GE
Water & Process Technologies
Analytical Instruments

Application Note

Taking the Mystery Out of the Maximum Allowable Carryover (MAC) Calculations for Cleaning Validation

Using the Sievers TOC Derivation of the Fourman and Mullen calculation will eliminate inconsistent and arbitrary limits*

One of the main objectives of the cleaning process in pharmaceutical manufacturing is to remove product or cleaning agent residues so there is no possibility for potential contaminants to transfer to the next product being manufactured. One necessary component of ensuring that this does not occur is to establish scientifically justified acceptance criteria limits. This application note presents a step-by-step understanding specific for establishing acceptance criteria with the use of TOC. A practical technique in utilizing the Sievers derivation is to build upon the traditional Fourman and Mullen approach to calculate acceptable limits for cleaning validation.

Sievers Derivation to Acceptance Criteria

The Sievers derivation for acceptance criteria is a multiple step calculation and applies the Carbon contribution and the API contribution factor to the final acceptance criteria result. Each of the steps are characterized as follows:

[1] Acceptable Daily Intake

The Acceptable Daily Intake (ADI) is considered a safety level and regularly used in acceptance criteria calculations incorporating toxicology levels to reduce the risk of carryover from batch to batch. A NOEL value is calculated to an ADI value by applying a safety factor depending upon the product being manufactured.

$$NOEL = \frac{LD_{50}}{\text{Empirical Factor}}$$ [1]

ADI = NOEL x Average Patient Weight x Safety Factor

Where: NOEL = No observable effect level
LD50 = A value at which half the test animals given the test substance die

Average Patient Weight = 60 Kg
Safety Factor = Typically .001

[2] Absolute Amount Limit (MAC) in Subsequent Product

The MAC can be calculated to demonstrate the absolute amount of concentration of product "A" in the subsequent product "B." Most of these factors in this calculation can be found fairly easily in regulatory filings, product labels[2] and company specific validation documents, (e.g. Master plans, protocols, qualifications or procedures). The following modified equation (originally developed by Foreman and Mullen) gives the maximum allowable concentration.

$$MAC = \frac{(ADI)\,(A_{min.dose})\,(B_{batch})}{(B_{max\ dose})}$$

Where: MAC =Maximum Allowable Concentration (mg/L)
ADI = Acceptable Daily Intake (mg)
$A_{min.dose}$ = Minimum Dose of Product "A" (mg)
B_{batch} = Batch Size of Subsequent Product "B" (mg)
$B_{max\ dose}$ = Maximum Dose of Product "B" (mg)

[3] Absolute Limit Per Surface Area

Once the MAC has been calculated, the next step is to determine the residue limit of a possible contaminant level on the surface area of the shared manufacturing equipment.

$$\text{Limit per Surface Area} = \frac{MAC}{SSA}$$

Where: MAC = Maximum Allowable Concentration (mg/L)
SSA = Shared Surface Area of equipment used to manufacture products "A" & "B" (cm^2)

At times some factors in the MAC calculation can not be determined. For example, during development stages it may be premature to determine the dosing regimen for Product "A" and "B." Therefore, it is suggested that one uses volume calculations to determine the capacity that the equipment can handle during normal operations.

MAC =

$$\frac{(ADI)(\text{Batch Volume Based on } \sum \text{ of Equipment Capability})}{SSA}$$

Where: MAC = Maximum Allowable Concentration (mg/L)
ADI = Acceptable Daily Intake (mg)
Volume of Rectangular Equipment = Length x width x depth (cm3)
Volume of Cylindrical Equipment = Radius x depth (cm^3)
Volume of Cone Equipment, (e.g. V-Blender) = Radius x depth/3 (cm^3)
SSA = Shared Surface Area of equipment used to manufacture products "A" and "B" (cm^2)

It is important to consider that this factor of the derivation assumes all product residue volume will be evenly distributed over all the shared surface areas of the equipment. The next step of the derivation provides a solution to determine the limit in the swab or rinse sample being analyzed by the validated TOC analytical method.

[4] Absolute Limit Per Sample for Analytical Response
There are two options when calculating the absolute limit in cleaning validation samples for an analytical response through direct (swab) and indirect (rinsate) samples.

$$\text{Limit per Sample} = \frac{(\text{Limit of SSA})(SA^*)}{V}$$

Where: Limit of SSA = The limit calculated for the MAC in relation to the shared surface area of the equipment (mg/L cm^2)
SA* = Swabbed area if swabs are being used (cm^2)
V = Volume used to desorb the swab, (extract the compound off of the swab tip) or the sample volume of the rinsate. (mL)

This derivation demonstrates the absolute limit for the swab sample or rinse sample for the TOC analytical response. The volume used to extract the compound of the swab should not be adjusted to compensate for a greater analytical response or lack of sensitivity that other TOC instruments see at low levels below 1 parts per million (ppm).

[5] API and Carbon Contribution Recovery Factor (Specific for TOC Analysis)
The API and carbon contribution recovery factor can be calculated with the molecular weight of the compound. Percent Carbon (% C) is derived from the empirical formula of the compound.

API & Carbon Contribution Recovery Factor =

$$\frac{\%\ \text{API of Product x (mg C) (100) x Limit per Sample}}{(MW)}$$

Where: % API of Product = Concentration of API in product
mg C = Amount of carbon compound in formula multiplied by 12
MW = Molecular weight of the compound
Limit per Sample = Amount of concentration in the sample (mg/L, ppm)

This step is crucial in determining the acceptance criteria for the use of TOC for cleaning validation, given that TOC is an analytical method that is specific in determining carbon concentrations in solution.

Moving Forward

Scientifically speaking the MAC is defined as the total concentration of product "A" in the final batch of product "B." This only assumes that all of the residual of product "A" will be homogeneously mixed within that specific batch of product "B." Most importantly, knowledge of the product, process, cleaning agent, cleaning process and the analytical method strengthens the foundation for establishing the criteria that best demonstrates the cleaning process capability and insures that subsequent products will not be contaminated. Use of the Sievers derivation, which contains the percent carbon factor, allows the MAC equation to be used to calculate quantifiable TOC limits; without the percent carbon factor, the MAC yields a quantifiable compound concentration, not a TOC concentration.

References

1 D L Conine, B D Naumann, and L H Hecker, Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices, Quality Assurance: Good Practice, Regulation, and Law, Vol. 1, No. 3, pp. 171-180 (1992)

2 FDA Website: http://www.access data.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

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