Multi-Product Biopharmaceutical Manufacturing Facilities

CHANGEOVER

Points To Consider

Changeover Procedures in a Multi-Product Facility - Points to Consider

- Why is changeover required
- Developing the changeover procedure
- Executing the changeover procedure
- What are the agencies looking for/at
  - Highlighted throughout presentation

Why is Changeover Required

- Because QA says so!
- ICH Q7A (www.ich.org):

5.24	Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.
6.20	Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
12.76	Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

Developing the Changeover Procedure (Documentation)

- You must have documentation in place that covers the following:
  - Overall guidance for bringing new products into the facility
  - Strategy for Establishing Routine Controls in Multi-Product Manufacturing Facilities
  - High-level change over plan/philosophy
  - Cleaning Validation and acceptance criteria
  - Actual changeover batch records

A good documentation package is critical when it comes to successful inspections

Developing the Changeover Procedure (Documentation)

- New Product Considerations
  - Some of the issues to address include:
    - The regulatory filing/licensing status of current and new products.
    - Cleaning effectiveness of product contacting equipment
    - Equipment or plant limitations (process scale, BDS storage requirements, etc)
    - Assessment to ensure chemical compatibility of a new product stream(s) with respect to product contacting surfaces.

Developing the Changeover Procedure (Documentation)

- Establishing Controls in Multi-Product Facilities
  - Equipment controls:
    - All non-dedicated, re-usable product contact equipment must have been demonstrated as capable of being cleaned according to the facility cleaning validation plan.
    - Dedicated equipment
    - Single use disposables
  - Environmental controls / flow requirements (people, process, equipment)
  - Processing Controls
  - Scheduling restrictions

Developing the Changeover Procedure (Documentation)

- Changeover plan/philosophy
  - Describe the facilities criteria for Product Changeover.
    - Different product manufactured (different product codes).
  - The Policy should also outline the following:
    - Changeover record requirements
    - Sampling and testing requirements
      - to include requirements for failed samples
    - Test Method requirements

Developing the Changeover Procedure (Documentation)

- Changeover Batch Records
  - Remove all equipment, materials and documentation not necessary for subsequent production.
  - Clearly label all mobile product specific equipment with product part numbers, date cleaned and status of cleaning. Remove and store in a secure location.
  - Discard all partially used solutions and opened disposables.
  - Clean and sample equipment.
  - Product contact elastomers are replaced (with documentation)
  - If changeover pertains to a room, perform cleaning/decontamination following SOP

Developing the Changeover Procedure (Documentation)

- Sampling and Testing Requirements
  - Visually inspect that all systems are clean and free draining.
  - The Changeover Batch Record will list in detail where samples are to be taken, amounts of sample, storage conditions and acceptance criteria.
    - Take final rinse water samples for all process fluid contact systems. Perform TOC, pH and conductivity tests, as required.
    - Take swab samples for all sites as specified in changeover batch record.
  - All "out of specification" results obtained from the Changeover procedures will require an Investigation into failure and written deviation report.

Developing the Changeover Procedure (Documentation)

- Test Method Requirements
  - Qualify Assay for rinse and swab samples.
  - Determine accuracy by recovery studies of product in rinse and swab samples.
  - Determine Limit of Detection and Limit of Quantitation of product in rinse and swab samples.
    - Qualification must show the ability to detect product at required specification.

Developing the Changeover Procedure (Validation)

- Validation PQ's and product changeover requirements should match
  - Makes changeover useful as a Validation maintenance tool.
    - Changeover (if frequency is sufficient) can cover the period re-evaluation of your cleaning effectiveness
- Acceptance criteria
  - MACO (Maximum allowable carryover)
    - the most easily defended should be preferred method if possible
  - LOD (Limit of Detection of your assay)
    - simplest when products are early in lifecycle or enough information is not available for a true MACO calculation

The better your acceptance criteria are defined and justified up front, the easier your changeover and inspections will be

Executing the Changeover Procedure

- Planning
- Training
- Resources
- Failure resolution
- Release

Executing the Changeover Procedure (Planning)

- Schedule
  - Production schedule to be defined as far ahead as possible
  - Fit changeover activities into production schedule
  - Product changeover should also tie-in with a preventative maintenance program to take advantage of downtime
  - Account for testing time

Executing the Changeover Procedure (Training)

Changeover activities are not routine for most personnel, so training becomes critical.

- Safety (people and product)
  - Changeover may be done in close proximity to equipment that is still in use
  - documentation a must (LOTO procedures, BR's, etc)
- Consistency
  - Visual inspection of equipment is not quantitative
  - Swabbing can be variable if not well defined

Training documentation will be looked at during inspections

Executing the Changeover Procedure (Resources)

- Staffing
  - Balance of permanent, full-time personnel and contracted help
- Equipment
  - Ensure that test instruments are in sufficient number and are set up to minimize test times
- $$
  - Financially, changeover can be a very significant cost to the multi-product facility.
- Inventory
  - Must account for the availability of a significant number of parts (disposables and/or elastomers)

Executing the Changeover Procedure (Failure Resolution)

- While changeover simply requires clearance of product between campaigns, it is important to fully investigate failures
  - Failures during changeover are not all due to "sampling" or "operator" error
  - Ensure that failures are reviewed for systemic trends
    - Are systems compliant with existing validation?

Incomplete or insufficient failure investigation is probably the most frequent regulatory hit surrounding product changeover

Executing the Changeover Procedure (Release)

- Utilize some sort of Quality "tag out" or "hold" on your equipment/areas while changeover is in progress
  - Maintains good control of your process
- QA department should review all changeover activities and formally "release" equipment and areas back into production.

Summary

- Documentation, Documentation, Documentation
- Build QA responsibility into the procedure to demonstrate control over your process
- Do not under-estimate the time or resources needed to execute a proper changeover (especially as you fist start to implement your process)
  - The actual physical changeover is a long learning process; it will become more efficient over time
- Training is critical
  - Safety
  - Consistency