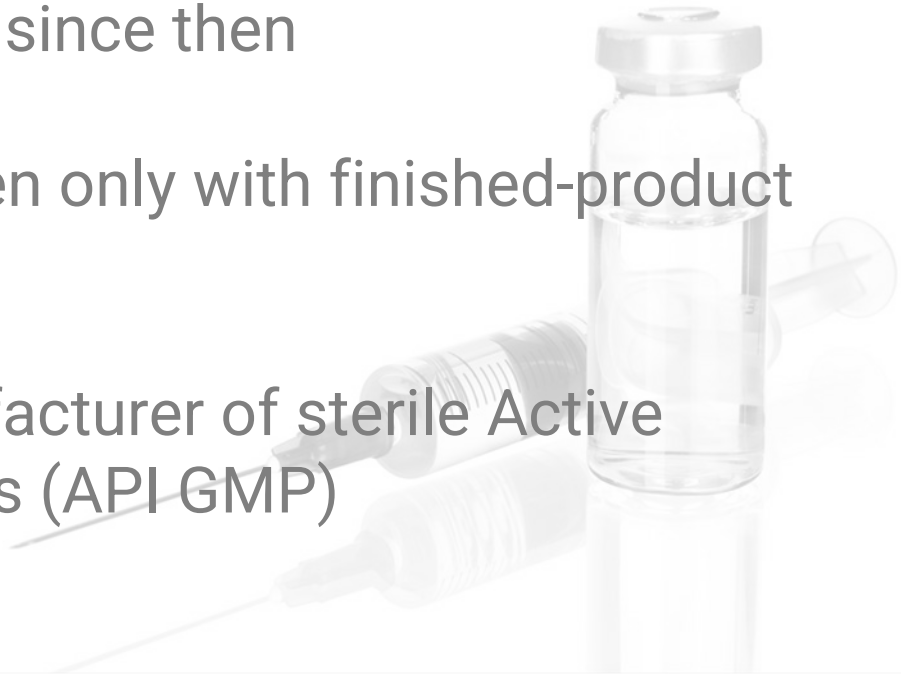
GMP update on Single Use Systems (Part 2)

Contents:

- New Annex 1 requirements

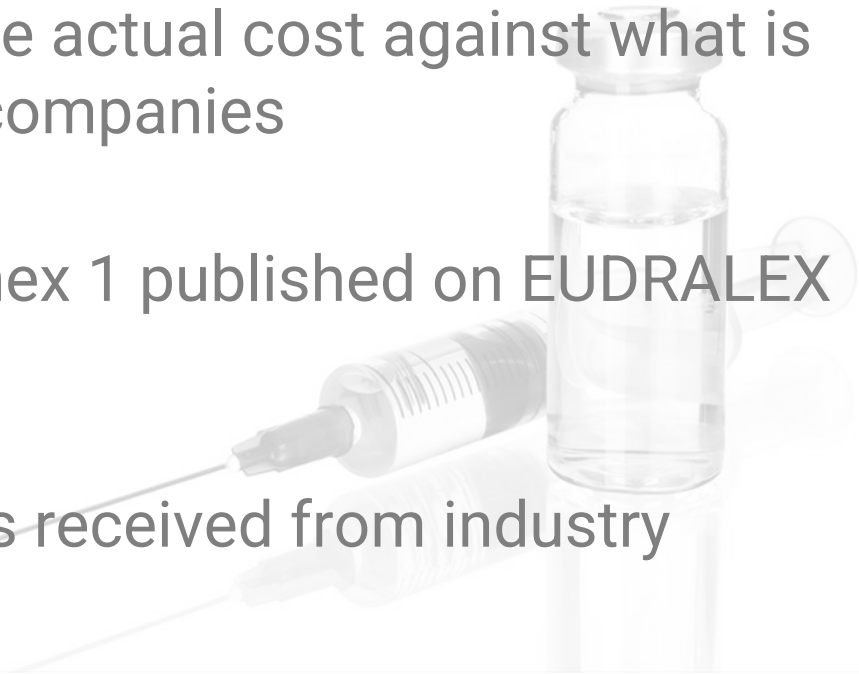
Annex 1 update

- 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 by *Andy Hopkins* from 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
  - Andy Hopkins leaves MHRA
- 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
  - See VOLUME 4 , DOCUMENTS and CONSULTATIONS

  - This presentation covers **some of the new requirements of this latest DRAFT version of 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 **appropriate technologies** should be implemented
  - Personnel must have appropriate skills, training and **attitudes**
  - 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.
  - 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 regularly reviewed

Personnel

- Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
  - 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 growing**
  - The need to be involved in **aseptic process simulation**

Personnel

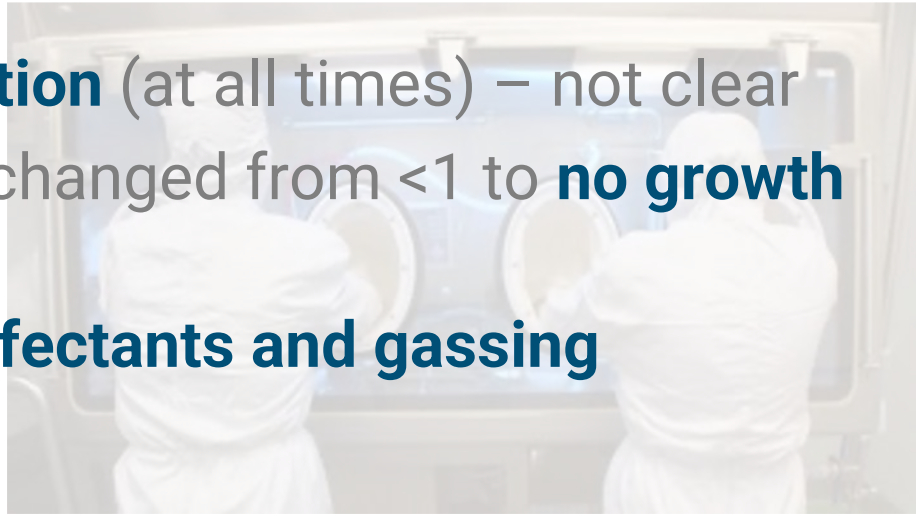
- Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
  - **Exclusion of entry** to cleanroom
  - No **mobile phones**!
  - **Eye covering** required
  - **Garments be sterilised**
  - Need to be **checked for integrity** before 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.
  - 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

- General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology.
  - More guidance on use of **isolators** and **Restricted Access Barrier System** (RABS)
  - **Particle monitoring in operation** (at all times) – not clear
  - Microbial limits for Grade A changed from <1 to **no growth is expected**
  - Additional guidance on **disinfectants and gassing**



Equipment

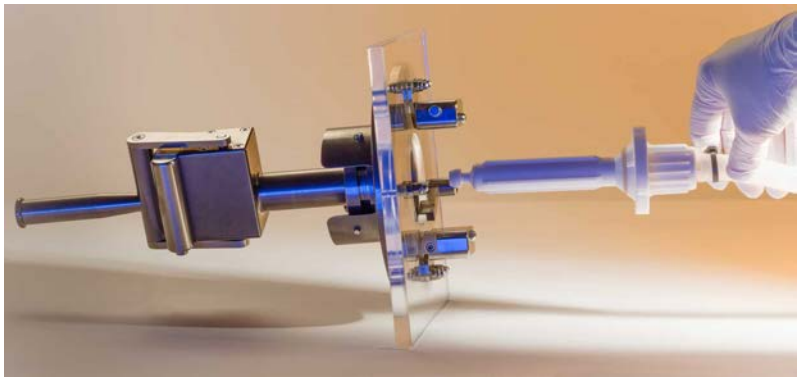
- General guidance on the design and operation of equipment
  - Area to be **cleaned, disinfected and/or sanitised after maintenance**
  - Cleaning processes **validated** (including mention of disinfectant residues)

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

- Discusses the approaches to be taken with regards to aseptic and terminal sterilisation processes as well as lyophilisation and Blow Fill Seal (BFS).
  - 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**

Single Use Systems (Annex 1 DRAFT 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 services.***

Single Use Systems (8.121)

- 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.

Single Use Systems (8.122)

- There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:
  - The **interaction between the product and product contact surface** (such as adsorption, or the formation of leachables and extractables).
  - The **fragile nature of the system** compared to fixed reusable systems.

Single Use Systems (8.122)

- There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:
  - 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**.
  - The performance of the **pre-use integrity test for sterilizing grade filters**.

Single Use Systems (8.122)

- There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:
  - The **risk of holes and leakage**.
  - The **potential for compromising the system** at the point of opening the outer packaging.
  - The **risk of particulate contamination**.

Single Use Systems (8.123 - 124)

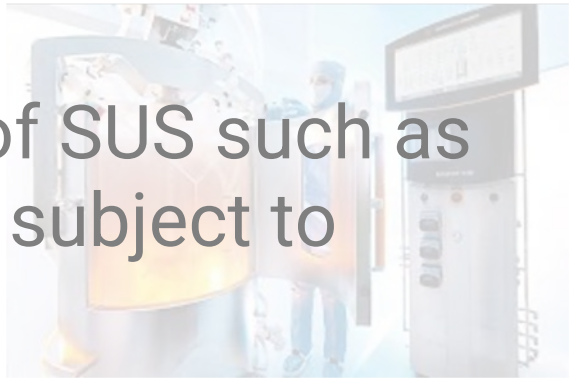
- **Sterilization processes for SUS should be validated** and shown to have no adverse impact on system performance.
- **Assessment of suppliers** of disposable systems **including sterilization** is critical to the selection and use of these systems.
- **For sterile SUS, verification of sterility should be performed as part of the supplier qualification** and **on receipt and use of each unit**.

Single Use Systems (8.125 - 127)

- The **adsorption and reactivity** of the **product with product contact surfaces** should be **evaluated**.
- The **extractable and leachable profile** 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.
- SUS should be designed to **maintain integrity throughout processing** under the intended operational conditions

Single Use Systems (8.128 - 129)

- **Acceptance criteria** should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes.
- **On receipt**, each piece of SUS should be **checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification**.
- **Critical manual handling operations** of SUS such as assembly and connections should be subject to appropriate controls



References

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