Setting Rational MAC-Based Limits Part I—Reassessing the Carryover Criterion

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“New Perspectives on Cleaning” is an ongoing series of articles dedicated to cleaning process development, characterization, validation, and monitoring. This column addresses scientific principles, strategies, and approaches associated with cleaning that are faced in everyday work situations.

Reader questions, comments, and suggestions are requested for future discussion topics. Please submit comments to the column coordinator Rizwan Sharnez at rsharnez@amgen.com or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

SUMMARY
The maximum acceptable carryover (MAC) criterion is widely used to set cleaning validation limits for contaminants. It is based on the assumption that all the residual contaminants in the cleaned equipment will carryover into the next batch that is manufactured in that equipment. Thus, the MAC criterion is based on a worst-case mass balance (WCMB) for the contaminant. This article demonstrates that the conventional approach for setting cleaning validation limits is far more conservative than a WCMB. Consequently, it leads to acceptance criteria that are much more stringent than necessary. This often results in cleaning validation limits that are impractical to achieve. Additionally, in some instances the acceptance criteria can be well below the limit of quantitation (LOQ) of the analytical method.

An alternate approach for setting rational cleaning validation limits based on the MAC criterion and WCMB is described. The limits are used to derive more meaningful acceptance criteria for cleaning validation samples. For a typical pharmaceutical process, limits based on the proposed approach are shown to be about an order of magnitude higher than those based on the conventional approach.

An important benefit of setting rational MAC-based limits is that higher acceptance criteria for cleaning validation samples can be justified. With higher acceptance criteria, it is possible to replace complex product-specific assays with relatively simple non-specific assays such as total organic carbon (TOC).

INTRODUCTION
An important objective of cleaning validation for multiproduct equipment is to demonstrate acceptable carryover of the previously manufactured product (A) into the subsequently manufactured product (B). This is often accomplished by imposing a reasonable limit on the amount of A (M_{A,MAX}) that can be present in a dose of B. This limit is typically defined in terms of the minimum therapeutic dose of A (TD_{MIN,A}) and a safety factor (SF) (see Reference):

\[ M_{A,MAX} \leq TD_{MIN,A} / SF \]

In terms of the concentration of A (C_A = M_{A,MAX}/D_{B,MAX}) in the largest (worst-case) dose of B (D_{B,MAX}), the above inequality can be expressed as follows:

\[ C_A \leq TD_{MIN,A} / SF / D_{B,MAX} \]

Further, the maximum acceptable carryover of A into a manufacturing batch of B (MAC_{A,B}) is related...
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to $C_A$ by the following equation:

$$\text{MAC}_{AB} = (C_A) (B_{B,\text{MIN}})$$

Where, $B_{B,\text{MIN}}$ is the smallest batch of B (worst-case) that is manufactured in the facility. Thus,

$$\text{MAC}_{AB} \leq (TD_{\text{MIN,A}} / SF) (B_{B,\text{MIN}} / D_{B,\text{MAX}})$$

[Equation 1]

The above MAC-based limit can be expressed in terms of acceptance criteria for cleaning validation samples. Consider an equipment train used to manufacture products A and B that has a shared product-contact surface area $SA_{AB}$. The average surface concentration of A ($\overline{SC}_A$) on the clean-shared surface area (i.e., after the cleaning is performed) is related to the surface analysis samples by Equation 2:

$$\overline{SC}_A = \sum (SS) / N \ (i = 1 – N)$$

[Equation 2]

Where $\sum (SS)$ is the sum of all the surface analysis sample data for the shared equipment train, and $N$ is the number of surface analysis samples. Further, the maximum value of $\overline{SC}_A$ can be expressed in terms of MAC$_{AB}$ as follows:

$$(\overline{SC}_{A,\text{MAX}}) (SA_{AB}) = \text{MAC}_{AB}$$

[Equation 3]

Equation 3 is based on the assumption that all the mass of A on the clean shared surface area of the equipment train will carryover into the next batch of B. This represents a worst-case scenario from the standpoint of contamination. Additionally, the locations within the equipment train that are selected for surface analysis represent a worst-case from the standpoint of cleanability. Thus, the data from the surface analysis samples also represent a worst-case scenario from the standpoint of contamination.

Combining equations 1 through 3 gives the following equation:

$$\overline{SC}_{A,\text{MAX}} = \sum_{\text{MAX}} (SS) / N \leq \text{MAC}_{AB} / SA_{AB} \ (i = 1 – N)$$

[Equation 4]

Where $\sum_{\text{MAX}} (SS)$ is the maximum acceptable limit for the sum of all the surface analysis sample results for the shared equipment train, and MAC$_{AB}$ is defined by Equation 1. Note that Equation 4 does not explicitly limit each of the surface samples; instead, it limits only the sum of all the surface samples. Thus, the practice of using Equation 4 to set limits for specific surface samples (e.g., individual swab sites) greatly limits the flexibility inherent in the criterion.

In the following section, the conventional approach of setting predetermined limits on all the surface analysis samples is compared with the proposed approach of setting a predetermined limit only on the sum of all the surface samples. The comparison is elucidated through a case study based on a typical multiproduct equipment train. The case study is based on the carryover of one product into another (i.e., cross-contamination of multiproduct equipment); however, the underlying principles for converting MAC-based limits to acceptance criteria for cleaning validation samples are the same for most contaminants, and so the approach described here can be extended to other applications, such as the carryover of cleaning agents.

The case study demonstrates that the conventional approach is far more conservative than the worst-case scenario that is physically possible. This drawback of the conventional approach results in acceptance criteria that are much more stringent than necessary. The resulting cleaning validation limits are often impractical to achieve or significantly below the LOQ of the analytical method.

The proposed approach is based on a realistic worst-case mass balance and provides more meaningful acceptance criteria for cleaning validation. For a typical pharmaceutical process, limits based on the proposed approach are shown to be about an order of magnitude higher than those based on the conventional approach. A significant benefit of higher cleaning validation limits is that complex product specific assays can be replaced by relatively simple non-specific assays such as TOC.

**CASE STUDY**

The problem statement for the case study is delineated in this section. Consider an equipment train that consists of ten unit operations, each with its own cleaning circuit. The equipment train is used to manufacture two products, A and B. Using the following parameters, calculate the acceptance criteria for surface analysis samples of product A based on the conventional and proposed approaches described in the previous section:

- $SA_{AB} = 10^5 \text{ cm}^2$
- $N = 100$ (i.e., an average of 10 surface analysis samples per system)
Substituting these parameters into Equation 1 gives the following:

\[
\text{MAC}_{AB} \leq (10^{-2} \text{ g} /1000) (10^5 \text{ g} /1 \text{ g}) = 1 \text{ g}
\]

Further, Equation 4 becomes the following:

\[
\sum_{\text{MAX}} (SS)_i / (100) \leq (1 \text{ g}) / 10^3 \text{ cm}^2 \quad (i = 1 – 100)
\]

Therefore,

\[
\sum_{\text{MAX}} (SS)_i \leq 1 \mu \text{g per cm}^2 \quad (i = 1 – 100)
\]

[Equation 5].

**Conventional Approach**

With the conventional approach, the acceptance criterion for each one of the 100 surface analysis samples would be < 0.01 µg per cm², thereby ensuring that the sum of all the surface analysis sample results could not exceed 1 µg per cm². Thus, even if 99 samples were below the LOQ of the analytical method (i.e., no more than 0.001 µg per cm²), and one sample was 0.01 µg per cm², the cleaning validation would fail. However, the mass balance would indicate that the actual carryover of A into B \( \text{CO}_{AB} \left[= (\text{SA}_{AB}) \left(\sum (SS)_{100}\right)\right] \) would be no more than:

\[
(10^8 \text{ cm}^2) \left[ (0.001 \mu \text{g/cm}^2) (99) + (0.01 \mu \text{g/cm}^2) (1) \right] / 100
\]

Therefore,

\[
\text{CO}_{AB} = 1.09 \times 10^6 \mu \text{g} = 0.109 \text{ g}
\]

Which is approximately an order of magnitude lower than \( \text{MAC}_{AB} \) (1 g).

This analysis indicates that with the proposed approach the cleaning validation could pass even if one sample in each of the 10 systems was as high as 0.09 µg per cm². Conversely, with the conventional approach the cleaning validation would fail even if 1 of the 100 samples were to exceed 0.001 µg per cm².

**CONCLUSION**

The conventional approach for setting MAC-based cleaning validation limits is more conservative than the worst-case scenario that is physically possible. Consequently, the conventional approach results in acceptance criteria that are much more stringent than necessary. The resulting cleaning validation limits are often impractical to achieve or significantly below the LOQ of the analytical method. The proposed approach is based on an overall worst-case mass balance and provides more meaningful acceptance criteria for cleaning validation samples.

A typical multiproduct equipment train consisting of 10 unit operations and 100 surface analysis samples was used to demonstrate the difference between the two approaches. The results indicate that with the conventional approach the cleaning validation would fail even if 1 of the 100 surface analysis samples exceeds the predetermined limit. Conversely, with the proposed approach the cleaning validation could pass even if one of the surface analysis samples from each of the 10 operations was up to 9 times higher than the limit specified by the conventional approach. The case study demonstrates that from the perspective of acceptable permutations of surface analysis samples, the proposed approach provides more degrees of free-
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dom as compared to the conventional approach. It also underscores the importance of utilizing the MAC-based criterion to derive acceptance criteria for the lot that is manufactured in the equipment train, and not for specific surface sampling sites. Thus, failure limits derived on the basis of an acceptable carryover of a contaminant should be expressed in terms of acceptance criteria for the lot as a whole.

**REFERENCE**

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**ARTICLE ACRONYM LISTING**

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<tr>
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<td>D$_{B,\text{MAX}}$</td>
<td>Largest (worst-case) dose of B</td>
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