



Common
Cleaning
Validation
Pitfalls

Dawn Tavalsky

Director of Validation

1. True/false: Based on routine monitoring data *after* the validation (qualification) runs are complete, my facility/company revises **TOC** limits downward based on process capability for future validation (qualification) runs.

4 T
8 F

2. True/false: Based on routine monitoring data *after* the validation (qualification) runs are complete, my facility/company revises *bioburden* limits downward based on process capability for future validation (qualification) runs.

2 T

10 F

3. Which of the follow describes you facility's approach to sampling recovery studies *for bulk active manufacture*?

A. We run sampling recovery only on the final bulk active product.

B. We run sampling recovery on both the final bulk active product and on one "product" representative of an upstream process.

C. We run sampling recovery on the final bulk active and more than one "product" representative of earlier process stages.

D. Other : Ran recovery of three upstream product samples as during qualification of the TOC method;

A 4

B 2

C 4

D 2

4. What is the rationale for your cleaning validation limits for actives in *bulk manufacture*?

- A. Process capability
- B. Industry Standard Practice
- C. MACO (carryover calculation) based on dose
- D. MACO (carryover calculation) based on toxicity
- E. Limit of Detection/Quantitation of method
- F. Other: Viral as well; Start with B and move to A after sufficient data have been captured to determine process capability; Leverage the biotech Guideline written as a result of Biotech Roundtable I; Downstream (Purification on) Not more than 10 ppm of 1 product in another product, Upstream (all processing before purification) the limit must be based on the capabilities of the purification process to remove impurities; Process Validation that active is removed by Cleaning Process and limit at Cleaning Process capability for TOC removal;

A 3

B 6

C 3

D 3

E 1

F 4

NA 1

5. What is the rationale for your cleaning validation limits for actives in *fill/finish*?

- A. Process capability
- B. Industry Standard Practice
- C. MACO (carryover calculation) based on dose
- D. MACO (carryover calculation) based on toxicity
- E. Limit of Detection/Quantitation of method
- F. Other: Start with B and move to A after sufficient data have been captured to determine process capability; Use disposable gamma radiated containers for API in CT; Not more than 10 ppm of 1 product in another product; Process Validation that active is removed by Cleaning Process and limit at Cleaning Process capability for TOC removal;

A 3

B 3

C 3

D 3

E 1

F 3

NA 3

6. What types of products are run in your facility?

A. Commercial products

B. Clinical trial products

C. Both commercial and clinical trial products

A 1

B 1

C 10

7. What type of facility do you have?

A. Dedicated to one bacterial product

B. Multiproduct for more than one bacterial product

C. Dedicated to one mammalian product

B. Multiproduct for more than one mammalian product

E. Multiproduct for both bacterial and mammalian products in a common area

F. Multiproduct for both bacterial and mammalian products in separate and distinct areas

G. Other: Use disposable gamma radiated containers for API in CT; multiproduct for bacterial and viral vaccine products; F at US sites, E in European sites;

A 0

B 1

C 0

D 6

E 1

F 3

G 4

8. For CIP cleaning *for validations runs*, which acceptance criteria do you use?

- | | |
|---|------|
| A. Rinse conductivity | A 12 |
| B. Swab conductivity | B 0 |
| C. Rinse Total Protein | C 1 |
| D. Swab Total protein | D 1 |
| E. Rinse TOC | E 12 |
| F. Swab TOC | F 11 |
| G. Rinse pH | G 1 |
| H. Bioburden count | H 10 |
| I. Bioburden - exclusion of objectionables | I 3 |
| J. Rinse Endotoxin | J 11 |
| K. Cleaning agent w/specific method | K 1 |
| L. Other: Visual Inspection; Product/process related compounds as required; Visually Clean; | L 4 |

Note: For one answer on I, do only if over a certain threshold.

9. For CIP cleaning *for routine monitoring* of cleaning processes after the validations runs, which do you measure?

A. Rinse Conductivity

B. Swab Conductivity

C. Rinse Total Protein

D. Swab Total protein

E. Rinse TOC

F. Swab TOC

G. pH

H. Bioburden count

I. Bioburden - exclusion of objectionables

J. Rinse Endotoxin

K. Cleaning agent w/specific method

L. Other: Visual Inspection; F-product changeover but not lot to lot; Visually Clean;

Note: For one answer on I, do only if over a certain threshold.

A 12

B 0

C 1

D 1

E 9

F 4

G 1

H 6

I 1

J 5

K 0

L 4

10. What is the basis for your CV acceptance criteria for bioburden?

A. Same as WFI specs

B. Same as Purified Water specs

C. Related to the product's specifications for bioburden

D. Other: more allowed if post cleaning sterilized; Industry Standard Practice/Process Capability/LOQ; company directive on cleaning validation provides equation; B for upstream processes, A for downstream processes; Collect API bioburden and endo for each product, collecting bioburden data for in process equipment to determine process capability and to support or extend the current clean hold time; Between A and B; Final rinse water quality specifications and capability of the cleaning process (e.g. historical data); Related to the ability of subsequent step (e.g., SIP) to remove/reduce bioburden;

A 3

B 1

C 3

D 8

11. What is the basis for your CV acceptance criteria for endotoxin?

A. Same as WFI specs

B. Related to the product's specifications for endotoxin

C. Other: Collect API bioburden and endo for each product, collecting bioburden data for in process equipment to determine process capability and to support or extend the current clean hold time; A for downstream, B for upstream; Final rinse water quality specifications and capability of the cleaning process (e.g. historical data);

A 9

B 3

C 3

12. Have you done degradation studies for at least some of your bulk actives?

A. Yes

B. No

A 8

B 4

13. If you answered “Yes” to Question 12, do you use a dose-based MACO (carryover) calculation for the acceptance criteria?

A. Yes

B. No

C. Not applicable

D. Other: A (for incomplete degradation & inspectors want to see it) or C;

Note: For the one answer for A, it was added “for agencies”.

A 1

B 6

C 4

D 1

14. For Clean Hold Studies, what rinse solution is used?

A. Ambient WFI

B. Hot WFI

C. Buffer normally used in that equipment

D. Growth promotion buffer

E. Other: Media,

A 9

B 4

C 0

D 1

E 1

Note: Above includes one answer that was "A - Hot WFI for cleaning,
D - Growth promotion buffer for sampling

15. For a New Product Introduction into a multi-product facility, how many CV runs do you perform if there is supporting data that the new product is less challenging to clean than the current worst case already validated.

A. Three

B. Two

C. One

D. None

E. Other: None if the ARL for new product is higher than what we have demonstrated for more difficult products (haven't yet seen any ARL lower than what we've demonstrated); Limited verification studies may be performed to demonstrate that the product was adequately removed prior to the manufacture of the next product.

A 1

B 0

C 7

D 3

E 2

16. What is your practice for Ultrafiltration Membranes?

A. They are always dedicated to a specific product

B. They can be used for a different product if CV is successful

A 8

B 2

NA 2

17. When performing MAC (carryover) calculations, is total shared surface area based on:

- A. All shared surface areas in drug substance *and* drug product manufacturing
- B. All shared surface areas in drug substance *or* drug product manufacturing (do not combine)
- C. All shared surfaces starting from final purification.
- D. Do not use MAC calculation
- E. Other: upstream equipment for upstream limits (bioreactors/harvest), downstream equipment train for downstream limits (drug substance mfg only); Shared equipment between Drug substance and Drug product, the surface area of equipment must be used in both calculations;

A 0

B 2

C 3

D 6

E 2

18. When certain surface areas have been excluded from a carryover calculation, are they justified (scientifically documented)?

- A. Yes
- B. No

A 3

B 2

NA 7

19. Do you follow the “not more than 10 ppm of one product can be in another product” guidance?

- A. Yes
- B. No

A 5

B 7

20. After validation has been completed, during routine manufacturing what type of testing is performed at changeover from one product to a different product?

A. Rinse, Swab, and visual inspection

B. Rinse & visual inspection

C. Swab & visual inspection

D. Only visual inspection

E. None

F. *Other*: Depends upon cleanability of product A vs. product B;

A 5

B 1

C 0

D 2

E 1

F. 3

21. For validating a spray device, do you test:

A. At the design flowrate of the spray device.

B. At a lower flowrate (worst-case approach).

C. At both a lower flowrate and a higher flowrate than design.

A 9

B 3

C 0

22. For fixed (stationary, non-rotating) spray devices, do you flow rinse water:

- A. For a set time that is found to be effective at removing riboflavin, but may be longer than the actual CIP phase rinse/ wash times.
- B. For a time that matches the lowest rinse/ wash time of the CIP program.
- C. For a set time that is shorter than the actual CIP phase rinse/ wash times.
- D. *Other*: Perform spray ball coverage testing at a lower flowrate

A 2

B 3

C 6

D 1

23. For riboflavin testing in a fixed (stationary, non-rotating) spray devices, do you flow rinse water:

A. In a continuous flow (without interruption)

B. In a series of "burst-rinses" that allows the rinse water to fully drain between each burst.

A 5

B 7

24. For spray coverage testing, do you:

A. Use only cold/ ambient water.

B. Use only hot water.

C. Use cleaning chemical, hot or cold.

D. Run the entire CIP program.

E. *Other:*

A 9

B 6

C 0

D 0

E 1

25. Post CIP, we store our clean equipment dry by:

- A. Leaving the equipment vented with a low point drain open.
- B. Performing a series of air-blow steps to fully dry it, and then leave it vented.
- C. Performing a series of air-blow steps to fully dry it, then close it off.

D. We do not dry our equipment, but perform a steam-in-place on the equipment within a specified time after completion of the CIP cycle to address bioburden proliferation.

E. We do not dry our equipment, but instead rely on clean-hold validation studies to establish hold times.

F. *Other*: Perform air-blows on all equipment and TFLs, SIP specific equipment within a specified hold time post CIP;

Note: one answer for E included “use airblows but not fully dry”.

A 1

B 3

C 6

D 2

E 2

F 2

26. When returning equipment to service after long term storage, we:

A. Determine the necessary return to service requirements on a case by case basis.

B. Treat it as we would equipment that exceeded a clean-hold time.

C. Treat it as we would equipment that exceeded a dirty-hold time.

D. Other: Return to Service SOP; may choose to perform a media hold;

A 3

B 7

C 4

D 1



Other Common Problems in Cleaning Validation

When does Dirty Hold Time Start?

When do you do Clean Hold Validation?

What rationale do you use to Bracket Equipment?

Validated Analytical Methods

Drying Equipment after Cleaning



Other Common Problems in Cleaning Validation

Rouge

Sprayball Replacement

Detergent Replacement

Small scale coupon studies

Questions? More Information?



Dawn Tavalsky

Dawn.tavalsky@genzyme.com