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Selecting Worst-Case Products for Grouping

This Cleaning Memo supplements my July 2001 Cleaning Memo on the same topic. This current Cleaning Memo does not add anything radically different to that earlier one. The purpose for this Cleaning Memo is to discuss an alternative means for selecting the worst-case product in a product grouping. One alternative for selecting worst-case products has been laboratory screening. In this lab screening, different products were placed on coupons of a suitable substrate (stainless steel, for example). The spiked coupons were cleaned by a lab procedure that simulates actual production cleaning. The product which took longest to clean under identical conditions of time, temperature and cleaning agent concentration was selected as the most difficult to clean. Determination of cleanability was typically determined by visual cleanliness of the surface.

A recent publication (R. Sharnez et al, In Situ Monitoring of Soil Dissolution Dynamics: A Rapid and Simple Method for Determining Worst-case Soils for Cleaning Validation, *Journal of Pharmaceutical Science and Technology* Volume 58, Number 4, July-August 2004, pages 203-214) takes this one step further. In this publication by scientists at Merck and Drexel University, the lab cleaning is monitored on a continuous basis for conductivity. As soil (product) is dissolved from the surface, the conductivity of the cleaning solution increases until, at a certain time, the conductivity levels off (all conducting species have been dissolved from the surface). The coupon is then rinsed, and analyzed in different ways to confirm that the coupons are truly cleaned, and that the conductivity measurements were relevant to the cleaning of the coupon. Methods for this confirmatory check included TOC and cleaning agent specific methods.

As the authors point out, this method is applicable under these conditions:

a. The soils are ionic in nature;
b. There is a linear relationship between soil concentration and conductivity; and
c. The change in conductivity over the time of cleaning is significant and measurable.

The products evaluated by the authors included parenteral solutions and parenteral suspensions. For the solutions, the cleaning agent was water alone. For the suspensions an alkaline cleaner was used for cleaning.

The key issues for control and consistency of the studies included the spatial orientation of the conductivity probe to the coupons, the amount (thickness) of soil on the coupon, and the stirring rate (agitation). A blank was used for each study to account for conductivity of the combination of the cleaning solution and the unspiked coupon.

The worst-case soil among a group was determined by normalizing the conductivity measurements at the various times. Normalization was performed by determining the ratio of the corrected conductivity at any time to the conductivity at the end of the experiment. A plot of normalized conductivities for different products allows a quick determination of which product is most difficult to clean. One of the key values of this methodology is to identify situations where one product may appear to be easier to clean in the early stages of cleaning, but in fact as cleaning progresses, it is found to be more difficult to clean.

It should be noted that while conductivity measurements are featured, the authors studied the parenteral suspensions by taking samples and doing off-line measurements of the cleaning solution by ICP for an

undisclosed common ingredient in all the suspension formulations. There may be situations where other in situ or off-line measurements, such as by UV spectrophotometry or even by TOC, might be useful techniques in comparing different products for cleanability.

This paper offers pharmaceutical manufacturers one option for selecting the worst-case product in a more defendable manner.