Annex 15 and Cleaning Validation

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This Session

Annex 15 (2001) Cleaning Validation

Annex 15 (2015) Cleaning Validation & its impact

Annex 15 (2001) Cleaning Validation

Seven clauses only – in summary:

- (36) Cleaning validation is required. Rationale for limits should be logical. Limits should be achievable and verifiable
- (37) Associated analytical methods should be validated and sufficiently sensitive
- (38) Normally only for product contact. "Consider" non-contact surfaces. Cleaning methods, clean and dirty hold periods to be defined.
- (39) Matrixing of similar products and "worst case" single studies acceptable.
- (40) 3 consecutive successful studies = validated
- (41) Test until clean cannot be used in place of validation
- (42) placebos with similar properties can be substituted for hazardous materials

Annex 15 (2001) – Typical CV Practice

Matrix products by similar properties

Identify 1 or 2 worst case products, based on understanding of toxicity (LD50 if available) and 'cleanability'/solubility in cleaning fluid

Modify selections based on limits of detection for analytical methods

Annex 15 (2001) – Typical CV Practice

Use PI006 to provide 'logical rationale' for acceptance criteria - most stringent, and applicable, of:

- 1/1000th of a daily dose in the following product
- <10ppm in next product
- Visually clean when the limit of detection is quantifiable
- Below limit of detection for potent/sensitising products

Annex 15 (2001) – Typical CV Practice

Perform a recovery study

Calculate allowable carry over

Perform a simulated contamination or actual batch

Perform trials, reducing *at least* one intended critical cleaning parameter (time, temp., concentration, water volume, etc.)

After three consecutive, successful trials, declare cleaning validated.

What are we leaving in 2001?

Toxicology often limited to basic literature search

- Onus placed on level of safety in rules of thumb

No specific requirements around microbiology

No specific requirement for justifying effort

- three trials encouraged

Sampling requirements not well understood

Treating manual and automatic cleaning the same

But now … new Annex 15 (2015)

10.1 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.

Covers 2001 (36) and:

- New aspects
  - Simulation OK (analogies with 2001(42))
  - Matrixing of equipment OK
  - In both cases, must be justified (science and risk)

New Annex 15 (2015)

10.2	A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

Covers 2001 (41) and:

- Confirms visual inspection as important, but not acceptable as sole criteria
- Meaning of "alone" not elaborated upon
  - May need to be supplemented by other methodology
  - May need to be supplemented by quantification of visual limits.

New Annex 15 (2015)

10.3 It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

Completely new

- Effectively contradicts 2001 (40)
  - Allows for verification until validation complete (akin concurrent validation)
  - Verification would appear to be more than "final rinse passes", given the phrase "sufficient data".

New Annex 15 (2015)

10.4	Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.
10.15	Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.

Completely new

- Automated processes to be validated and the level of automated impacts the validation effort
- **<u>Manual processes require routine revalidation</u>**

New Annex 15 (2015)

10.5 For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

Completely new

- Required to understand the factors influencing effective and performance including potential variable factors
  - Historically well understood as part of cleaning validation

New Annex 15 (2015)

10.6 Limits for the carryover of product residues should be based on a toxicological evaluation[2]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

Significant redefining of requirements around limits

- To be based on toxicological evaluation (with reference to EMA HBELs guidance)
- Documented risk assessment
- Explicitly required for cleaning agents as well as products
- Challenges exist to meet this clause

New Annex 15 (2015)

10.6.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

10.6.2 If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

Caveats for 10.6

- Exemption to tox evaluation allowed it specified circumstances
- Exemption for testing "feasibility" provided, but not elaborated
- Still challenges exist to meet the clause

New Annex 15 (2015)

10.7	The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

Completely new

- But very vague. Suggests cleaning to microbial/endotoxin limits which provide a high degree of safety for such limits applicable to the next product, but could be clearer

New Annex 15 (2015)

10.8 The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.

Analogies with 2001 (38) but expanded

- Dirty and clean hold times must be defined and based on the influence of those times on cleaning effectiveness and performance.

New Annex 15 (2015)

10.9	Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.

Completely new

- The effect on ease of cleaning should influence the length of campaigns
- Validation should be based on the maximum campaign length

New Annex 15 (2015)

10.10 Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity, and potency.

Worst case concept similar to 2001 (39)

- Scientific rationale required
- New products to be comparatively assessed.

New Annex 15 (2015)

10.11 Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.

Completely new

- Sample locations should be clearly nominated and rationale provided

New Annex 15 (2015)

10.12 Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

Completely new

- Standard sampling methods recommended
- Consideration to be given to the appropriateness of sampling methods and materials
- Recovery studies explicitly required

New Annex 15 (2015)

10.13 The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

Significant change from 2001 (40)

- More definitive than the equivalent statement for process validation. 3 batches not the expectation.
  - Risk based approach.
  - **Proof** of validation.

New Annex 15 (2015)

10.14 Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of the PIC/S GMP Guide.

Completely new

- A nod to the appropriateness of dedicated equipment and/or other methods of cross-contamination prevention.

Key Changes

- Routine revalidation of manual processes
- Toxicological evaluation for limits
- Proof of validation required ≠ 3 batches

ANY QUESTIONS?