ISO TC 198 Sterilization of health care products
Revising ISO 13408 aseptic processing standards
to reflect best practice

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ISO Technical Committee 198

Sterilization of health care products

- Develops international voluntary consensus standards specifying requirements for:
  - Cleaning, disinfecting, sterilising and aseptic processing of health care products (HCPs); and
  - Associated equipment and ancillary products used in ensuring effective application of these processes

- Published 54 standards/technical specifications (18 under development):
  - Applicable to industrial and health care facility processes

- 31 ‘P’ (participating) members (including Australia)

- 25 ‘O’ (observer) members

# encompass medical devices (including IVDs), medicines and cellular based products
## via Standards Australia
ISO TC 198: Working Groups

- 1: Ethylene oxide sterilization
- 2: Radiation sterilization
- 3: Moist heat sterilization
- 4: Biological indicators
- 5: Terminology
- 6: Chemical indicators
- 7: Packaging
- 8: Microbiological methods
- 9: Aseptic processing

- 10: Liquid chemical sterilization#
- 11: General criteria for sterilization processes and sterilizing equipment
- 12: Information for reprocessing of resterilizable devices
- 13: Washer-disinfectors
- 14: Dry heat sterilization#
- 15: Assurance of sterility
- 16: Vapourized hydrogen peroxide sterilization

# Disbanded (no active work program)
ISO TC 198: Working Group 9

• Responsibility for developing and revising:
  – ISO 13408 *Aseptic processing of health care products* series of standards (Parts 1-7); and
  – ISO 18362 *Manufacture of cell-based health care products: Control of microbial risks during processing*:

• Members are technical specialists:
  – ~56 experts from 14 countries (product manufacturers, equipment manufacturers, regulatory and inspection bodies, consultants and testing laboratories)

• Committed to:
  – Closing gaps in current editions of these standards;
  – Revising standards to more accurately reflect current industry best practices; and
  – Not excluding future technologies or innovation
ISO 13408 Series

• Critical standards for aseptic processing of HCPs:
  – Used by industry, conformity assessment bodies and regulatory agencies to demonstrate satisfactory aseptic processing of HCPs:
    ▪ e.g. medical device - to deem compliance with Essential Principles
  – Can complement and provide additional guidance to Codes of GMP

• Acceptance of standards by industry and regulators:
  – Requires high level trust in standards to gain ‘international buy-in’
  – Sometimes need to steer between divergent views of different geographical areas to achieve consensus, e.g. PUPSIT
ISO 13408 Series

- Part 1: General requirements
- Part 2: Sterilizing filtration
- Part 3: Lyophilization
- Part 4: Clean-in-place technologies
- Part 5: Sterilization-in-place
- Part 6: Isolator systems
- Part 7: Alternative processes for medical devices and combination products
ISO 18362 *Manufacture of cell-based health care products: Control of microbial risks during processing:*

- Sterile products and ‘microbiologically controlled low bioburden products unlikely to cause harm in recipient’

- Limited ‘Amendment’ in progress:
  - Enable recognition as a joint ISO-EN standard
  - Delete normative reference to ISO 13485 from subclause 9.2.1 of ISO 18362
  - Avoids opening ISO 18362 to full technical revision ahead of scheduled 2021 systematic review
WG9: Current Work Program – ISO 13408

- ISO 13408-1 *Aseptic processing of health care products – Part 1: General requirements:*
  - Undertaking substantial technical revision of 2008 edition (‘parent’ standard) - DIS ballot due late 2020

  - Reconfirmed at 2019 systematic review (possible early revision 2020/2021 to address deficiencies)

- ISO 13408-6 *Aseptic processing of health care products – Part 6: Isolator systems*
  - Finalising significant technical revision of 2005 edition (FDIS ballot early 2020)

- Primary aims of revisions:
  - Promote acceptance and reliable implementation of QRM (including microbiological risk management)
  - Provide guidance for all types of aseptic processing
  - Recognise advances in sterile manufacturing technology and ‘future-orientate’ standards
ISO 13408-4:2005 Aseptic processing of health care products

Part 4: Clean-in-place-technologies
ISO 13408-4

• 2019 systematic review ballot:
  – 14 countries confirmed ‘as is’
  – 3 countries proposed ‘revise/amend’ (including Australia):
    ▪ Do we need a specific standard if requirements for clean-in-place are identical for aseptically processed and terminally sterilized product?
    ▪ Current edition is silent on biological contaminants

• Given WG9 workload:
  – Agreed to reconfirm ISO 13408-4 ‘as is’
  – Reconsider need for early revision 2020/21 prior to next scheduled SR
ISO 13408-6:2005 Aseptic processing of health care products

Part 6: Isolator systems
ISO 13408-6

• Major technical revision nearing completion:
  – Finalising for joint ISO-EN FDIS ballot early 2020

• Scope:
  – *Specifies the requirements for and provides guidance on the specification, selection, qualification, bio-decontamination, validation, operation and control of isolator systems related to aseptic processing of health care products and processing of cell based health care products*
  – Excludes restricted access barrier systems (RABS) and isolator systems for sterility testing or biosafety containment.
ISO 13408-1:2008 Aseptic processing of health care products

Part 1: General requirements

Deliberations of WG9 (not TGA or other party)
ISO 13408-1: Why Modernise/Revise?

• Need to modernise standard to recognise:
  – Different geographical regulatory approaches to aseptic processing
  – New approaches to aseptic processing that are transforming classical aseptic processing
  – Future improvements in aseptic processing rely on improved use of technology for existing and new products

• To reduce and control risk, revised standard focuses on important relationship between:
  – Risk-based process design
  – Microbiological contamination control
  – Risk management
ISO 13408-1: Why Modernise/Revise?

• Current edition skewed to traditional clean room processes:
  – Aseptic processing is broader than large scale vial filling in a clean room
  – Doesn’t encompass alternatives to traditional clean rooms
  – Doesn’t address both ends of the aseptic processing scale:
    ▪ manual processing in a cleanroom
    ▪ automated/robotic processes in isolator systems with no operator intervention
  – Doesn’t encourage higher end technologies for aseptic processing

• Revised Part 1:
  – What type of structure/format?
    ▪ identify critical, high level requirements for aseptic processing for normative sections
    ▪ ? annexes for specific topics, guidance and rationale for guidance
ISO 13408-1: Fundamentals

• Core risks for aseptic processing:
  – Non-viable particulates (NVP)
  – Microbiological contamination

• Cornerstones for aseptic processing:
  – Risk-based process design
  – Microbiological contamination control
  – Risk management

• Risk-based process design:
  – How we design a process for a product
  – Microbiological contamination control strategy is an input to risk-based process design
  – Output from process design is ‘validation starting point’ to demonstrate process effectiveness
ISO 13408-1: Fundamentals

• Requirement for product to be supplied sterile to be identified as input to process design and development

• Sterile product to be terminally sterilised wherever possible in preference to aseptic processing

• Rationale to select aseptic processing to be documented:
  – Include strategies investigated to overcome detrimental effects on product of terminal sterilisation
  – Include cogent reasons to support the selection of aseptic processing
  – When product:
    ▪ Contains a material or substance incompatible with terminal sterilisation
    ▪ Or is manufactured traditionally by aseptic processing, e.g. some ophthalmic preparations
      additional justification to support selection of aseptic processing is not necessary.
ISO 13408-1: Examples of challenges

• Advanced aseptic processing technologies:
  – Show cause for not adopting barrier technology in preference to conventional clean room
  – Should we reward adoption of advanced aseptic processing technologies and continuous monitoring?
    ▪ ? reduced sampling where technologies provide greater assurance of sterility and patient safety

• Monitoring of isolator systems:
  – Is it valid to require installation of active air sampling locations in an isolator based on accepted locations for a conventional clean room?
    ▪ ? ‘punishment’ for investing in advanced technologies rather than reward
    ▪ ? demotivate adoption of advanced technologies
    ▪ ? consider a risk-based approach to selecting locations rather than a specific number of locations per defined area of isolator
ISO 13408-1: Examples of challenges

• Monitoring of isolator systems:
  
  – Validated bio-decontamination process and 12 months environmental monitoring data showing no growth:
    • Is environmental monitoring still necessary?

  – Dilemma:
    • Probable scientific justification to suggest ‘no’
    • Codes of GMP require environmental monitoring

  – Is there a compromise?:
    • Is it feasible to:
      – Reduce the level of monitoring in comparison to clean room requirements?
      – Omit settle plates but retain active sampling?
ISO 13408-1: Examples of challenges

- Disinfection:
  - ISO 11139:2018 definition: *a process to inactivate microorganisms to a level previously specified as being appropriate for a defined purpose*

- Problematic for application of *disinfection* in aseptic processing:
  - Microbiocidal activity of *disinfectant* validated
  - *Disinfection process* not validated
    - No specification to quantify log reduction of microorganisms on clean room surface via disinfection
    - Monitor its efficacy via environmental monitoring

- Disinfection can be ‘cleaning’:
  - e.g. isolator systems - disinfectant use prior to validated bio-decontamination process

- Include Note to definition to manage problem
ISO 13408-1: Examples of challenges

• Process simulation (media fills):
  - Demonstrate suitability of process/line
  - Should we design on a case by case basis rather than one-size-fits-all ‘clean room’ approach?:
    ▪ manual clean room process – ? more onerous requirements (potential for more interventions)
    ▪ robotic system in an isolator – ? less onerous requirements than for clean room
  - After successful initial media fill qualification:
    ▪ is 6 monthly requalification necessary for all processes?
    ▪ is reduced frequency possible?
      • e.g. can we adopt risk management approach for processes with continual monitoring/verification for each product batch?
ISO 13408-1: Examples of challenges

• Periodic process simulation (media fills):
  – Should the nature of the process and type of monitoring determine frequency of periodic media fills?
    ▪ controlling entrainment of organisms into a closed system:
      • does this mitigate the need for periodic media fills or reduced frequency?
  – Does continuous monitoring of NVPs and viable particulates provide more information about process than 6 monthly media fills, especially when operators are not present in aseptic processing area?
    ▪ can monitoring identify an out-of-specification quickly?
    ▪ if yes, process hasn’t been ‘running in the dark’ for 6 months
    ▪ does a periodic media fill add value?
    ▪ are other controls and monitoring feasible options?
ISO 13408-1: Examples of challenges

• Product release:
  – Need assurance of sterility to have confidence in patient safety
  – Can’t measure ‘sterility’:
    ▪ need to demonstrate sterility but can’t measure ‘what isn’t there’
  – Can efforts in risk-based process design, microbiological contamination control and risk management justify parametric/real-time release for some aseptic processes?
    ▪ e.g. continuously monitored robotic line within an isolator system