Dispelling the Myths of Cleaning Validation

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CV myths

- "Things the FDA doesn't allow"
- Covers 8 myths
- Will discuss issues relating to those myths
- Rationale: not unnecessarily restrict scientifically justified options

Myth #1

- "Regulatory authorities don't like rinse water sampling"
- Fact: FDA and PIC/S guidance documents says rinse water sampling is one of two acceptable sampling methods

Issues

- "Direct measure" of target residue
- Relating rinse water concentration to potential contamination
- Rinse recovery
- Adequate coverage of rinse solution

Myth #2

- "You must correlate rinse sampling results with swab sampling results"
- Fact: Rinse and swab measure two different things; don't expect correlation

Issues

- Swabs focus on small area
- Rinses focus on larger area
- Swab measures worst case
- Rinse measures average

Issues

- If both done correctly on same surfaces, may pass on rinse but fail swab
- If both done correctly on same surface, if swabs pass, rinse should also pass

Myth #3

- "You can't use non-specific analytical methods"
- Fact: Non-specific methods such as TOC are widely used and are accepted by regulators

Issues

- TOC limit set on dose based calculations, not PW/WFI specs
  - Calculate and express limit as active
  - Convert analytical TOC value to active
  - Compare measured value to limit

Issues

- Assume worst case,all TOC due to target residue
- Note: Correctly applied, TOC is more stringent than specific method for target residue

FDA support

- Human Drug CGMP Notes --

"We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation."

Myth #4

- "If you use TOC, you must correlate it with HPLC"
- Fact: As long as TOC is validated with appropriate standards, do not need to "correlate" with HPLC

Issues

- What's point of running both TOC and HPLC on same standard for correlation?
- Method validation of TOC with target analyte is adequate and sufficient

Issues

- In CV protocols, TOC will never correlate with HPLC results
  - TOC is subject to interferences
  - Can't express exactly how much target residue present, but can assure is at or below measured amount
  - As long as interference increase TOC, will be worst case

Myth #5

- "Any residue is unacceptable"
- Fact: With newer methods or with TOC, will always find some residue

Issues

- Detection limits of analytical methods achieve lower levels
- Issue is whether residue is medically safe and whether it affect product quality
- But, any *visible residue* is generally unacceptable

FDA support

- Human Drug CGMP Notes --
  "Should equipment be as clean as the best possible method of residue detection or quantification?"

ANSWER: "No…"

Myth #6

- "Dose-based (MAC) limits calculations are unacceptable"
- Fact: Are referenced in FDA and PIC/S guidance documents

Issues

- Have been misused
- Safeguards against unreasonably high limits
  - Consider cumulative residues from equipment train
  - Default limits (such as 10 ppm)
  - Visually clean criterion
  - Reasonable "safety" factors

Issues

- Are defaults arbitrary?
- Yes, but so what?
- If medically safe limit is X ppm, and I set my limit is below that, from a regulatory perspective, should there be a concern?

Issues

- Consider other medical or safety concerns unrelated to "dose"
  - Allergenic
  - Cytotoxicity
  - Reproductive hazards
- May result in –
  - Limits = LOD of best method
  - Dedicated equipment

Myth #7

- "Recovery percentages at different spiked levels should be linear"
- Fact: Recovery percentages are highly variable. It is not reasonable to expect linear response

Example

Spike	Recovery
1.0 $\mu g/cm^2$	91%
2.0 $\mu g/cm^2$	81%
3.0 $\mu g/cm^2$	71%

Issues

- Swabbing is a manual procedure (analogy to manual cleaning)
- High variability in recoveries recovery for one individual
- High variability in recoveries among individuals
- As practical matter, will use lowest

Myth #8

- "You can't validate manual cleaning"
- Fact: You will validate manual cleaning processes

Issues

- Manual cleaning more variable than automated processes
- Consistency of manual cleaning depends on adequate detail in written procedure and adequate training of operators
- Requires more attention to validation maintenance

Origin of myths

- Probably misinterpretation or misapplication of 483's
  - Example: "Your use of rinse water sampling is inappropriate to…."
  - Faulty conclusion: Can't use rinse water sampling
  - Correct response: Use rinse sampling correctly

Suggestions

- Don't chase latest 483
- Design a comprehensive, defendable cleaning validation program
- Confirm (or disprove) "You can't…" statements by regulatory documents (Human Drug CGMP Notes, Warning Letters, Guidance Documents, GMPs)

- Q&A
- Discussion