calculating maximum allowable carryover (MAC) for cleaning validation

The United States Food and Drug Administration (FDA) released guidance for current Good Manufacturing Process (cGMP) validation in January 2011.[1] Within that guidance, the traditional approach of process validation has been replaced with a life cycle approach as the best practice recommendation. The life cycle approach is broken into three stages: Design, Qualification, and Verification. The three stages are no longer viewed as static steps but rather dynamic stages to be constantly reviewed and updated during the lifetime of the process. This new direction for process validation applies directly to cleaning validation (CV) as well.

The traditional objective of any pharmaceutical manufacturing cleaning process is to remove or reduce the Active Pharmaceutical Ingredient (API), degradants, excipients, and cleaning agent residues. This is important to ensure product integrity and patient safety.

With the new life cycle approach to process validation, the traditional practice of measuring a single API with a specific method does not elicit the necessary process understanding and, therefore, is no longer compliant with US FDA best practice guidance. As a nonspecific method, Total Organic Carbon (TOC) analysis measures both product and process related residues as a function of their carbon containing properties. TOC analysis provides efficient feedback necessary to continuously evaluate the validated state of the cleaning process and, therefore, is compliant with FDA best practice guidance.

A key question for any cleaning validation process is how to establish practical, achievable, verifiable, and scientifically defensible acceptance criteria limits. This application brief presents a framework for how to establish acceptance criteria limits using TOC to comply with FDA best practice guidance for the life cycle approach to cleaning validation.

know your process

One of the many challenges to implementing a cleaning validation process is that each manufacturing process is unique. Raw materials, process flow diagrams, manufacturing procedures, run rates, Minimum Batch Size (MBS), and order of operations are a just a few of the factors that can affect cleaning processes. Additionally, how each manufacturer cleans and how each manufacturer measures also present unique challenges to implementing a cleaning validation process. These factors are not addressed in this application brief but must be understood prior to calculating MAC.

product change over

The need for determining MAC for a given product stems from the practice of product change over in a production facility. Product change over, just as it sounds, occurs when a vessel is emptied of one product (Product A) and then refilled with a different product (Product B), as shown in **Figure 1**. The MAC value is how much of Product A can safely be present in Product B without any danger to the patient.

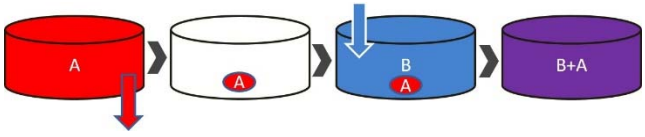

Figure 1: Product change over from A to B illustrating carryover of A into B.

reference values in developing acceptance criteria

MAC calculations start by identifying clinical reference values for each product. These may include, but are not limited to, Therapeutic Daily Dose (TDD), Acceptable Daily Intake (ADI), Lethal Dose for 50% of population (LD_{50}), or Permitted Daily Exposure (PDE). Clinical reference values may be found in literature or online, including PubChem DSSTox FDA Maximum Daily Dose Database (DSSTox FDAMDD).[2] Regardless of the citation source for starting reference values, they must be scientifically defensible. Starting reference values in this application brief originate from DSSTox FDAMDD.

MAC from TDD

When determining MAC from TDD, the current product in the tank (Product A) and the next product in the tank (Product B) must be known (see **Figure 1**). The known identity of both products allows identification of a defensible starting clinical reference value. Depending on what types of compounds Product A and B are, a different Safety Factor (SF) in the calculation is used based on the risk assessment of those compounds.[3] A typical safety factor value is 1000.[3]

$$MAC_A = \frac{TDD_A \; x \; MBS_B}{SF \; x \; TDD_B}$$

MAC from LD_{50}

As with TDD, when determining MAC from LD_{50}, the current product in the tank (Product A) and the next product in the tank (Product B) must be known (see **Figure 1**). Next, calculate the No Observed Effect Limit (NOEL) using the LD_{50} reference value for Product A. Then, calculate MAC from the derived NOEL value. Please note that the denominator value of 2000 in the NOEL equation is an empirical constant referenced in literature.[3]

$$NOEL_A = \frac{LD_{50\ of\ A} \; x \; 70 \; kg \; (avg. patient \; mass)}{2000}$$

$$MAC_A = \frac{NOEL_A \; x \; MBS_B}{SF \; x \; TDD_B}$$

MAC to product limit

A MAC value alone is not sufficient to release equipment for use. Once MAC has been determined, the value must be converted into an actual product limit (in ppm). The product limit accounts for the sampling method with the MAC value.

Two common sampling methods are:

1. collecting a swab sample from inside the tank
2. collecting a rinse grab sample

Product Limit from Swabbing

If sampling involves swabbing a specified area in the tank, the target value may be calculated using the MAC value, assuming an even, homogenous API deposition throughout the active surface area.

$$Product\ Limit\ \left(\frac{mg}{dm^2}\right) = \frac{MAC(mg)}{Active\ Surface\ Area\ (dm^2)}$$

Product Limit from Rinse

If sampling involves collecting a final rinsate from the tank, the MAC value is converted into a concentration (mg/L) based on final rinse volume.

$$Product\ Limit\ \left(\frac{mg}{L}\right) = \frac{MAC(mg)}{Total\ Rinse\ Volume\ (L)}$$

product limit to TOC limit

Specific product limits are not directly transferrable to a TOC method. The specific product limit, depending on the sampling method, can be converted to a TOC limit by multiplying by relative mass percentage of carbon from the chemical formula of the product.

When a specific method limit has been previously calculated, converting from the specific cleaning validation method, such as HPLC, to a nonspecific method, such as TOC, can be achieved using the percentage carbon in the chemical formula. For example, if a specific API limit for HPLC is established at 10 ppm and the percentage carbon is 50%, the TOC limit would be 5 ppm.

example using TDD

In this example, Product A is Epinephrine and Product B is Diazepam. The clinical reference values are as follows[2]:

$$TDD_A(Epinephrine) = 0.0167 \; \frac{mg}{kg \; bw}$$

$$TDD_B(Diazepam) = 0.667 \; \frac{mg}{kg \; bw}$$

The example process information on Minimum Batch Size (MBS), safety factor, and average patient mass (kg body weight) are as follows:

$$Avg. Patient \; Mass = 70 \; kg \; bw$$

$$MBS_B(Diazepam) = 7.0\,x10^7 mg$$

$$SF = 1000$$

With this information, the MAC value of Epinephrine into Diazepam ($MAC_{A\,in\,B}$) can be calculated.

$$MAC_{A\,in\,B} = \frac{\left(0.0167\ \frac{mg}{kg\ bw}\ x\ 70\ kg\ bw\right) x\ (7x10^7 mg)}{1000\ x\ (0.667\ \frac{mg}{kg\ bw}\ x\ 70\ kg\ bw)}$$
$$= 1752\ \text{mg}$$

The MAC value must now be converted to a product limit by considering the sampling method. In this example, the method is swabbing a 1 dm^2 area inside a tank. The active surface area of the tank is 80% of the total based on the fill level of the tank.

$$Active\ Surfance\ Area = 1500\ dm^2\ x\ 0.8$$
$$= 1200\ dm^2$$
$$Epinephrine\ Product\ Limit = \frac{1752\ mg}{1200\ dm^2}$$
$$= 1.46\ \frac{mg}{dm^2}$$

The TOC vial volume of 40 mL is also known. Since the sampling method is swabbing, the swab will be broken off in the vial; therefore, the final product limit concentration for Epinephrine is as follows:

$$Vial\ Volume = 0.040\ L$$
$$Epinephrine\ Product\ Limit = \frac{1.46\ mg}{0.040\ L}$$
$$= 36.5\ ppm$$

With the product limit established, the TOC limit can be determined by the percent carbon in the chemical formula for Epinephrine, $C_9H_{13}NO_3$.

$$\%\ Carbon\ (Epinephrine) = \frac{9\ x\ 12.010\ \frac{g}{mol}}{183.207\ \frac{g}{mol}}\ x\ 100$$
$$= 59\%$$
$$TOC\ Limit\ (Epinephrine) = 36.5\ ppm\ x\ 0.59$$
$$= 21.5\ ppm$$

The example illustrates that when starting with defensible clinical reference values, the MAC value for Epinephrine in Diazepam is 1.46 mg/dm^2. When TOC technology is deployed for a cleaning validation process, based on MAC and sampling method, the TOC limit for Epinephrine in Diazepam is determined to be 21.5 ppm.

conclusion

Based on recent guidance from the FDA, the life cycle approach should be considered best practice when implementing a cleaning validation process. The life cycle approach calls for continuous monitoring and updating to the design, qualification, and verification of the cleaning validation process. When choosing an analytical method to measure the effectiveness of the cleaning validation process, it should be noted that specific methods, looking at a single API, do not comply with the best practice recommendation as changes in other non-quantified contaminants will go unnoticed.

Nonspecific methods, such as TOC, comply with the best practice recommendation by measuring the total contaminants in the cleaning process rather than just a specific API. Degradants, excipients, and cleaning residues are just a few potential contaminants that are not captured in a specific method, such as HPLC, but are captured in a nonspecific method, such as TOC.

This application note demonstrates that the determination of acceptance criteria limits for TOC in cleaning validation can be easily calculated and defended when starting from justifiable clinical reference values. This, in conjunction with the US FDA best practices for cleaning validation, highlights a few of the many appealing aspects driving industry leaders to adopt TOC analysis for cleaning validation on a large scale.

References

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