408-1 hatched
- September 2018 (London) – Decision to initiate revision (NWIP)
  - Parallel development with CEN/TC 204 under the Vienna Agreement
  - Chosen to be project leader

Standards development timeline

- June 2019 (Arlington) – key turning point
  - Scope change
    - 1st and 2nd editions focused on the manufacturing process
    - 3rd edition less focused; overall topic of aseptic processing
  - Expansion of structure
    - Inclusion of additional annexes
      - Risk Management
      - Processing zones
      - Standards comparisons on cleanrooms and filters
      - Robotics
      - Clothing systems
      - Rapid and alternative microbiological methods
    - Deletion of media fill tables

Aseptic processing principles



Standards development timeline

- First working draft sent out for comment in September/October 2019
- December 2019 (Seoul) – review and resolution of comments (half)
- Multiple online meetings in early 2020 to resolve remainder of comments

Standards development timeline

- **COVID!!!**
  - All meetings virtual
- June and December 2020 – Full WG meetings
  - Smaller meetings based on section work
    - Monthly, even weekly
- January – March 2021: ISO/CD 13408-1 ballot
  - CD approved with about 200 comments
- April 2021 – Started comment resolution
  - Sub-group met semi-monthly to monthly
- July 2021 – Comments resolved; new draft reviewed
  - Decision to submit for DIS rather than 2nd CD

Standards development timeline

- December 2021 – Mar 2022: ISO/DIS 13408-1 ballot
  - Approved; almost 300 comments
- April – July 2022: Resolution of comments; re-drafting
  - Subgroup meet 11 times, 3 hours each
- July 2022: Revised DIS presented to WG9
  - Decision: forward to TC198 for final editorial work before FDIS
    - Submitted in August 2022
- December 2021 (Arlington): In person!!!
  - FDIS pending HAS assessment at CEN

Standards development timeline

- April – June 2023: FDIS ballot
- June 2023: FDIS approved!
  - 40 editorial comments; quickly resolved
- ISO13408-1:2023 published **August 15, 2023**
- Approved for US adoption in December 2023
  - Still waiting on ANSI for publication
- FDA Consensus Document status: **December 18, 2023**
- EN ISO13408-1:2024 published **April 23, 2024**

Key points

- Goal: Revise and modernize to reflect best practices
  - Promote acceptance and reliable implementation of QRM (including microbiological risk management)
  - Provide guidance for all types of aseptic processing
  - Be 'future-oriented' and recognize advances in sterile manufacturing technology
- Challenge example: Previous version was focused on traditional cleanroom
  - Did not encompass alternatives to a cleanroom
  - Did not address wide spectrum as aseptic processing
    - Manual processing in a cleanroom or hood
    - Automated/robotic processes in isolator system without operator intervention

Key points

- Scope

  “This document specifies the general requirements for, and offers guidance on, processes, programs and procedures for development, validation and routine control of aseptic processing of health care products.

  This document includes requirements and guidance relative to the overall topic of aseptic processing.

  Specific requirements and guidance on various specialized processes and methods related to sterilizing filtration, lyophilization, clean-in place (CIP) technologies, sterilization in place (SIP) and isolator systems are given in the other parts of the ISO 13408 series.”

Key points (Main changes)

- A complete restructuring of the document;
- Inclusion of a diagram to explain the relationship between the ISO 13408 series and ISO 18362;
- Revision of the normative references;
- Alignment of definitions with ISO 11139:2018;
- Positioning of the document to recognize current and future advances in sterile manufacturing technology, acknowledging that new approaches to aseptic processing are transforming classical aseptic processing;

Key points (Main changes)

- Promotion of aseptic processing principles and the systematic implementation of quality risk management (QRM), including for aseptic process design, and microbiological contamination and particulate contamination control;
- Provision of guidance for different types of aseptic processing, for example, manual processing systems to automated robotic processing systems;
- Deletion of tables from the previous edition of this document referring to acceptance criteria for process simulation (media fill) qualification and requalification;

Key points (Main changes)

- Encouraging adoption of advanced aseptic processing technologies and continuous process improvement to improve assurance of sterility;
- Recognition that alternative or rapid microbiological methods (RMMs) provide timely microbiological data vital for process monitoring and control, and for product release;
- Inclusion of a series of informative annexes providing guidance on defining an aseptic process, including risks to be considered, aseptic processing areas (APAs), classification of cleanrooms, aseptic process flow, closed systems and robotics, and qualification of a cleanroom clothing system.

Key points: Introduction

- Terminal sterilization versus aseptic processing
  - "Health care products intended to be sterile should be **terminally sterilized** in their final sealed container by a terminal sterilization process, which has been validated to achieve a specified sterility assurance level (SAL)."
  - "Where a health care product is intended to be sterile and cannot withstand terminal sterilization in its final container, **aseptic processing provides an acceptable alternative** for product manufacture."
  - "Aseptic processing produces a sterile product in its final container by the assembly of component parts (e.g. product, container and container closure) that have been sterilized separately by validated and controlled processes suitable for each component part."
  - "It is important to control all possible sources of contamination so that the aseptic manufacturing process maintains sterility of previously-sterilized components during product filling or assembly, and sealing."

Key points: Introduction

- “Assurance of sterility for an aseptically processed product should not be confused with the term, ‘sterility assurance level (SAL)’. SAL is a mathematical extrapolation applicable only to a validated and controlled terminal sterilization process of known microbial lethality and which is delivered to each individual sealed unit of product subject to that process. Due to the variability and chance nature of occurrence of microbial contamination during aseptic processing, aseptic process simulation (APS) does not result in a mathematical probability of there being a single, viable microorganism in a contaminated unit, but rather results in an indication of what can happen in the routine processing of subsequent product batches (see ISO/TS 19930:2017, Clause 4).”

Key points: Introduction

- “Three key activities in the development and operation of an aseptic process to reduce and control particulate and microbial contamination risks:
  - Process design;
  - Risk assessment;
  - Contamination control strategy (CCS).”
- Accomplished using a risk-based management approach

Key points

- Section 5 Principles of aseptic processing
  - 5.1 General
    - "Aseptic processing is an activity composed of individual unit operations"
    - Aseptic processing includes all activities from set-up to product manufacture to final packaging.
    - Key activities diagram (previously shown)
  - 5.2 Use of an aseptic process
    - Terminal sterilization versus aseptic processing
    - "The rationale for selection of aseptic processing for a product shall be documented." (list of ideas to be included in rational)
  - 5.4 Aseptic processing zones
    - Critical processing zone
    - Direct support zones
    - Indirect support zones

Key points

- Section 6 Process design, development and risk management
  - "A formal, risk-based design and development process shall be used to develop the aseptic process."
  - New technologies should be considered.
    - Process analytical technologies (PATs)
    - Real-time testing
  - Identification of critical control points and process parameters
  - Environment and air handling
    - Relies heavily on ISO14644 series (references)

Key points

- 6.8 Personnel
  - "Greatest source of contamination"
  - Training
  - Health
  - Operator interventions
  - Service personnel
  - Cleanroom clothing systems
    - Qualification described in Annex G
- 6.9 Aseptic processing equipment
  - "Shall be fit for its intended purpose."
  - Automated processes and robotics (further guidance in Annex E)
  - Single use systems and connecting devices

Key points

- Section 7 Contamination control strategy (CCS)
  - CCS shall be implemented and address at least:
    - Cleaning and disinfection programs
    - Sterilization programs (including control of endotoxin and depyrogenation processes
    - Maintenance and calibration programs
    - Environmental monitoring program
    - Containment of potent or toxic substances
    - Control of raw materials and components
    - Personnel training and qualification programs
    - Cleanroom clothing systems and gowning procedures

Key points

- Section 8 Demonstration of the effectiveness
  - 8.1 Equipment qualification and validation
  - 8.2 Aseptic process validation
    - Establishment and management of interventions
    - Process simulation (media fill)
      - All parts of the aseptic process, all aseptic manipulations – can be subdivided into unit operations, but all will be simulated
      - Maximum: hold times, interventions (including unscheduled), filling times
      - Representative configurations (bracketing)
      - In conjunction with a comprehensive EM program
      - Numbers of units: sufficient to be representative
      - No failures
    - Initial qualification (minimum of three successful runs)
    - Periodic performance requalification (minimum of one successful run)

Key points

- 8.3 Maintenance of process
  - Review of process at specified intervals (annual)
  - Changes to process
  - Review of risk assessment (down with process review)
  - Significant event (batch non-sterility)

- Section 9 Product release
  - Specified
  - Criteria based on:
    - Sterility
    - Non-pyrogenicity
    - Absence of mycoplasma (if needed)
  - Encouraged to use rapid or alternative microbiological methods (Annex H)

Key points

- Annexes (informative)
  - A: Aseptic processing – Typical elements
  - B: Risk management (includes several examples of assessment tools)
  - C: Typical processing zones (diagrams and figures)
  - D: Comparison of classification of cleanrooms and filters
  - E: Example of an aseptic process flow chart
  - F: Closed systems and robotics
  - G: Sterile cleanroom clothing system qualification
  - H: Rapid and alternative microbiological methods

Table D.1 — Classification systems

ISO 14644-1	FDA guidance for aseptic processing, September 2004 [40]		EU GMP Guide Annex 1:2008 [38]			
ISO class number: N (particles ≧ 0,5 µm/m³) defined in "as-built," " at-rest" or "in operation“ a	Clean area classification (particles ≧ 0,5 µm/ft³) (particles ≧ 0,5 µm/m³) "in operation"	Microbiological active air action levels (cfu/m³)	Classification (particles ≧ 0,5 µm/m³) “at-rest"	Microbiological air sample (cfu/m³) “at-rest"	Classification (particles ≧ 0,5 µm/m³ “in operation"	Microbiological air sample (cfu/m³) “in operation"
5 (3 520)	100 (100) (3 520)	1	Grade A/B (3 520)	< 1/10	Grade A (3 520)	< 1
6 (35 200)	1 000 (1 000) (35 200)	7	Not defined	Not defined	Not defined	Not defined
7 (352 000)	10 000 (10 000) (3 520 000)	10	Grade C (352 000)	100	Grade B (352 000)	10
8 (3 520 000)	100 000 (100 000) (3 520 000)	100	Grade D (3 520 000)	200	Grade C (3 520 000)	100
9 (only applicable for operational) (35 200 000) b	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined

a According to ISO 14644-1, the air cleanliness class by particle concentration of air in a cleanroom or clean zone shall be defined in one or more of three occupancy states, i.e. "as-built," "at-rest" or “in operation". It is appropriate to apply the “operational (in operation)” state in associating class

Table D.2 — Comparison of HEPA and ULPA filters

ISO 29463-5 [26]			EN 1822 [29]			IEST-RP-CC001.6 [44]			JIS Z 8122 [47]	
Filter class and group	Overall value MPPS efficiency (%)	Local Value a MPPS efficiency (%)	Filter group Filter class	Integral value MPPS efficiency (%)	Local Value a MPPS Efficiency (%)	Filter type	Collection efficiency (%)	Local leak values Collection efficiency (%)	Filter type	Collection efficiency (%)
ISO 35H	≧ 99,95	≧ 99,75	H13	≧ 99,95	≧ 99,75					
						Type A,B,E	≧ 99,97 at 0,3 µm	A : - B,E : Two flow leak test	HEPA filter	≧ 99,97 at 0,3 µm
						Type H,I	≧ 99,97 at 0,1 to 0,2 µm or 0,2 to 0,3 µm	H: - I: Two flow leak test		
						Type C	≧ 99,99 at 0,3 µm	≧ 99,99 at 0,3 µm		
ISO 40H	≧ 99,99	≧ 99,95				Type J	≧ 99,99 at 0,1 to 0,2 µm or 0,2 to 0,3 µm	≧ 99,99 at 0,1 to 0,2 µm or 0,2 to 0,3 µm		
ISO 45H	≧ 99,995	≧ 99,975	H14	≧ 99,995	≧ 99,975	Type K	≧ 99,995 at 0,1 to 0,2 µm or 0,2 to 0,3 µm	≧ 99,992 at 0,1 to 0,2 µm or 0,2 to 0,3 µm		
ISO 50U	≧ 99,999	≧ 99,995				Type D	≧ 99,999 at 0,3 µm	≧ 99,995 at 0,3 µm		
ISO 55U	≧ 99,999 5	≧ 99,997 5	U15	≧ 99,999 5	≧ 99,997 5	Type F	≧ 99,999 5 at 0,1 to 0,2 µm or 0,2 to 0,3 µm	≧ 99,997 5 at 0,1 to 0,2 µm or 0,2 to 0,3 µm	ULPA filter	≧ 99,999 5 at 0,15 µm
ISO 60U	≧ 99,999 9	≧ 99,999 9				Type G	≧ 99,999 9 at 0,1 to 0,2 µm	≧ 99,999 at 0,1 to 0,2 µm		
ISO 65HU	≧ 99,999 95	≧ 99,999 75	U16	≧ 99,999 95	≧ 99,999 75					
ISO 70U	≧ 99,999 99	≧ 99,999 9								
ISO 75U	≧ 99,999 995	≧ 99,999 9	U17	≧ 99,999 995	≧ 99,999 9					

a Local penetration values lower than those given here may be agreed upon between the supplier and customer.

NOTE 1 Filters and filter elements are classified in groups and classes based on their efficiency or penetration for the MPPS particles by testing as prescribed in Clause 6 and in ISO 29463-5.

NOTE 2 In addition to EN 1822-1 ISO 29463-1 gives a classification system for high efficiency air filters. Similar to EN 1822-1 filter elements are classified in groups and classes according to their filtration performance (efficiency or penetration).

NOTE 3 Group H: HEPA filters, Group U: ULPA filters.

Other Aseptic Processing "Standards"

- FDA Guidance for Industry -Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (2004)
- PDA Technical Report No. 44, Quality Risk Management for Aseptic Processing (2008)
- PDA Points to Consider No. 1 Aseptic Processing (Revised October 2023)
- PDA Points to Consider No. 2 Aseptic Processing (2016)
- PDA Technical Report No. 22, Process Simulation for Aseptically Filled Products (Revised 2011)
- PIC/S Recommendation on the Validation of Aseptic Processes (2011)
- EU Volume 4 Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use – Annex 1 Manufacture of Sterile Medicinal Products (August 2022)

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Thank you!

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