Cleaning Validation: A Case Study

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Certain Coventry™ polyester swabs are recommended for use in Cleaning Validation programs for the sampling of surfaces of process equipment used in the production of active pharmaceutical ingredients. Recently a pharmaceutical customer presented us with a special issue involving a competitor's polyester swabs. This issue brought up interesting points related to how polyester swabs are used by the Pharmaceutical Industry, and I would like to discuss this issue in this article.

First, let's do a brief review of the subject of Cleaning Validation as used in the Pharmaceutical Industry. Pharmaceutical manufacturers engaged in producing active pharmaceutical ingredients (APIs), are required by law to have a formal program for insuring that the methods used to clean process equipment between production runs of APIs are effective , verifiable and documented. According to the Active Pharmaceutical Ingredients Committee Working Group, the definition of Cleaning Validation is " the process of providing documented evidence that the cleaning methods employed within a facility consistently control potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product, to a level which is below (a) predetermined level". Such validation of the cleaning procedures may be required by customers, may be a regulatory requirement or an internal company quality control requirement.

If cleaning procedures are inadequate the next batch of product may contain API precursors, by-products or degradation products, the active ingredient, solvents and other materials used in the manufacturing process, micro-organisms, as well as cleaning agents and machine lubricants. The cleaning process used to prevent such contamination from batch to batch must be shown to be effective in controlling carryover of these contaminants from the previous production batch. Validation is achieved by swabbing or rinsing the process equipment and analyzing extracts of the swabs or rinse water for the contaminants of interest.

There are usually three levels of cleaning, the level to be attained depending on a consideration of the next product to be made with the equipment in question. Equipment usage, the stage of manufacture and the nature of the potential contaminants all play a role in determining the level of cleaning that needs to be achieved. Once these elements have been considered and the cleaning level determined, the process of cleaning validation can begin.

The validation procedure will: establish the maximum acceptable level of each contaminant, determine the cleaning procedure to be used in terms of the equipment to be tested and the cleaning agents to be used; characterize the products to be analyzed; and validate the analytical methods and sampling procedures to be used. A validation protocol is prepared and a validation report issued to document the findings of the validation procedure.

The sampling procedure requires that the surface of the process equipment be tested for residual contaminants and/or APIs by swabbing selected small surface areas of the equipment or by rinsing large surface areas. Swabbing will not cover large areas but is mainly used to sample worst-case locations on the equipment. Rinse sampling will cover larger areas and those surfaces that are not accessible to swab testing. Once collected the swabs are extracted with a solvent that removes contaminants, and the solvent extract is then analyzed by an appropriate scientific method, like TOC (total organic carbon) analysis or HPLC (high performance liquid chromatography) or other methods, to determine the type and amount of contaminants in the extract. This amount is then extrapolated to calculate the total amount of contaminant present on the equipment surface that could be carried over into the next processed batch. In a like manner rinse water samples can be extracted with a solvent or concentrated and then analyzed. Should the analysis show that a particular contaminant level is above the established maximum acceptable level the equipment is cleaned again and again tested, until all possible contaminants are below the maximum acceptable level. Once this is achieved the equipment is ready for use in processing the next batch of product or intermediate.

When using swabs for sampling, care must be taken to insure that products extracted from the swabs themselves do not interfere with the sampling method. Sometimes materials extracted from the swabs can mask the presence of the contaminants collected from

the equipment surface as they are detected in the same manner as the contaminant of interest. Recently such a situation occurred with pharmaceutical end user. They were using a competitor's polyester swab for cleaning validation, extracting the swabs with a solvent blend and analyzing the solvent extract using HPLC. In running a "blank" on the competitor's swabs (extracting clean swabs with the solvent blend and analyzing them by HPLC), they detected a peak in the chromatogram at the same wavelength of light as the product they were interested in measuring in the sample swabs used to wipe the equipment. This peak indicated that something was being extracted from the clean, unused swab that had a similar light absorption as the contaminant they were trying to analyze. This blank signal was not consistent, so they could not simply subtract the blank amount from the amount determined for the swabs used in the analysis. They asked if we had a swab that would not have extractable products that would interfere with their analysis.

What they were seeing is a common observation when using polyester swabs. Polyester fabric will contain extractable "oligomers" which are short chains of the ester molecule but much smaller than the polyester molecule. These oligomer contaminants are easily extracted from the polyester fibers by many of the solvents commonly used in such analyses. The oligomers that can be extracted will usually be different for swabs from different a manufacturer, reflecting different sources of the polyester material used in the swab construction, and different oligomers will have different light absorption wavelengths. In the present case the oligomers extracted from the competitor's polyester swab just happened to absorb light at the same wavelength as the contaminant for which the customer was testing, so the oligomer absorption interfered with the customer's analyses.

To solve this problem the customer had a choice of trying a different swab from a different manufacturer or using a cleaner swab, like the 36061I, which would aid in reducing the total amount of oligomer extractables in each sample.. If a different manufacturer's swab is used it is likely the source of the polyester material used in the swab construction would be different and different oligomers would be extracted. These different oligomers may have a light absorption wavelength that would be different from the wavelength with which the customer is concerned, so there would be no interference with the customer's analysis procedure. It is possible to use a special cleaning procedure to temporarily reduce the amount of oligomer contamination in the competitor's swab, even though the offending peaks would return slowly over time, equiring repeated treatment of batches of swabs used in the analysis.

In summary such issues with the materials used in quantitative sampling procedures occur frequently and must be taken into account when designing a cleaning validation procedure. The choice of materials used in the analysis can sometimes effect the accuracy of the analytical procedure and complicate the performance of the procedure.

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