Strategies for Setting Rational MAC-Based Limits Part II—Application to Rinse Samples

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"New Perspectives on Cleaning" is an ongoing series of articles dedicated to cleaning process development, 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. These can be submitted either to column coordinator Rizwan Sharnez at rsharnez@amgen.com or to managing editor Susan Haigney at shaigne@advanstar.com.

SUMMARY
The maximum acceptable carryover (MAC) criterion is widely used to set cleaning validation acceptance limits for multiproduct equipment. The conventional approach for setting cleaning validation limits based on the MAC criterion results in acceptance criteria that are much more stringent than necessary. This often results in cleaning validation limits that are impractical to achieve and, in some instances, well below the limit of quantitation of the analytical method.

In this series we describe strategies for setting rational MAC-based limits for multiproduct equipment. The limits are used to justify more reasonable acceptance criteria for cleaning validation. This results in shorter cycles and higher success rates for cleaning operations. It also facilitates the utilization of simpler and more cost-effective non-specific assays, such as total organic carbon and conductivity. Part I of this series applied this approach to samples for surface analysis. Part II deals with the application of this approach to rinse samples.

INTRODUCTION
The maximum acceptable carryover (MAC) criterion is used to set cleaning validation acceptance limits for multiproduct (shared) equipment. It is based on a worst-case mass balance (WCMB) for the previously manufactured product (1). The WCMB approach is based on the conservative assumption that all the residual contaminant in the cleaned equipment will carryover into the next batch that is manufactured in that equipment.

In Part I of this series we described how the conventional approach for setting MAC-based cleaning validation limits is far more conservative than the worst-case scenario that is physically possible (2). This results in acceptance criteria for surface analysis (e.g., swab samples) that are much more stringent than necessary. The resulting cleaning validation limits are often impractical to achieve and, in some instances, well below the limit of quantification.
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titation (LOQ) of the analytical method. To address this issue, we proposed an alternate approach based on setting rational MAC-based limits. The proposed approach is based on a WCMB; however, failure limits are established for the equipment or lot as a whole, but not for specific surface sampling sites. Instead, failure limits for specific surface sampling sites are set based on process capability, visual inspection, and default limits, such as the 10-ppm criterion. This results in more reasonable acceptance criteria for swab samples. For a typical pharmaceutical process, swab limits based on the proposed approach were shown to be about an order of magnitude higher than those based on the conventional approach.

In this discussion we apply the above concepts to the practice of verifying MAC limits through rinse sampling. The analysis indicates that, with the proposed approach, it is possible to justify acceptance criteria for rinse samples that are an order of magnitude higher than those based on the conventional approach. This results in more efficient cleaning cycles and fewer unwarranted cleaning validation failures. Higher rinse limits also facilitate the elimination of complex product-specific assays (PSAs) in favor of simpler and more cost-effective non-specific assays, such as total organic carbon (TOC) and conductivity. This strategy is particularly useful for biological active pharmaceutical ingredients (APIs) for which product-specific immunoassays (PSA), such as EIA and ELISA, can be misleading and difficult to develop for cleaning applications. For instance, PSIAs can result in false negatives because the epitopes that these assays are designed to recognize are often destroyed when the API is exposed to extremes of pH and temperature during cleaning.

MAC-BASED ACCEPTANCE CRITERIA FOR RINSE SAMPLES

This section describes the conventional and proposed approaches for deriving the MAC-based acceptance criteria (AC) for rinse samples. AC based on the proposed approach (AC_p) is substantially greater than the AC based on the conventional approach (AC_c), and the difference increases exponentially with the rinse recovery factor.

Rinse Recovery Factor

The mass of component A in the rinse (M_R) is correlated to the mass of component A on the surface that is being rinsed (M_S) by the rinse recovery factor (RRF):

\[ \text{RRF} = \frac{M_R}{M_S} \]  

[Equation 1]

Conceptually, the RRF is similar to a swab recovery factor, with the rinse being analogous to the swab. It is determined by spotting coupons with the soil that is being cleaned, and subjecting them to a simulated rinse at small scale that is representative of the final rinse at full scale (3).

As the efficiency of the rinse step increases, \( M_R \rightarrow M_S \) and RRF \( \rightarrow 1 \) (or 100%). Conversely, as the efficiency of the rinse step decreases, \( M_R \rightarrow 0 \), and RRF \( \rightarrow 0 \). Thus, RRF can vary between the limits of 0 and 1, which represent 0 and 100% recovery, respectively.

Rinse Volume-Weighted Approach

For an equipment train that is shared between two products A and B, the maximum acceptable carryover of A into a manufacturing batch of B (MAC_{AB}) is given by the following equation (2):

\[ \text{MAC}_{AB} \leq \left( \frac{TD_{MIN,A}}{SF} \right) \left( \frac{B_{MIN}}{D_{MAX}} \right) \]  

[Equation 2]

Where, \( TD_{MIN,A} \) is the minimum therapeutic dose of A, \( B_{MIN} \) is the smallest integral batch of B (worst-case) that is manufactured in the facility, \( D_{MAX} \) is the largest (worst-case) dose of B, and SF is the safety factor.

It should be noted that the estimate of \( B_{MIN} \) must account for any splits during processing. For instance, if the batch is split into \( S \) equal sublots before being filled, then the limit calculated on the basis of the sublots should be multiplied by \( S \) to get the actual MAC limit for the shared equipment train.

The above MAC-based limit can be expressed in terms of acceptance criteria for rinse samples. The rinse samples are collected from the final rinse of each of the cleaning cycles. If the shared equipment train consists of \( N \) cleaning circuits, and if \( V_i \) (i=1-N) represent the final rinse volumes for the \( N \) circuits, then the total volume of all the final rinses is \( V_T = \Sigma V_i \).

The acceptance criteria for the previous product A in the rinse for each of the \( N \) circuits is derived by distributing MAC_{AB} across the shared equipment train. For rinse sampling, the optimal solution is obtained by using the following rinse volume-weighted approach (4):
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\[
M_{S,i} = \text{MAC}_{AB} \left( \frac{V_T}{\Sigma} \right) \quad (i=1-N) \quad \text{[Equation 3]}
\]

Where, \( M_{S,i} \), the mass of A on the surface of the \( i^{th} \) circuit, is the maximum allowable carryover of A for the \( i^{th} \) circuit. Note that by definition, \( \Sigma M_{S,i} = \text{MAC}_{AB} \).

Also, \( M_{R,i} \), the mass of A in the effluent rinse for the \( i^{th} \) circuit, is given by,

\[
M_{R,i} = V_i \cdot C_i \quad \text{[Equation 4]}
\]

Where, \( V_i \) is the volume of the final rinse for the \( i^{th} \) circuit, and \( C_i \) is the concentration of the previous product A in \( V_i \). When \( M_{S,i} \) is given by Equation 3, \( C_i \) becomes the acceptance criterion for the \( i^{th} \) circuit (\( AC_i \)), and Equation 4 becomes:

\[
M_{R,i} = V_i \cdot AC_i \quad \text{[Equation 4a]}
\]

**Conventional Approach**

The conventional approach is based on the premise that \( M_{S,i} \), defined by Equation 3, is the mass of A on the surface of the \( i^{th} \) circuit before the final rinse step. Thus, in accordance with Equation 1, the rinse recovery factor for A (RRF) can be expressed as:

\[
\text{RRF} = \frac{M_{R,i}}{M_{S,i}} \quad \text{[Equation 1b]}
\]

Substituting for \( M_{S,i} \) and \( M_{R,i} \) from Equations 3 and 4a, respectively, gives:

\[
\text{RRF} = \frac{AC_i \cdot V_i}{\text{MAC}_{AB}} \quad \text{[Equation 4b]}
\]

In Equation 4b, \( AC_i \) represents the acceptable limit of A in the rinse for the \( i^{th} \) circuit (i.e., the acceptance criterion for the \( i^{th} \) rinse sample). Thus,

\[
AC_i = \frac{(\text{MAC}_{AB}/V_i) \cdot \text{RRF}}{1 - \text{RRF}} \quad \text{[Equation 5a]}
\]

Note that RHS of Equation 5a is independent of \( i \), so the subscript \( i \) can be dropped. Thus,

\[
AC_p = \frac{(\text{MAC}_{AB}/V_i) \cdot \text{RRF}}{1 - \text{RRF}} \quad \text{[Equation 5d]}
\]

Where the subscript \( P \) denotes the proposed approach.

The above analysis indicates that the rinse volume-weighted approach results in a uniform acceptance criterion for all the rinse samples. This results in the highest possible acceptance criterion that can be justified for rinse samples (4). Thus, the rinse volume-weighted approach represents an optimal solution for deriving the acceptance criteria for rinse samples.

**Comparison of Conventional and Proposed Approaches**

Combining Equations 5b and 5d gives:

\[
\frac{AC_p}{AC_c} = \frac{1}{(1- \text{RRF})} \quad \text{[Equation 6]}
\]

Because RRF varies between 0 and 1 (i.e., 0 \( \leq \) RRF \( \leq \) 1), Equation 6 indicates that the acceptance criterion obtained with the proposed approach (\( AC_p \)) is always greater than or equal to that obtained with the conventional approach (\( AC_c \)). As RRF \( \rightarrow \) 0, \( AC_p \rightarrow \infty \); and as RRF \( \rightarrow \) 1, \( AC_p \rightarrow AC_c \). Thus, as RRF increases from 0 to 100%, the ability of the final rinse to remove any residue of product A increases exponentially as shown in the Table.
CONCLUSION

MAC-based acceptance criteria for cleaning validation are derived with the assumption that all the residual mass of the previously manufactured product A that is on the cleaned surfaces of the equipment train will carryover into the next batch of B. This represents a worst-case scenario from the standpoint of contamination.

The conventional approach for setting MAC-based limits for rinse samples is far more conservative than the worst-case scenario that is physically possible. This 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 reasonable acceptance criteria for rinse samples. For a rinse recovery of 90%, 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 justifying higher cleaning validation limits is that complex product-specific assays can be replaced by relatively simple and more cost-effective non-specific assays, such as TOC or conductivity. It also can be leveraged to develop more efficient cleaning cycles to reduce cleaning validation failures.

The analyses presented in this series are 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.

REFERENCES

4. Sharnez, R., Unpublished results. *JVT*

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SUBSCRIPTS

- **C**: Conventional
- **i**: Cleaning Circuit Number
- **P**: Proposed
- **R**: Rinse
- **S**: Surface
- **T**: Total

ARTICLE ACRONYM LISTING

- **A**: Product A
- **AC**: Acceptance Criteria
- **API**: Active Pharmaceutical Ingredient
- **B**: Product B
- **B_{MIN}**: Smallest batch size of B
- **D_{MAX}**: Largest (worst-case) dose of B
- **LOQ**: Limit of Quantitation
- **M**: Mass
- **MAC**: Maximum Acceptable Carryover
- **MAC_{AB}**: Maximum Acceptable Carryover of A into a Manufacturing Batch of B
- **N**: Total Number of Cleaning Circuits
- **PSA**: Product-Specific Assay
- **PSIA**: Product-Specific Immunoassays
- **RRF**: Rinse Recovery Factor
- **SF**: Safety Factor
- **TD_{MINA}**: Minimum Therapeutic Dose of A
- **TOC**: Total Organic Carbon
- **V**: Volume
- **WCMB**: Worst-Case Mass Balance

### Table: Acceptance criterion (AC) for final rinse samples as a function of the RRF. Subscripts P and C denote proposed and conventional approaches, respectively.

<table>
<thead>
<tr>
<th>RRF (%)</th>
<th>AC/AC_{C}</th>
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<tr>
<td>→ 100</td>
<td>→ infinity</td>
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<td>25</td>
<td>1.33</td>
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<tr>
<td>→ 0</td>
<td>→ 1</td>
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