Australian Government
Department of Health
Therapeutic Goods Administration

ISO TC 198 Sterilization of health care products

Revising and modernising aseptic processing standards to reflect best practice

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TGA Health Safety Regulation

‘The mind is a wonderful thing.
It starts working the minute you're born and
never stops working until you get up to speak in public.’
(Unknown)

ISO Technical Committee 198

Sterilization of health care products

- Develops international voluntary consensus standards that specify 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 (20 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

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:*
    - Sterile products and 'microbiologically controlled low bioburden products unlikely to cause harm in recipient'

- Members are technical specialists:
  - 69 experts from 16 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 TC 198 WG9: ISO 13408 Work Program

- ISO 13408-2: *Aseptic processing of health care products – Part 2: Sterilizing filtration*
  - Major technical revision published 2018

- ISO 13408-6 *Aseptic processing of health care products – Part 6: Isolator systems*
  - Finalising significant technical revision of 2005 edition (publication possibly late 2019/early 2020)

- ISO 13408-1 *Aseptic processing of health care products – Part 1: General requirements*
  - Undertaking substantial technical revision of 2008 edition ('parent' standard)

- Primary aims of revisions:
  - Promote acceptance and reliable implementation of QRM (including microbiological risk management)
  - Provide guidance for all types of aseptic processing
  - 'Future-orientated' and recognise advances in sterile manufacturing technology

ISO 13408-6:2005 Aseptic processing of health care products
Part 6: Isolator systems

ISO 13408-6

- Technical revision nearing completion
- 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 13408-6: Examples of challenges

- Terminology:
  - ? Use ‘sealed’ / ‘non-sealed’ or ‘open’ / ‘closed’
  - ? Retain commonly used terms or consider different risk levels between the two types

- Consensus:
  - Entire isolator system protects critical processing zone within an isolator
  - Assess all components of system via QRM in terms of contamination control and risks relative to product, including choice of ‘open’ / ‘closed’ isolator, isolator interfaces (different cleanliness levels, ingress, egress), background environment etc.

- Isolator system:
  - Definition - *isolator with transfer system(s) and ancillary isolator equipment*
  - ‘Isolator system’ used throughout standard (where applicable)

ISO 13408-6: Examples of challenges

- Critical and non-critical contact surfaces:

  - Critical surfaces[‡]:
    - direct and indirect[#] product contact surfaces
    - sterilized via validated process prior to loading isolator
      - e.g. stopper bowl [#] (stoppers contact bowl and product)
      - recognises some stopper bowls are too big for separate sterilisation so in-situ cleaning and bio-decontamination might be the only feasible option

  - Non-critical surfaces[‡]:
    - non-product contact surface
    - bio-decontaminated via validated process

[‡] inclusion of diagrams in annexes to distinguish between surfaces

ISO 13408-6: Examples of challenges

- Bio-decontamination:
  - Internal surfaces of, and surfaces within the isolator and its transfer system(s)
  - Validated process to render non-critical surfaces within the isolator and its transfer system/s free from viable microorganisms (is NOT sterilization)
  - Recognises bio-decontamination is conducted on cleaned surfaces with minimal organic contamination (clean environment)
    - bioburden on surfaces is important to determine target spore log reduction (SLR)
    - packaged, sterilized items stored in Grade C likely to have lower bioburden than items stored in non-controlled environments

ISO 13408-6: Examples of challenges

- Bio-decontamination SLR:
  - Inappropriate to mandate 6 SLR (need to consider expectations of different regulators)
  - ‘NOTE Within the context of a defined starting point that takes into consideration cleaning of the isolator prior to the bio-decontamination process and monitoring of the isolator during use, there has been historic acceptance of a six-log spore reduction of a suitable, resistant microorganism or inoculated carrier, as a means of providing assurance that a bio-decontamination process results in a satisfactory aseptic processing environment.’
  - User to specify SLR to be achieved following bio-decontamination process:
    - employ risk management to determine specified SLR
    - SLR <6 requires robust justification under QRM

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

- Major technical revision in progress:
  - Draft international standard (DIS) ballot late 2020

- Scope:
  - Specifies the general requirements for, and offers guidance on, processes, programmes and procedures for development, validation and routine control of the manufacturing process for aseptically-processed health care products

- 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 13408-1: Examples of challenges

- 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 should focus on important relationship between:
  - Risk-based process design
  - Microbiological contamination control
  - Risk management

ISO 13408-1: Examples of challenges

- Current Part 1 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: Examples of challenges

- 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: Examples of challenges

- Advanced aseptic processing technologies:
  - Show cause for not adopting barrier technology in preference to conventional clean room
  - Should adoption of advanced aseptic processing technologies and continuous monitoring be rewarded?
    - ? reduced sampling where technologies provide greater assurance of sterility and patient safety
  - 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
    - ? demotivator for adopting advanced technologies
    - should a risk-based approach to selecting locations be considered rather than a specific number of locations per defined area of isolator?

ISO 13408-1: Examples of challenges

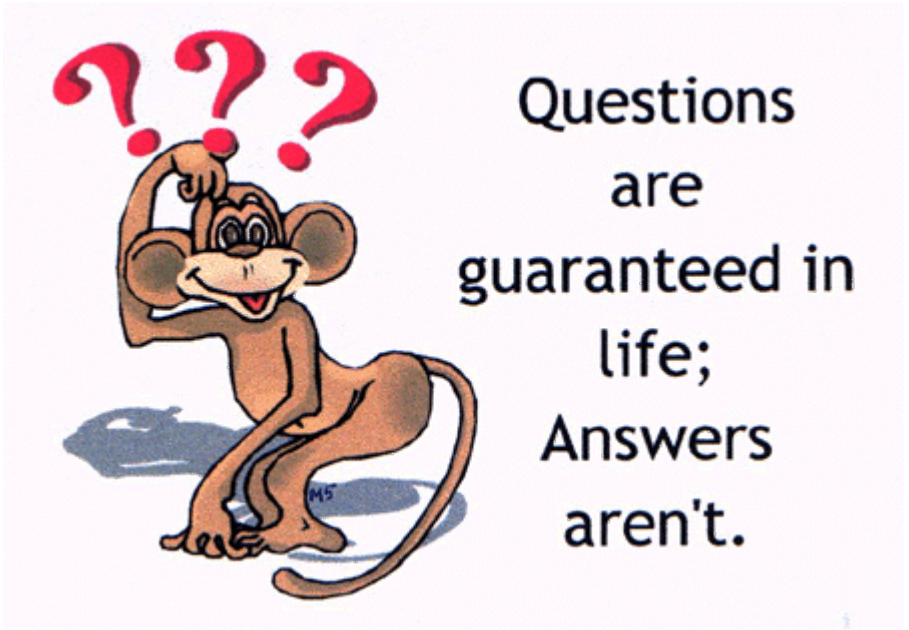
- Process simulation (media fills):
  - Should it be designed on a case by case basis rather than one-size-fits-all ‘clean room’ approach?:
    - manual clean room process – more onerous requirements (potential for more interventions)
    - robotic system in an isolator – less onerous requirements
  - After successful initial media fill qualification to demonstrate suitability of process/line:
    - is 6 monthly requalification necessary for all processes?
    - is it feasible to adopt a risk management approach 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?
    - process hasn't been 'running in the dark' for 6 months so does a periodic media fill add value?
    - is a periodic media fill the 'holy grail'?
    - 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 release for some aseptic processes?
    - e.g. continuously monitored robotic line within an isolator system


Questions are guaranteed in life; Answers aren't.

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