



IRISH MEDICINES BOARD

# Cleaning Validation Equipment & Facility considerations & potent materials

---

*IMB Information Day , 27<sup>th</sup> September 2012*

---

Victor Garvin,  
GMP Inspector

# Content of session

## Scope - Liquid & Solid Non-sterile Dosage Forms & APIs

- Purpose of Cleaning & Cleaning Validation
- References to Cleaning in the GMP Guidelines
- Cross Contamination Prevention Strategy
- Cleaning Validation Acceptance Criteria
- Dedicated Facilities – Potent Materials
- Equipment Cleaning Challenges / Issues with Manual Cleaning
- Common Deficiencies
- Some Additional Points to Consider



IRISH MEDICINES BOARD

## Why clean?

- Cleaning is performed to remove product and non-product contaminating materials which could effect patient health &/or the quality of medicines
- Effective cleaning is an essential component of QA and GMP and patient safety
- Ineffective cleaning can lead to adulterated product, which can be contaminated by the previous product, by cleaning agents, and by other extraneous materials introduced into, or generated by, the process.



## Why validate cleaning procedures?

- Cleaning validation confirms the reproducibility and efficiency of cleaning procedures
- A cleaning validation plan & its execution should demonstrate that the quality features built into facilities, equipment, utilities, and cleaning processes operate consistently and reliably
- The monitoring and removal of microbiological contamination (including endotoxins) as well as chemical and other contamination (detergent residues) should also form part of cleaning validation



## Part 1 Chapter 3 Premises & Equipment

**3.1** Premises & Equipment ... layout & design ... permit effective cleaning and maintenance ... to avoid cross-contamination, build up of dust & dirt

**3.2** Premises should be carefully maintained ... they should be cleaned and, where applicable, disinfected according to detailed ... procedures

**3.7** Premises should be laid out in such a way ... to allow production to take place ... to the requisite cleanliness levels



## Part 1 Chapter 3 Premises & Equipment (continued)

**3.9** Where ... materials ... etc ... are exposed to the environment, interior surfaces (walls, floors, ceilings) should be smooth and free from cracks ... and should permit easy and effective cleaning and ... disinfection

**3.10** Pipe work, light fittings, ventilation points and other services ... designed & sited ... to avoid ... recesses which are difficult to clean ... be accessible from outside the ...

**3.11** Drains ... open channels ... should be avoided if possible ... if necessary ... they should be shallow to facilitate cleaning & disinfection



## Part 1 Chapter 3 Premises & Equipment (continued)

**3.14** In cases where dust is generated; ... specific provisions should be taken to avoid cross-contamination and facilitate cleaning

**3.36** Manufacturing equipment should be designed so it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

**3.37** Washing and cleaning equipment should be chosen and used in order not to be a source of contamination



## Part 1 Chapter 5, Production

### Prevention of cross-contamination in production

Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

- a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
- b) providing appropriate air-locks and air extraction;
- c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;





## **Part 1 Chapter 5, Production (continued)**

d) keeping protective clothing inside areas where products with special risk of cross contamination are processed;

e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) using “closed systems” of production;

g) testing for residues and use of cleaning status labels on equipment.



## Part 2 4 Buildings and Facilities

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance...to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure...



## Part 2 Chapter 5 Process Equipment

**5.10** Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

**5.21** Written ... cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner ...



# Cross Contamination Prevention Strategy

<b>Design</b>	Premises & Equipment
<b>Define</b>	Cleaning Procedures & Analytical Methods
<b>Evaluate</b>	Effectiveness, Validation Procedures & Analytical Methods
<b>Monitor &amp; Record</b>	Visual, Sample, Cleaning Log, Observations and Incidents

Cleaning Super Hero



IRISH MEDICINES BOARD

# Cleaning Validation Acceptance Criteria

- NMT 0.1% of a dose should appear in the maximum daily dose of another
- NMT 10ppm should appear...
- No quantity of residue visible on equipment after cleaning (spiking studies need to confirm concentrations were most actives are visible on equipment surfaces)
- For certain allergenic ingredients such penicillins, steroid & cytotoxics, the limit should be below the detection limit of best assay methods available – in practice this may mean that dedicated plants are used to prepare these products



IRISH MEDICINES BOARD

## Considerations for using Occupational Exposure Limits OELs

- Developed for operator not patient protection
- Need to focus on contamination risks to the product
- Knowledge gained can be use to establish cleaning limits but limits may change



# Dedicated Facilities – Potent Products

## High Potency Products

- Potential for cross contamination through HVAC – no recirculation single pass HEPA filtered at inlet & exhaust
- Cross contamination in a multi product facility – dedicated facility or operate on a campaign basis one product at a time



"Particles, particles, particles."



IRISH MEDICINES BOARD

# Dedicated Facilities – Potent Products

## High Potency Products (continued)

- Exposure of personnel to product and protection of products from personnel – self contained full-body suits with breathing air supply and contain product in equipment train
- Therapeutic effect at very low levels of cross contamination – cleaning verification after each manufacturing campaign for each product using validation assay methods



IRISH MEDICINES BOARD



# Dedicated Facilities – Potent Products

## Proposed Changes to Part 1, Chapters 3 & 5

- No change in requirement for dedicated facilities for penicillins & cephalosporins, & live pathogens
- Risk assessment approach linked to toxicology tool
- Toxicology tool under development
- Submissions from industry bodies considered
- Continued discussion between regulatory agencies & inspectors working groups



IRISH MEDICINES BOARD

## **Dedicated (non-penicillin) to Non-dedicated - some considerations**

- Transition from dedicated to non-dedicated facilities
- Detailed risk assessment part of project plan
- Importance of good detection methods e.g. analytical methods & sampling techniques



# Equipment Cleaning Challenges – Manual Cleaning

## Questions worth considering when developing cleaning methods

- When is a piece of equipment clean?
- What is the definition of visually clean?
- Does the equipment need to be manually scrubbed, what does this achieve compared to solvent wash?
- How variable are manual cleaning processes from batch to batch and product to product?



IRISH MEDICINES BOARD

# Equipment Cleaning Challenges – Manual Cleaning

## Questions worth considering when developing cleaning methods (continued)

- What solvent or detergent is appropriate?
- Are different cleaning processes required for different products?
- Must a cleaning process be applied more than once to ensure adequate cleaning?



IRISH MEDICINES BOARD

# Deficiencies

- Cleaning procedures not in place
- Cleaning procedures lacking sufficient detail
- Cleaning records lacking in detail
- Cleaning procedures ineffective
- Dirty and clean equipment hold times not evaluated or not followed
- Equipment with 'clean status' not visually clean
- Cleaning validation not performed or missing key elements i.e., detergent residue studies, new product introduction, assay methods validation etc



IRISH MEDICINES BOARD

# Some Additional Points to Consider

- Cleaning should effectively remove all residues from previous products
- Cleaning should address excipients when these are difficult to clean and may trap the active ingredient
- Cleaning validation approaches including risk assessment should not limit the effectiveness of cleaning all residues , i.e. Low toxicity should not be the basis for limiting the adequacy of cleaning



IRISH MEDICINES BOARD

# Thank You



IRISH MEDICINES BOARD