INFORMATION DAY 2010

Cross Contamination, Dedicated Facilities and Cleaning Validation

Crown Plaza Hotel, October 14th 2010

Chris Cullen
• Principle
• Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid crosscontamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.
3.36 Manufacturing equipment should be designed so that 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.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.
5.19 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;
Prevention of cross-contamination in production

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;
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.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.
<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Premises, Equipment.</th>
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</thead>
<tbody>
<tr>
<td><strong>Define</strong></td>
<td>Cleaning Procedures, Analytical Methods.</td>
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<tr>
<td><strong>Evaluate</strong></td>
<td>Effectiveness, Validate Procedures/Analytical Methods.</td>
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<td><strong>Monitor</strong></td>
<td>Visual, Sample, Maintain.</td>
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<tr>
<td><strong>Record</strong></td>
<td>Cleaning and Use Logs, Observations and Incidents.</td>
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The Commission/EMEA and the FDA continue to share experience with a view towards determining the best international approach to the extent to which dedicated production facilities may be necessary for certain pharmaceuticals taking into account a risk based approach.
Proposed changes of Chapters 3 and 5

- Dedicated Facilities for Penicillin and Cephalosporins and for Live Pathogens.
- Risk Assessment approach linked to a toxicology tool.
- Toxicology Tool is being developed.
- Submissions by industry bodies have been considered by the WMA IWG. Continues discussion is encouraged.
• Transition from Dedicated to Non-Dedicated Facilities.
• Project Plan should include detailed Risk Assessment.
• Importance of development of detection tools – Analytical Methods, Sampling Techniques.
### Containment Controls

Exposure limits determine manufacturing safeguards

<table>
<thead>
<tr>
<th>Occupational Exposure Limit</th>
<th>Band</th>
<th>Production Requirements</th>
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</thead>
<tbody>
<tr>
<td>&gt;1–10 mg/m³</td>
<td>1</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>&gt;0.1–1 mg/m³</td>
<td>2</td>
<td>Good manufacturing practices (with local exhaust ventilation)</td>
</tr>
<tr>
<td>&gt;0.01–0.1 mg/m³</td>
<td>3</td>
<td>Essentially no open handling (ventilated enclosures required)</td>
</tr>
<tr>
<td>&gt;0.001–0.01 mg/m³</td>
<td>3+</td>
<td>Virtually no open handling (containment systems required)</td>
</tr>
<tr>
<td>≤0.001 mg/m³</td>
<td>4</td>
<td>No open handling (closed systems required)</td>
</tr>
<tr>
<td>≤0.001 mg/m³</td>
<td>5</td>
<td>No manual operations/human intervention (robotics or remote operations required)</td>
</tr>
</tbody>
</table>

*Source: Merck & Co.*
Considerations for using OELs

- The approach was developed for operator not patient protection.
- Patient protection focus is on what is inside the equipment/containment zone.
- Knowledge gained from OELs and other safety data is useful for establishing cleaning validation/verification limits.
- As knowledge develops limits may change – increase or decrease.
• The objectives of cleaning validation efforts in the API area are the same as those in the pharmaceutical production area but the areas are fundamentally different.

• The API facility includes reactors, transfer lines and pipes, pumps, filters, centrifuges and dryers making cleaning validation more challenging
• Areas that are not visible often represent worst-case locations in equipment.
• These surfaces cannot be visually inspected without the aid of remote access capabilities, such as a remote video system.
• Decision to use a remote video system, dismantle the equipment for direct visual examination, or monitor with an indirect test such as rinse sampling.
• Rinse sampling may be the most convenient form of monitoring but the effectiveness should be established.
API Cleaning Validation

- The application of the new approach may present challenges:
- For Products in Development.
- For Recovered and Unrecovered Intermediates due to a lack of knowledge regarding their toxicity.
- Pressure from some dedicated facilities to become multiproduct facilities.
Questions worth considering when developing cleaning processes

• Several questions should be addressed when evaluating the cleaning process.
• For example:
• At what point does a piece of equipment or system become clean?
• What does visually clean mean?
• Does the equipment need to be scrubbed by hand?
• What is accomplished by hand scrubbing rather than just a solvent wash

*PICs PI006/3*
High Potency Products

Utilities - Potential for cross contamination through HVAC
Single pass HEPA filtered air (in & out) – no recirculation

Facility - Cross contamination as a result of more than one product
Dedicated facilities or multi product facilities manufacturing one molecule only at a given time, on a campaign basis.

Personnel - Exposure of personnel to products, and protection of products from personnel
Self-contained full-body air suits with external breathing air supply, Equipment containment

Cleaning - Therapeutic effect at very low levels of cross contamination
Cleaning verification post each manufacture campaign of each molecule using validated methods
Questions worth considering when developing cleaning processes

• How variable are manual cleaning processes from batch to batch and product to product?
• What is the most appropriate solvent or detergent?
• Are different cleaning processes required for different products in contact with a piece of equipment?
• How many times need a cleaning process be applied to ensure adequate cleaning of each piece of equipment?

PICs PI006/3
• Risk Mapp has been reviewed by the IMB and the approach is viewed positively.

• Care needs to be taken with the risk assessment and the ADI calculations.

• Companies planning to use Risk Mapp may wish to contact their authorities in advance of inspections.
Impact of the new approach on existing Cleaning Validations?
How will the toxicology aspects be reviewed during inspections?
Can the classical approach or other alternative approaches be used?
Are the changes to Chapter 3 and 5 with respect to cleaning validation applicable to all molecules?
Cleaning should be effective at removing all residues from previous products.

Cleaning should not just include Active Ingredients but also excipients where these are difficult to clean and may trap active ingredients.

Cleaning validation approaches including Risk Mapp may provide assurance but should not be used to limit the effectiveness of cleaning all residues. i.e. low toxicity should not be the basis for limiting the adequacy of cleaning.
• Dedicated facilities also require effective cleaning focus on contamination with degradation products. Importance of interaction between the cleaning agent and the product components.

• API Facilities Importance of evaluation of difficult to clean areas, fixed pipework.