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Cleaning Validation

New Product Introduction & Assessing the Residues

IMB Information Day , 27th September 2012

Cormac Dalton

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)

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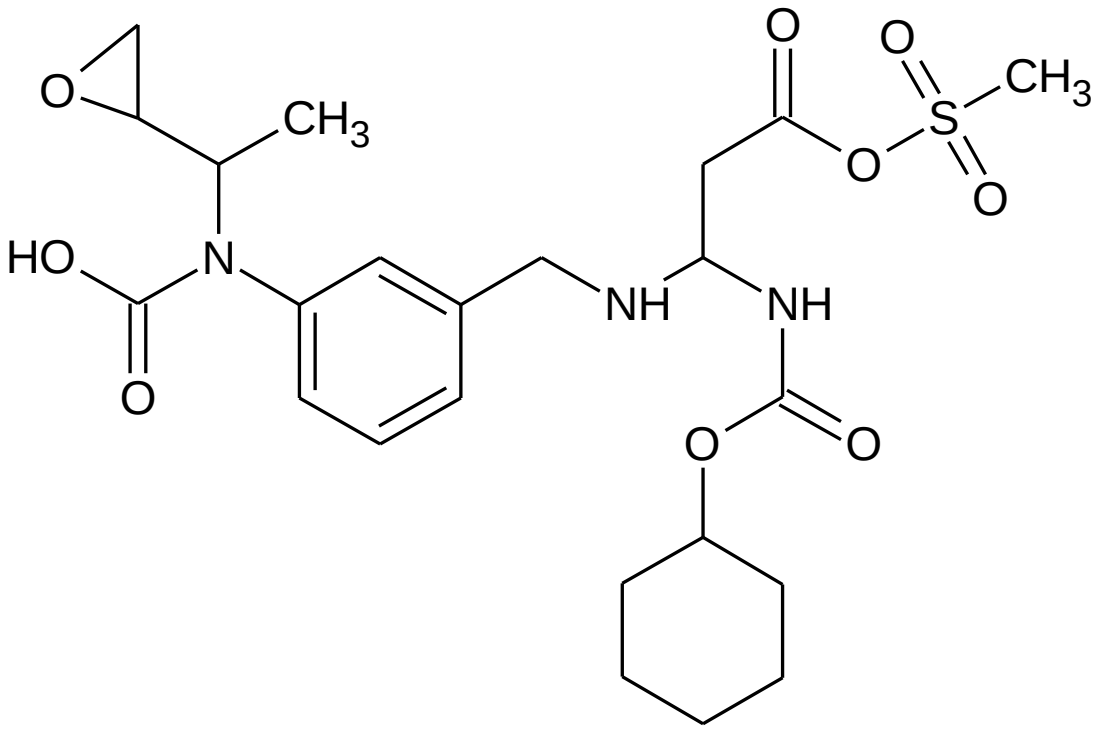
New chemical entity

- Consider the imaginary molecule below



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Starting point

- 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)

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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 beingmeasured?

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Solubility

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

	Values for estimating drug solubility based upon 'USP definition'
Descriptive Term	**Appropriate Volume of Solvent In Millilitres Per Gram of Solute**
Very soluble	Less than 1 part solvent needed to dissolve 1 part solute
Freely soluble	From 1 to 10 parts solvent needed to dissolve 1 part solute
Soluble	From 10 to 30 parts solvent needed to dissolve 1 part solute
Sparingly soluble	From 30 to 100 parts solvent needed to dissolve 1 part solute
Slightly soluble	From 100 to 1000 parts solvent needed to dissolve 1 part solute
Very slightly soluble	From 1000 to 10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble	More than 10,000 parts solvent needed to dissolve 1 part solute

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Solubility

- 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

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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

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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

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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.

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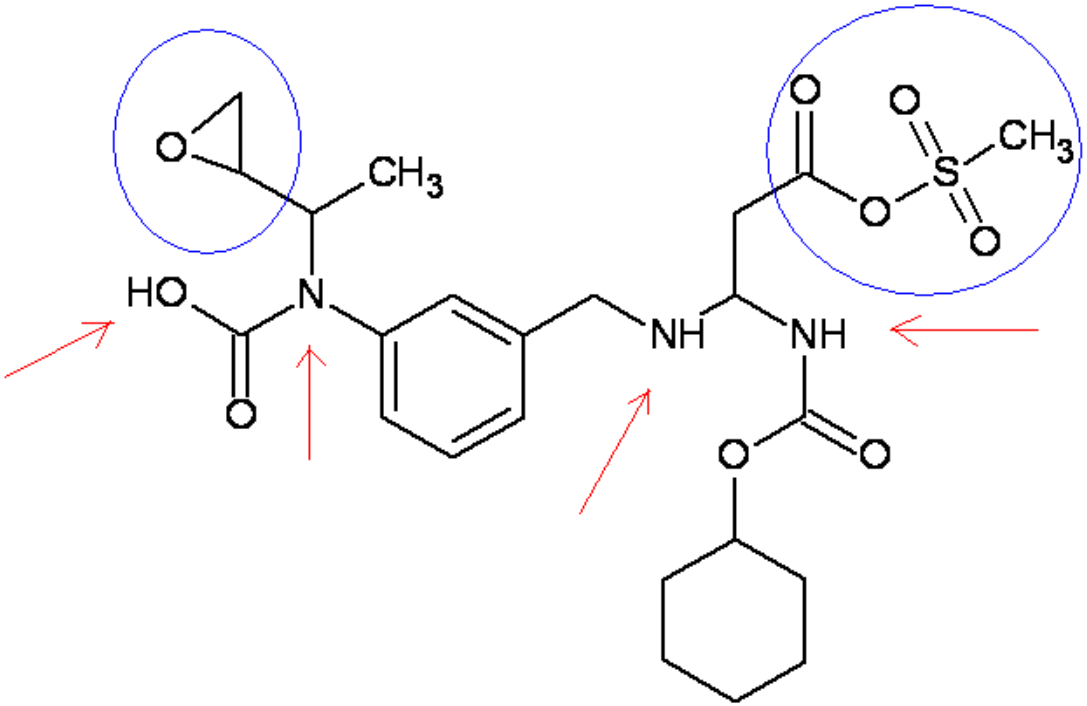
Our substance and reactivity



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

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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)

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Setting limits – PIC/S Guide

- 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

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PIC/S Guide (as of today)

- 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.

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PIC/S Guide (as of today)

- 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

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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

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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

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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*'

  http://www.imb.ie/images/uploaded/documents/GMP%20info%20day%20presentations/11_Cleaning%20Validation%20the%20Toxicological%20Approach_Lorcan%20Allen.pdf

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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

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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

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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

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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

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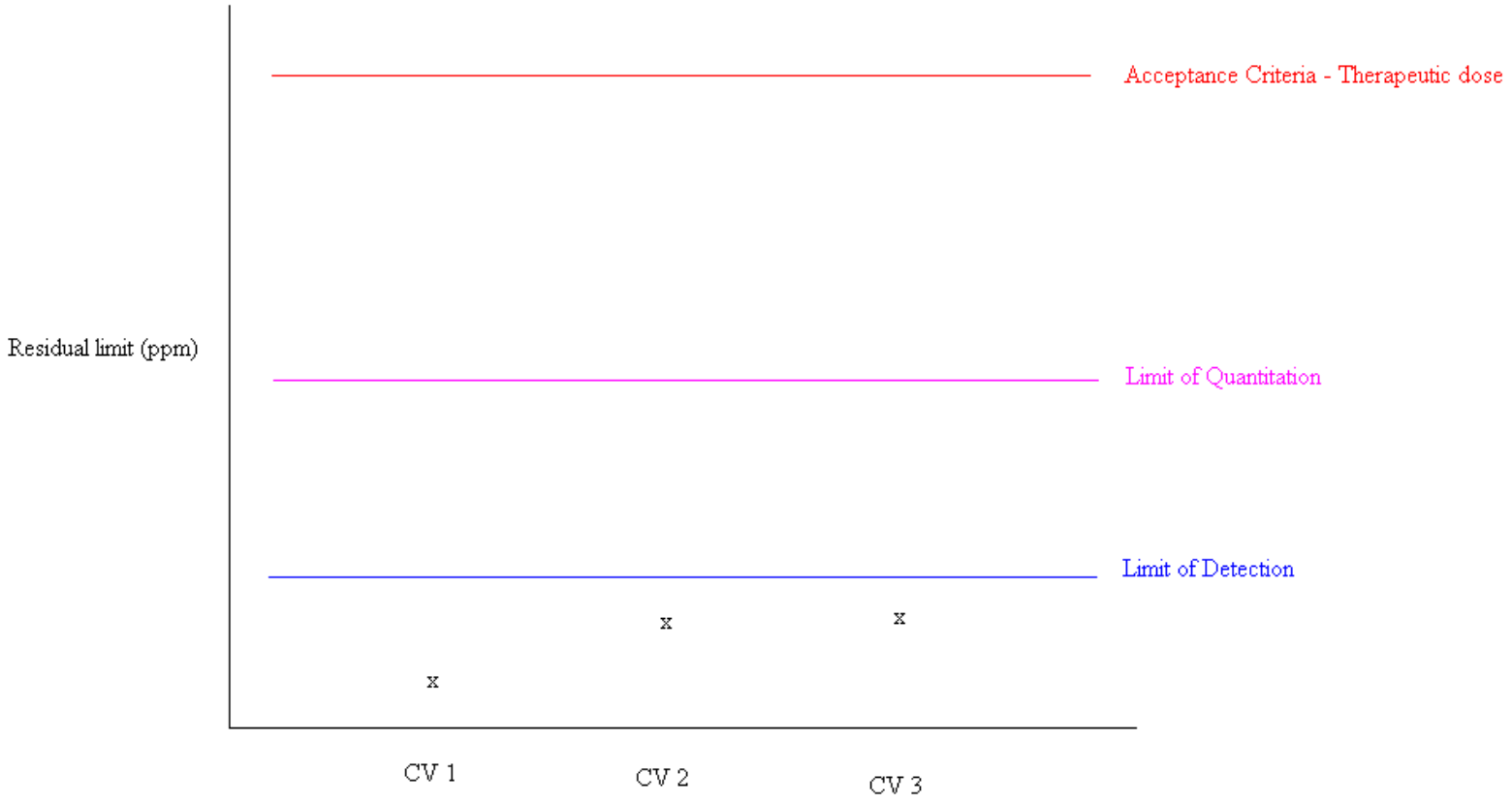
Output



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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

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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

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Thank you

- Thank you – any discussion comments?

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