Australian Government
Department of Health
Therapeutic Goods Administration

Single use technology

a regulatory perspective

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History

Period	SUT History
early 1980s	• filter manufacturers began to make small process-scale plastic filter capsules to replace "junior" size stainless-filter housing assemblies
the mid-1980s	• developments in disposable bio containers
the late 1980s and early 1990s	• introduction of large-scale single-use processing with 2D bags in volumes from 50 to 1600 L
mid to late 1990s	• 3D bags for process volumes up to 3000 L, along with the first generation of totes to contain them.
mid-1990s	• bag suppliers had begun offering single-use systems with filter capsules that were pre-attached to bio containers • filter manufacturers began offering filter capsules with tubing and bags pre connected. • Gamma-irradiated systems followed shortly thereafter, and they were being validated as sterile systems by mid • Increase in focus on Cleaning validation and Extractable/Leachable risks (Industry/Regulatory progression
mid 2000s	• more advanced totes and bio container designs offered reduced leakage risks
early 2000s	• introduction of large-scale tube welders and sterile connectors • the disposable rocking-bag bioreactor, • Increase in toxicological assessment of product-contact processing materials
the late 2000s	• stirred tankliner bioreactors and mixers came to market, with the larger filter capsule formats • disposable depth-filtration capsule systems and a new generation of disposable sensors.
2010's	• sterile disconnectors and single-use tangential-flow filtration systems.

Single use technology: currently observed by inspectors being used in the following areas

- Buffer preparation, mixing and holding
- Capsule filters
- Disposable tubing
- Bulk Product Storage/transport containers/bags
- Production scale bioreactors (including cell expansion-T flasks, wave bags)
- Ion exchange membranes
- Mainly in upstream processing. Chromatography systems “dedicated not disposable”. Expecting a change to fully disposable systems.

Cleaning

Pros

- Cleaning validation significantly reduced
- Removes the risk in the use of chemical cleaning agents and possible carry over between products
- Removes risk associated with manual cleaning processes

Cleaning

Cons

- May be surface additives, post-moulding treatment residues or particulates
- Need appropriate pre-use treatment/rinsing

Sterilization

Pros

- Reduces risk associated with inadequate / failed sterilisation
- Reduces sterilization validation studies
- Reduces the demand on WFI for pure steam

Sterilization

Cons

- For pre-sterilized SUT components, need assurance of sterilization (eg γ-irradiation, ETO, etc)
- For SIP SUT components, deformation/damage may compromise sterile integrity (eg. Triclover-connected SU pipe-work, cracking in SU pipework)

Cross contamination

Pros

- Use of aseptic connections for fluid transfer and less connections
- Reduction in the possibility of build up in product residues as a result of inadequate cleaning

Cross contamination

- In process sampling of production reactors now using disposable sampling bags and not highly operator dependent sampling using syringes or valves

Reduction in cross contamination

- Reduction in the transfer of stainless steel vessels into and between cleanrooms
- Elimination of storage requirements for stainless steel vessels and clean hold times

Challenges

- Integrity of the disposables, bags and filters not damaged during transport and storage
- Due diligence on gamma sterilization process and that the required SAL levels for the disposables are being met
- **Components leaching material into a bioprocess stream**
  - Studies for organic leachables are established, and the technologies for performing them are described with limits in the major pharmacopoeias

Challenges

Products binding to components

- It is critical to determine that single-use materials do not bind product

Components interacting and chemically modifying a product

- Comparable studies to assure that product remains stable while in contact with the many other materials present in a single-use process stream have become a definite requirement

Challenges

- Use of tubing for sterile and non sterile processes tends to be single use previously manufacturers reused tubing and issues included
  - Cleaning and storage
  - Sterilization – difficult for long tubing
  - Lifespan – leachables and extractables
  - Integrity – fine cracking, splitting

Supplier qualification

- Approved supplier
- Specifications are established
- The components are visually inspected to ensure that they are the correct components ordered and properly labelled
- Verification of gamma sterilization.
- Certificate of analysis/conformance is provided with the delivery/goods
- Assessment ie audit or questionnaire utilising risk based processes

GMP requirements

- Filters
- Equipment
- Supplier qualification
- Change Control
- Validation
- Risk assessment principles

GMP requirements

Filters

- The fibre shedding characteristics of filters should be minimal (Annex 1:112)
- The same filter should not be used for more than one working day unless such use has been validated (Annex 1:114)
- The filter should not affect the product by removal of ingredients from it or by release of substances in it. (Annex 1:115)

GMP requirements

Equipment

- Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned (clause 3.36, Part 1)
- Production equipment should not present any hazard to the products. The part of the production equipment that comes in contact with the product must not be reactive, additive, or adsorptive to such an extent that it will affect the quality of the product and thus present a hazard (clause 3.39, Part 1)

GMP requirements

- Good manufacturing process is concerned with suitable equipment and services (clause 1.2 Part 1)
- The heads of Production and Quality Control generally have some shared responsibilities e.g. the approval and monitoring of suppliers of materials (clause 2.7 Part 1)

Change control

- Written procedures should be in place to describe the actions to be taken if a change is proposed to a ……process equipment… that may affect product quality or reproducibility of the quality. Change control procedures should ensure that sufficient supporting data to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specs. (Annex 15: clause 43)

Validation

- Significant changes to the facilities, equipment and processes which may affect the quality of the product, should be validated. A risk assessment should be used to determine the scope and extent of validation (Annex 15, principle)

Quality Risk Management

- Quality risk management is a systematic process for the assessment, control, and communication and review of risks to the quality of the medicinal product. It can be applied proactively and retrospectively…. (clause 1.5, Part 1)
- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk (clause 1.6, Part 1)

Types of deficiencies / issues

- No process for determining the integrity of single use bags before use
- Reuse of sterilising filters without supporting evidence
- Inadequate leachable and extractable studies to support the single use bioreactor
- Filter validation studies not performed using the product to confirm parameters.

Conclusion

- SUT has been around for over 30 years
- Regardless of the evolving technologies, GMP requirements are still required to be met
- Examples of challenges and references to some relevant GMP requirements have been provided

Single use technology: a regulatory perspective

Thank you

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