Summary overview of Cleaning Validation

January 15th 2019

Overview of presentation

- Regulatory overview and expectations
- What are the issues – regulatory inspection findings
- What approach needs to be followed
- Collaborations / improvements - what are GSK doing
- Industry challenges

Regulatory (and industry) guidance

- All regulatory agencies have set out guidelines and expectations for cleaning validation
  - Eudralex – Volume 4
    - Chapter 3 – Premises and equipment
    - Chapter 4 – Documentation
    - Annex 15 – Qualification & Validation
    - Part 2 – Section 12 Validation of API processes – Section 12.7 (Cleaning
    - validation)
    - Guidelines on GMP specific to ATMP – Section 10.2 – Cleaning Validation
  - FDA
    - Validation of Cleaning processes (7/93) – Guide to inspections validation of
    - cleaning processes.
    - 21 CFR 211.63 – Equipment design, size & location
    - 21 CFR 211.67 – Equipment cleaning and maintenance
    - 21 CFR 211.182 – Equipment and cleaning and use log.
  - There are a number of professional bodies that have developed guidance for cleaning validation:
    - PDA Technical Report 29 – Points to Consider for Cleaning Validation
    - ISPE Baseline Guide Volume 7: Risk Based Manufacture of Pharma Products

Recent FDA warning letters and 483 observations

- Your equipment cleaning practices for non-dedicated equipment are inadequate. During the production of your drug product (b)(4), which was in a (b)(4), **our investigator observed a (b)(4) residue** on the (b)(4) exterior surfaces. After our inspection, you tested samples of tablets produced with **(b)(4)** manufactured in the same **(b)(4)** to assess the **potential for cross-contamination**. Your testing confirmed the presence of **(b)(4)** in **(b)(4)** tablets

- **You do not have cleaning procedures** for the equipment you use to manufacture multiple drug products. **You have not validated the methods** you use to clean your equipment. Your firm manufactures both oral and topical products, and some of these products contain (b)(4). Inadequate removal of residues from manufacturing equipment during cleaning can lead to cross-contamination of products subsequently manufactured on the non-dedicated equipment

Recent FDA warning letters and 483 observations

- Your high-performance liquid chromatography (HPLC) chromatograms for residual disinfectant showed significant peaks for rinse samples with a **retention time similar to that of your cleaning agent**, (b)(4). You failed to investigate these peaks

- **You have not conducted cleaning validation studies** to demonstrate that your cleaning procedures for non-dedicated production equipment are adequate to prevent potential cross-contamination between your API (e.g., (b)(4)), which include (b)(4) drugs.

- Your firm made changes to cleaning procedures and **failed to re-perform cleaning validation** or assess current validation for equipment used to manufacture OTC drug products including but not limited to the blender and tablet compress

What is cleaning validation?

- Cleaning Validation:
  - Cleaning validation is **documented evidence** that an approved cleaning procedure will **reproducibly** remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level. (EU GMP Annex 15 Glossary)

- **The key deliverable : develop a cleaning process using risk based scientific principles that meets the regulatory compliance guidelines and expectations**

- This is achieved by following a 3 stage validation lifecycle – just like Process Validation:
  1. Process development
  2. Process qualification
  3. Continued process verification

Risk based assessment to cleaning validation

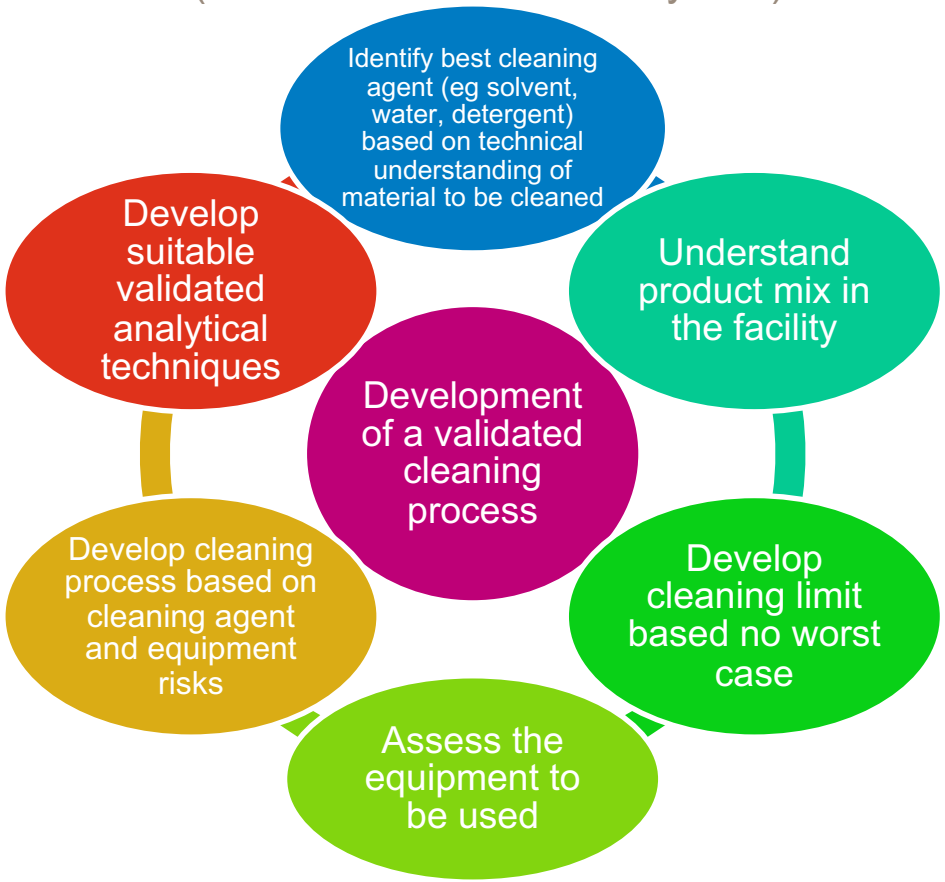
- Annex 15 requires that a quality risk management approach is applied.
  - Risk management should be used to determine if products can be manufactured in shared facilities
  - Risk management should be used to develop the cleaning strategy and cleaning validation strategy.
  - Cleaning validation, when effectively implemented, should provide confidence that the cleaning procedure will reproducibly remove product residues to required levels.
  - Cleaning validation does not preclude ongoing verification. Requirements for ongoing verification should be based on risk management and the extent of confidence demonstrated during cleaning validation.

`Development of cleaning processes

- Manufacturers should have a good practice guide for development of cleaning methods and cleaning validation strategy.
  - A structured assessment of requirements to disassemble equipment should be conducted and recorded.
  - This should utilise engineering drawings and a physical examination of the equipment by experienced/knowledgeable personnel.
  - A procedure should define how such an assessment should be conducted.
  - Cleaning methods must be reproducible, cleaning records must demonstrate completion of all key steps required to reach the MACO.

Key considerations during development

- The development of the cleaning processes must consider all variables in the cleaning process – taking into consideration the MACO (maximum allowable carryover)
  - People (cleaning)
  - Equipment layout
  - Cleaning method - TACT
  - Sampling
  - Rinse recovery all surfaces
  - Swab recovery - all surfaces
  - Analytical method
  - Visual inspection
  - Dirty hold time
  - Campaign length
  - Process deviations during cleaning development and cleaning verification



Cleaning limits

- There are different approaches for calculating cleaning limits
  - Toxicological approach - Health Based Value criterion (i.e. not more than Health Based Value of product A into Maximum Daily Dose of product B)
  - Therapeutic approach - 1/1000th dose criterion (i.e. less than 1/1000th Minimum Therapeutic Dose of product A into Maximum Daily Dose of product B)
  - 10 ppm level approach - i.e. less than 10 ppm of product A in product B
- Limits for carryover justified by EMA Health Based Exposure Limits Guide.
- Inspectors are increasingly looking for evidence of the approach being tailored to the Health Based Exposure Limits.
- MACO should be justified from the Health Based Exposure Limits and process capability.
- When determining your cleaning limit remember - cleaning is carried out for two reasons – to protect the patient and to protect the people working with the equipment (eg operators, maintenance people)

Opportunities for further improvements through new technologies / ways of working

- GSK (in partnership with Merck and Pfizers) are working with the Irish industry / academic collaboration PMTC (Pharmaceutical Manufacturing Technology Centre) which is focused on 3 research projects
    1. Selection & Optimum Delivery of Cleaning Agents
    2. Surface science
    3. Delivery of Cleaning Agents based on CFD Modelling

- The same group also have a collaboration in Singapore through ICES (Institute Of Chemical And Engineering Sciences) and A*STAR (Agency for Science, Technology and Research) that has started and will have a cleaning element to the collaboration work
    1. Fundamental understanding
    2. Visual inspection and PAT
    3. Methodology development

In summary - Industry challenges

- Industry are faced with the challenges of:
  - Carrying out cleaning in a compliant manner that meets the requirements of regulatory guidance and expectations
  - Developing cleaning processes that also meet the requirements of the business