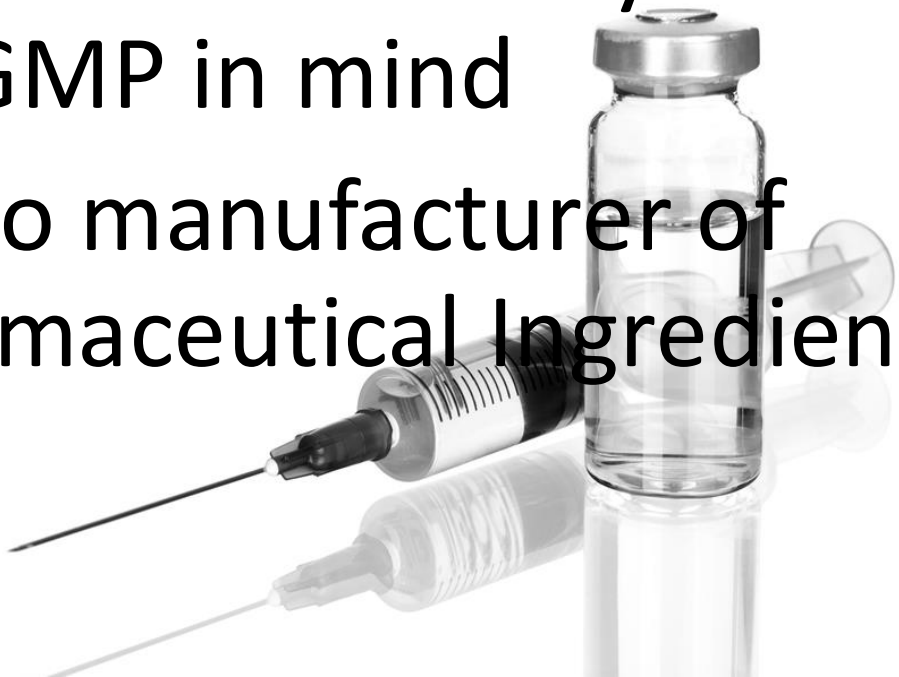
GMP update on Single Use Systems (Part 2)

Contents

- New Annex 1 requirements

Annex 1 update

- Current Annex 1 last updated in 2008
- There have been many advances in Sterile Product manufacturing techniques since then
- Current Annex 1 was written only with finished-product GMP in mind
- Now also applies to manufacturer of sterile Active Pharmaceutical Ingredients (API GMP)
  - Part 2 of EU GMP



Annex 1 update

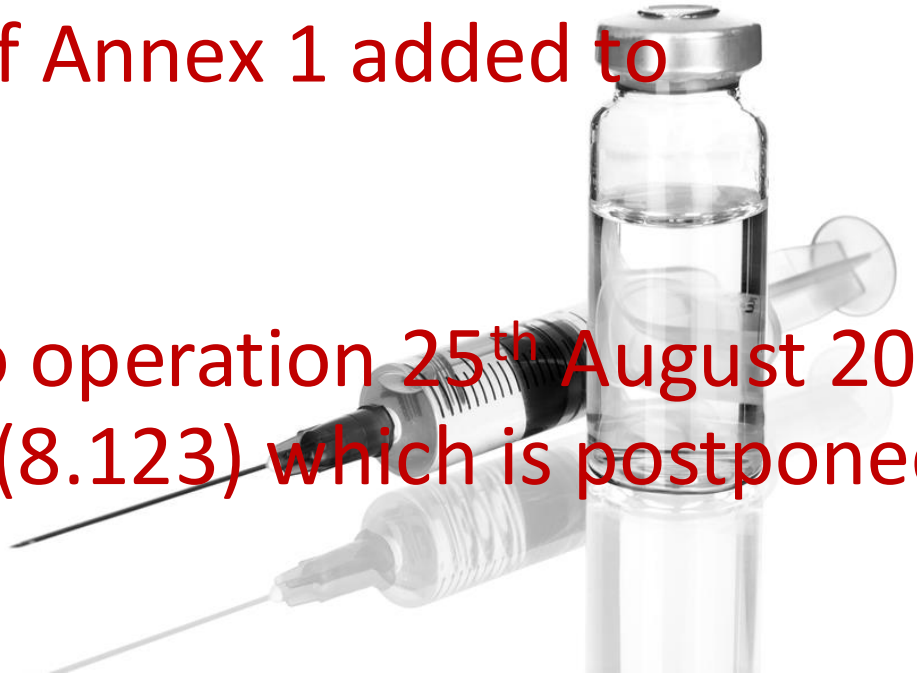
- Review of update to Annex 1 started in 2017
  - Led UK's Medicines and Healthcare-products Regulatory Agency (MHRA)
  - Not supposed to increase actual cost against what is currently done by most companies
- Late 2017:
  - Draft version of new Annex 1 published on EUDRALEX website
- Early – mid 2018:
  - Thousands of comments received from industry

Annex 1 update

- Mid – late 2018:
  - UK leaves the European Union (BREXIT)
  - The European Medicine's Agency (EMA) moves from London to Amsterdam
- Mid 2019:
  - Draft version of Annex 1 removed from EUDRALEX

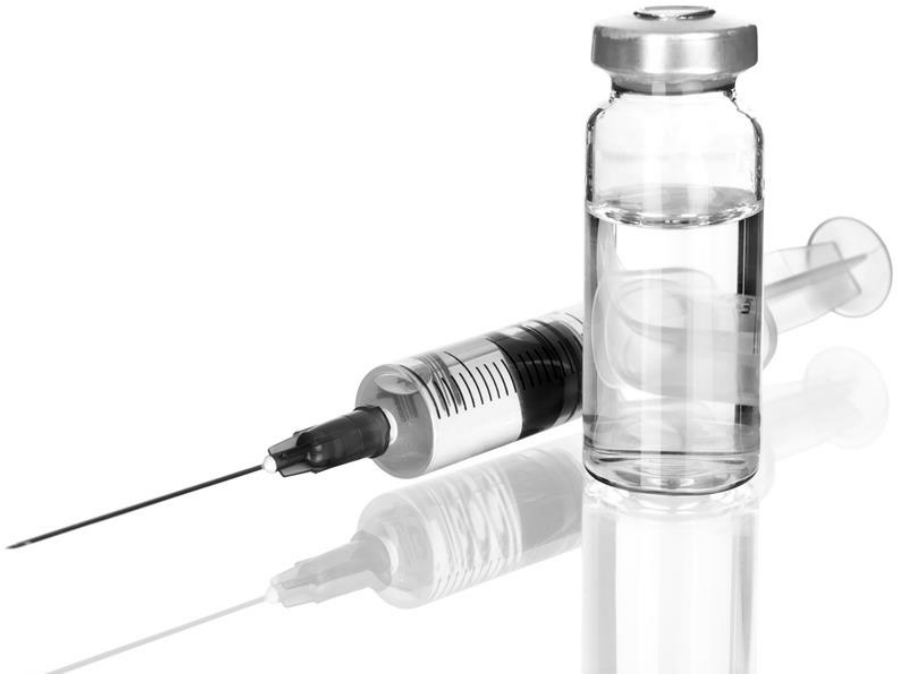
Annex 1 update

- 2020:
  - Covid-19
- 2021:
  - Second Draft version of Annex 1 added to EUDRALEX
- 2022:
  - New final version of Annex 1 added to EUDRALEX
- 2023
  - Annex 1 comes into operation 25th August 2023
  - (Except one clause (8.123) which is postponed for a year)



Annex 1 update

- This presentation covers some of the new requirements of the new version of EU GMP Annex 1



Annex 1 – new structure

1. Scope
2. Principle
3. Pharmaceutical Quality System (PQS)
4. Personnel
5. Premises
6. Equipment
7. Utilities
8. Production and specific technologies
9. Viable and non viable environmental and process monitoring
10. Quality Control
11. Glossary

Scope

- The annex covers sterile manufacture but can be used as a reference for non-sterile manufacturing
  - Grades of rooms
  - Clothing
  - Environmental monitoring

Principle

- General principles as applied to the manufacture of medicinal products
  - The use of *appropriate technologies* should be implemented
  - Personnel must have appropriate skills, training and attitudes

Principle

- General principles as applied to the manufacture of medicinal products
  - Processes, equipment, facilities and manufacturing activities should be managed in accordance with **Quality Risk Management (QRM)** principles that provide a proactive means of identifying, evaluating and controlling potential risks to quality

Principle

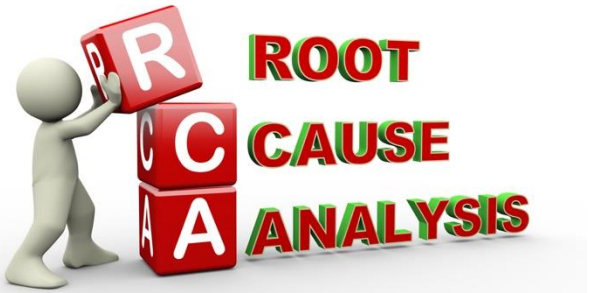
- General principles as applied to the manufacture of medicinal products
  - A **contamination control strategy** should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed
  - This assessment should **lead to corrective and preventative actions** being taken as necessary

Principle

- General principles as applied to the manufacture of medicinal products
  - The strategy should consider all aspects of contamination control and its life cycle with ongoing and **periodic review and update** of the strategy as appropriate

Pharmaceutical Quality System (PQS)

- Highlights the specific requirements of the PQS when applied to sterile medicinal products
  - Root cause analysis of failure
  - Risk assessment strategy
  - Risk assessment strategy documented and regularly reviewed



Personnel

- Guidance on the requirements for specific training, knowledge and skills
  - Minimum number of people in cleanroom
  - Maximum number determined by QRM principles
  - Maximum number determined by aseptic process simulation
  - Microbiological monitoring of arms and chest
  - The need for qualification of gowning
  - The need to be involved in aseptic process simulation

Personnel

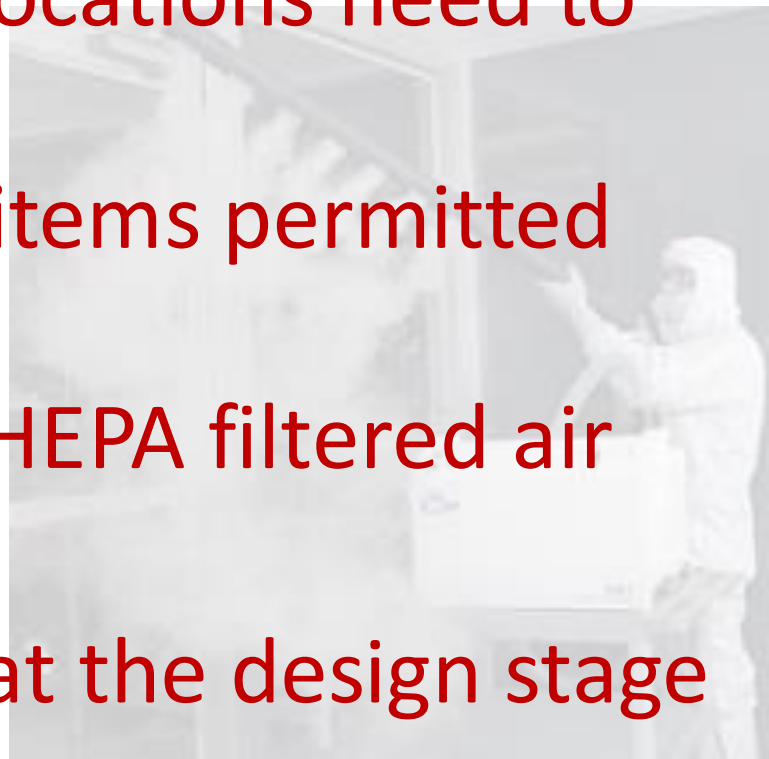
- Also gives guidance to the qualification of personnel
  - Exclusion of entry to cleanroom
  - No mobile phones!
  - Eye covering required
  - Cleanroom only socks
  - Garments be sterilised
  - Need to be checked for integrity before sterilisation
  - Only used once

Premises

- General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology

Premises

- General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology
  - Air speed measurement locations need to be justified
  - Need an approved list of items permitted into the cleanroom
  - Transfer hatches to have HEPA filtered air
  - Smoke studies videoed
  - Viewing windows added at the design stage



Premises

- More guidance on use of isolators and Restricted Access Barrier System (RABS)
- Particle monitoring in operation (at all times) for Grade A
- Microbial limits for Grade A changed from <1 to **no growth**
- Additional guidance on disinfectants and gassing

Equipment

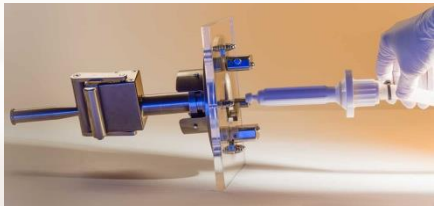
- General guidance on the design and operation of equipment
  - Area to be cleaned, disinfected and/or sanitised after maintenance
  - Cleaning processes validated (including mention of disinfectant residues)

Utilities

- Guidance with regards to the special requirements of utilities such as water, air and vacuum
  - More guidance on monitoring of water systems

Production and specific technologies

- Discusses the approaches to be taken with regards to aseptic and terminal sterilisation processes as well as lyophilisation and Blow Fill Seal (BFS)
  - Aseptic connections in Grade A
  - Transfer to freeze dryer in Grade A
  - **Engineering solutions to reduce aseptic connections**
  - Containers sealed by fusion to be 100% integrity tested
  - Eye tests for inspection personnel



Production and specific technologies

- Clear methods to distinguish between sterile and non-sterile items
- Additional guidance on specific types of sterilisation methods
- Pre-Use Post-Sterilisation Integrity Testing (**PUPSIT**) of sterile filters
- **Additional guidance on closed and single use systems**

Any questions?

Single Use Systems - EXERCISE

- In GROUPS – list 5 advantages and 5 disadvantages of using Single Use Systems
- 10 minutes plus feedback

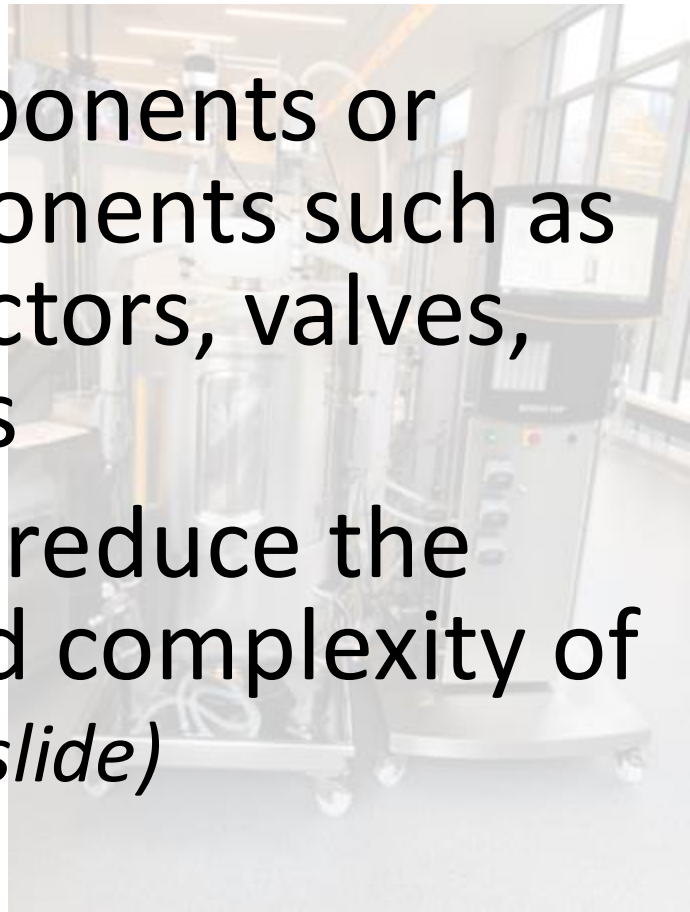
Any questions?

New Annex 1 - Single Use Systems (2.5)

- Elements to be considered within a documented Contamination Control Strategy (CCS) should include (but are not limited to) …
  - Vendor approval – such as key component suppliers, sterilization of components and single use systems (SUS) and critical service providers

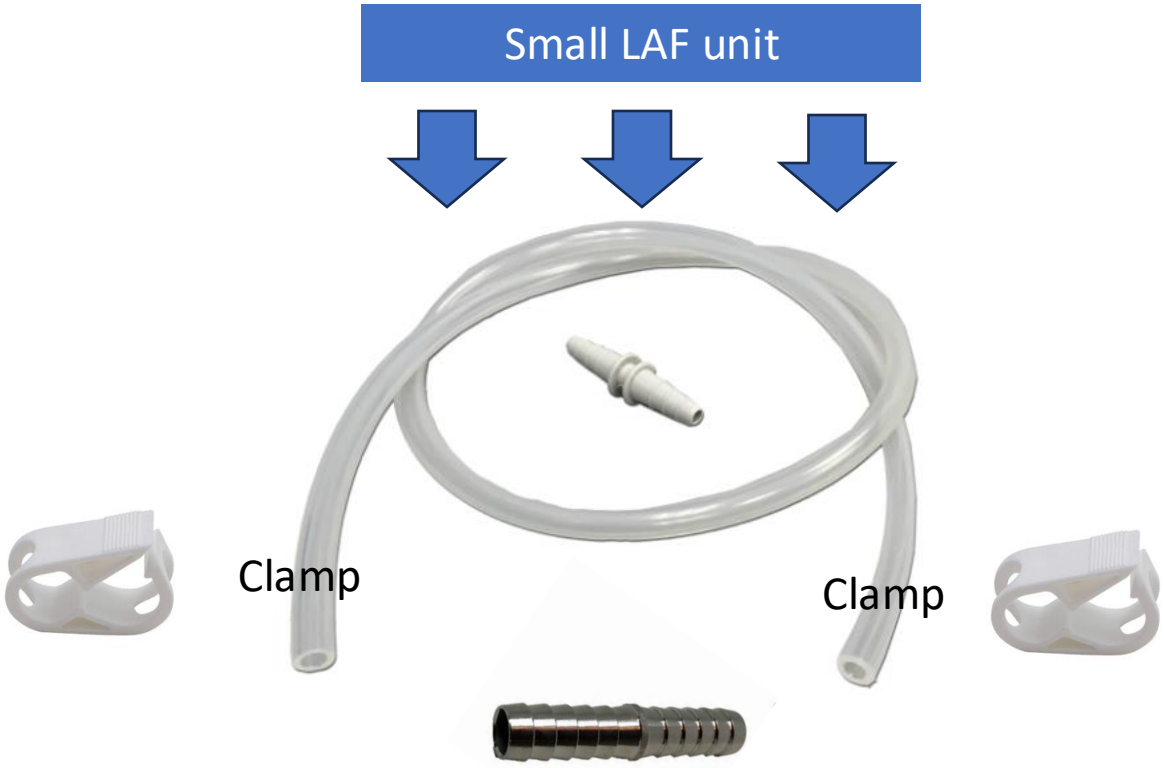
New Annex 1 - Single Use Systems (8.131)

- SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment
- SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors
- SUS should be designed to reduce the need for manipulations and complexity of manual interventions *(next slide)*



Reduce the need for manipulations and complexity of manual interventions

- In the old days – *spray and pray!*



Reduce the need for manipulations and complexity of manual interventions

- Modern approach

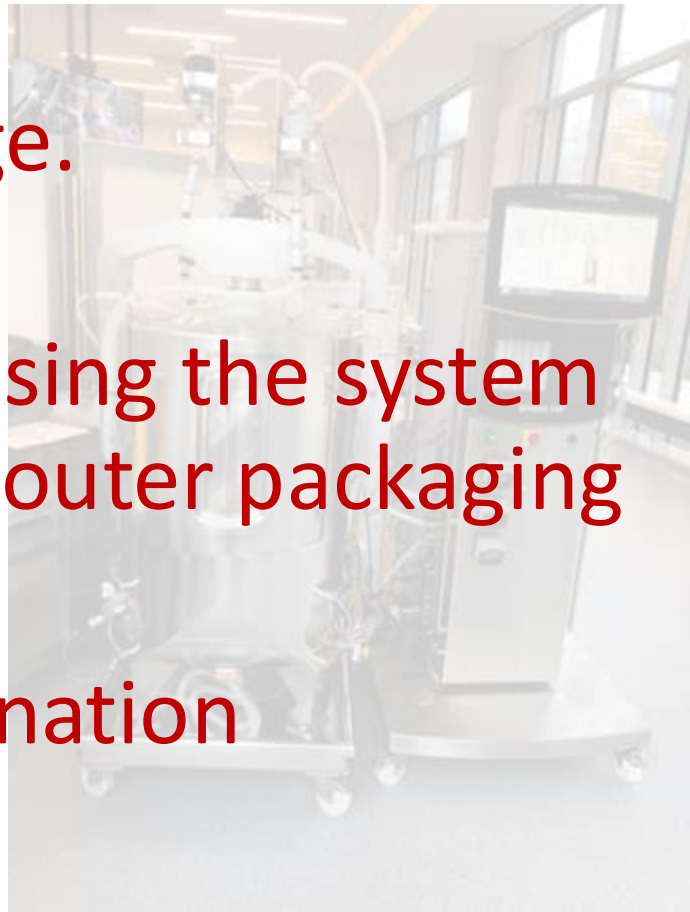



New Annex 1 - Single Use Systems (8.132)

- Specific risks associated with SUS
  - The interaction between the product and product contact surface
  - The fragile nature of the system compared with fixed reusable systems.
  - The increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made
  - The complexity of the assembly

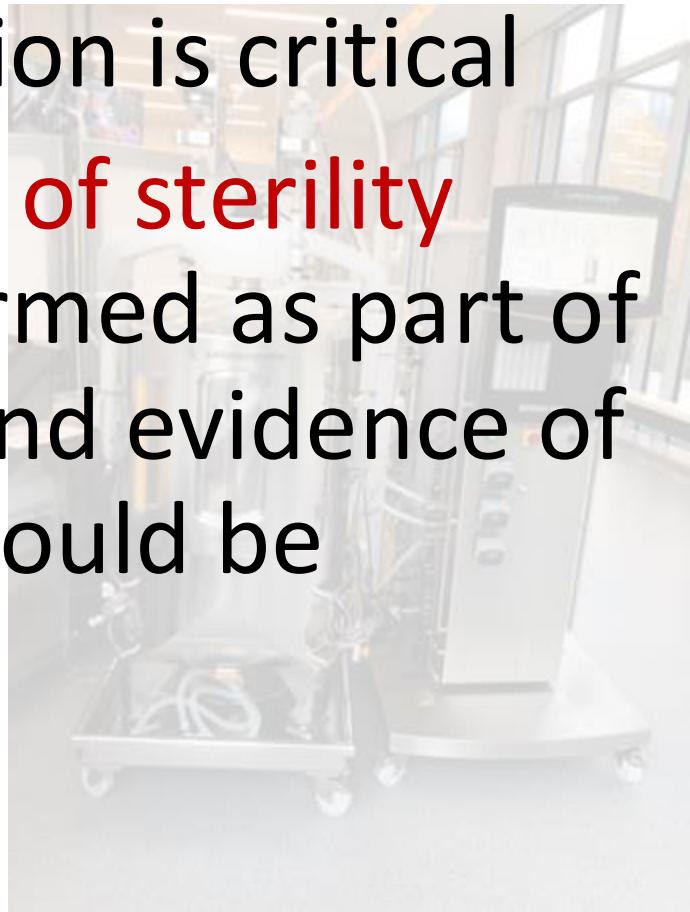
New Annex 1 - Single Use Systems (8.132)

- Specific risks associated with SUS
  - The performance of the pre- and post-use integrity testing for sterilising grade filters
  - The risk of holes and leakage.
  - The potential for compromising the system at the point of opening the outer packaging
  - The risk of particle contamination



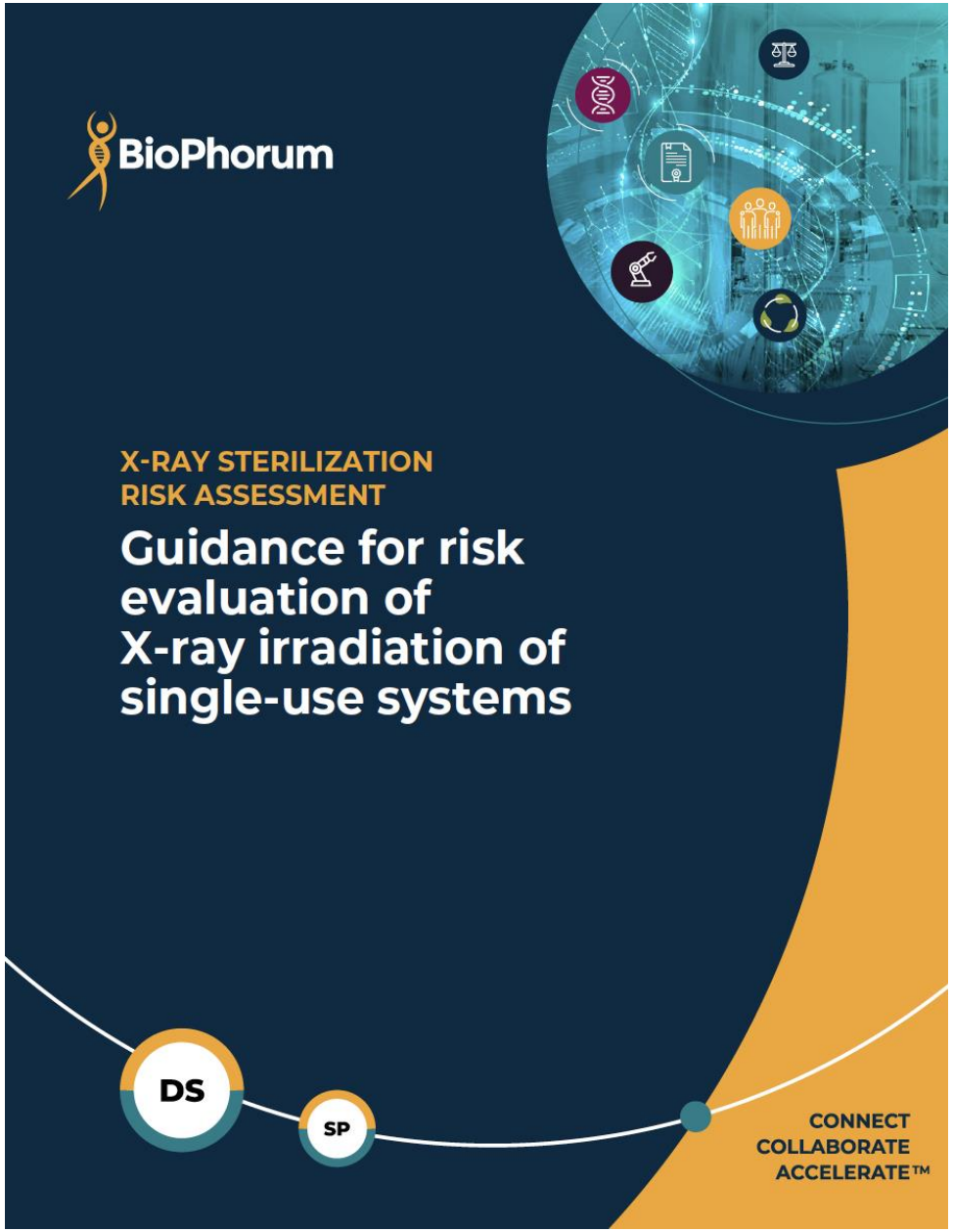
New Annex 1 - Single Use Systems (8.133 - 134)

- Sterilisation processes for SUS should be validated *(next slide)*
- Assessment of suppliers of disposable systems including sterilisation is critical
- For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt



Sterilisation processes for SUS should be validated

- Likely to be done by the supplier
  - Gamma irradiation traditionally used
  - Move now to start using x-ray



New Annex 1 - Single Use Systems (8.135 - 136)

- The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions

- The extractable and leachable profiles of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated

New Annex 1 - Single Use Systems (8.137)

- SUS should be designed to maintain integrity throughout processing under the intended operational conditions

New Annex 1 - Single Use Systems (8.138)

- Acceptance criteria should be established
- On receipt:
  - Manufactured, supplied and delivered in accordance with specification
- Prior to use:
  - Visual inspection of outer packaging
  - Labelling of item
  - Review of documents
    - Certificate of conformance
    - Proof of sterilisation

New Annex 1 - Single Use Systems (8.139)

- Critical manual handling operations of SUS, such as assembly and connections, should be subject to appropriate controls and verified during aseptic process simulation (media fills)

Any questions?

Single Use Systems - EXERCISE

- ADVANTAGES (feedback from previous delegates):
  - Lower CAPEX
  - Less chance of cross-contamination
  - Less cleaning validation
  - Flexibility
  - Less space
  - Smaller room
  - Lesser Grade of room
  - Less autoclaving
  - Less water
  - Less steam
  - Less energy

Single Use Systems - EXERCISE

- DISADVANTAGES (feedback from previous delegates):
  - Cost over time
  - Supplier delivery
  - Storage of bags
  - Checks on receipt
  - Adsorption
  - Leachables
  - Extractables
  - Can be complicated
  - Need to integrity test
  - Audit of supplier
  - Size limitation (2000 L max)

References

- EU GMP Directives and Guidelines:
- https://ec.europa.eu/health/documents/eudralex/vol-4_en