Cleaning Validation
New Product Introduction &
Assessing the Residues

IMB Information Day, 27th September 2012

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Content of session

• Cleaning considerations for new product introduction along with inspector expectations

• Sample deficiencies / Points to Note from inspections (presented throughout in blue text)
New chemical entity

- Consider the imaginary molecule below
When considering the introduction of a new molecule to the facility and its cleaning requirements, please rank these in order of importance:

• 1: Chemistry of the substance (manufacture & impurities)
• 2: Solubility data
• 3: Toxicological data (e.g. LD50 data)
• 4: Pharmacological data (e.g. clinical data)
Challenges

• Solubility
  • Let us imagine the molecule is poorly soluble

• Functional groups
  • potentially toxic epoxide
  • multi labile amine / amide groups
  • fragments with poor UV chromophores
  • potential methane sulfonate fragment (genotoxic)

• Setting limits
  • based upon what methodology?
  • what residues are being measured?
Solubility

- Published data (e.g. USP) – a good starting point

<table>
<thead>
<tr>
<th>Descriptive Term</th>
<th>Appropriate Volume of Solvent In Millilitres Per Gram of Solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>Less than 1 part solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10 parts solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30 parts solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 100 parts solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1000 parts solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>From 1000 to 10,000 parts solvent needed to dissolve 1 part solute</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>More than 10,000 parts solvent needed to dissolve 1 part solute</td>
</tr>
</tbody>
</table>
• Obtaining solubility information is paramount for a successful cleaning validation / verification study

• Quite often overlooked

• Default cleaning processes in place on site is often applied to new substance

• The cleaning strategy document did not contain information on the solubility of substances to be removed with the cleaning process
Choice of solvent

- The substance should choose the appropriate solvent based up sound science

- Organic solvents (typical in early API processes)
  - ideally native to the process
  - if non-native, a documented rationale for the solvent choice which assesses potential incompatibilities e.g. methanol to clean molecule with C=O residues

- Ensure the suitability and compatibility of cleaning solvents with raw materials used in the manufacturing process is assessed as part of the new active substance introduction
Water as cleaning solvent

- Ideal and simple

- EMA - Note for Guidance on Quality of Water for Pharmaceutical Use

- The quality of water used for cleaning (potable water) was not assessed in line with the EMA Note for Guidance recommendations

- However, often detergents are required
Detergents

- Becoming common practice

- Many companies have pre-existing CIP systems and automatically apply these systems to new substances

- They are typically acidic or basic in nature

- They can react with the substance to be cleaned

- Cleaning detergents were not formally assessed for their suitability for cleaning with regards to solubility and potential impact of materials e.g. degradation.
Our substance and reactivity

- Possible reaction sites (shown in red) and groups with potential tox concern (shown in blue)
Heat

• Important to understand the impact of heat on a cleaning process

• Increased temperature does not guarantee improved solubility and thus should be demonstrated

• Impact of heat on stability of detergent should be known

• Impact of heat on stability of residues should be assessed and documented

• There was no documented rationale for the choice of cleaning agent (water at 60°C)
• Carry-over of product residues should meet defined criteria, for example the most stringent of the following three criteria:

  • (a) No more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product,

  • (b) No more than 10 ppm of any product will appear in another product,

  • (c) No quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible
• For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods.

• In practice this may mean that dedicated plants are used for these products.
One cannot ensure that the contaminant will be uniformly distributed throughout the system. It is also an invalid conclusion to make the assumption that a residual contaminant would be worn off the equipment surface uniformly or that the contamination might only occur at the beginning of the batch.

In establishing residual limits, it may not be adequate to focus only on the principal reactant since chemical variations (active decomposition materials) may be more difficult to remove.
Setting limits practically

• Carry-over calculations use:
  • Daily dose of current product
  • Daily dose of next product
  • Minimum batch size of next product
  • Swab area
  • Shared equipment surface area
  • % recovery (correction factor)
  • Safety Factor (typically 1/1000)

• Important to challenge each factor as limits approach zero
Challenging limits

- Daily dose of next product
  - can patient over medicate (increase value)

- Minimum batch size of next product
  - what if manufacturing is interrupted (decrease value)

- Swab area
  - lab based on flat coupon (realistic?)
  - consider more practical swab recovery
Challenging limits (continued)

- Shared equipment surface area
  - full history (change control review)

- % Recovery – next slide

- Safety factor – scientifically sound?

- IMB Information Day 2010
  ‘minimal safety factor could be 10, maximal could be 120,000 or 1,200,000’
  [Link to document](http://www.imb.ie/images/uploaded/documents/GMP%20info%20day%20presentations/11_Cleaning%20Validation%20the%20Toxicological%20Approach_Lorcan%20Allen.pdf)

24-Sep-12
Acceptable recovery

• What is an acceptable recovery from a cleaning study?:

• 1. Not less than 80% with a correction factor

• 2. Not less than 70% with a correction factor

• 3. Not less than 50% with a correction factor

• 4. The recovery value is not that important, once it is ‘corrected for’ and is reproducible
Methods of sampling

- Common methods
  - Direct surface sampling
  - Rinse analysis
  - Visual inspection

- Operators involved in visual inspection of process equipment were not provided an adequate level of training to perform these duties

- Cleaning activities were not subject to an independent verification
Qualification of methodology

• All methodologies can be qualified

• Direct surface sampling
  ▪ classical spike, swab & recovery study

• Rinse analysis
  ▪ spike, immerse and analysis of ‘rinse’ solution

• Visual inspection
  ▪ known concentration
  ▪ quite often, a more sensitive method
Analytical methodology

- Appropriate for its use for the residue
  - TOC was used in one case for quantification of residual detergent...sodium hydroxide

- Appropriate level of validation according to ICH

- Understand the uncertainty of measurement

- Ensure solubility knowledge is shared between validation and QC

- The appropriateness of the TOC test method for analysis of the drug substance which demonstrated low solubility and low recovery of drug substance, was not adequately justified
Limits

- Limits of carry-over should be scientifically sound, practical and achievable

- A default limit (e.g. purified water specification) is not acceptable without an assessment of the impact of the residue (e.g. detergent) on the specification parameter

- The acceptance criteria limits (TOC and conductivity) for clean-in-place were not correlated to an acceptable quantifiable level of cleaning agent residues
Conclusion

• An inspector’s perspective is to look for:
  • Knowledge of the substance (residue)
    ▪ chemistry
    ▪ solubility
    ▪ compatibility with detergents and heat
  • Limits
    ▪ derived from scientifically sound principles
    ▪ practical and achievable
  • Robust analytical methodology
    ▪ appropriate technique & validated
Thank you

- Thank you – any discussion comments?