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Significance of Water Activity for Cleaning Validation

Sometimes I hear the opinion that bioburden doesn't need to be addressed in cleaning validation because of low water activity of the manufactured product (for example, for oral solid dosages). There is an element of truth in that opinion; however, it is necessary to see exactly what is meant. In this Cleaning Memo we will cover the water activity principle, and see how it might apply to bioburden measurements at the end of the cleaning process (in a cleaning process validation protocol) and the issue of bioburden proliferation during the clean hold time.

"Water activity" is not the same as "percent water", although the two may be related. Water activity is defined as the ratio of the vapor pressure of water above the product as compared to the vapor pressure of pure water at the same temperature. Water activity is a dimensionless number, and can vary from zero to one (0-1). It is generally recognized that high water activities (in the absence of any preservative or other inhibiting species) allow microorganisms to grow, and at low water activities microorganisms do not grow. Note the key word here is "grow". At low water activities, microorganisms may survive, but they do not grow (that is, do not reproduce). The cut-off between growth and no growth depends on the species, but as a general rule, below a water activity of 0.8 or 0.9, bacteria do not grow. Below a water activity of about 0.7, yeasts/molds do not grow. Below about 0.6, nothing will grow. Note that saying a product has a water activity of 0.55 does not mean it is sterile; remember that the key issue for water activity is microbial growth.

What does this mean for cleaning validation? If I have a product with a very low water activity, can I skip bioburden measurements in cleaning process validation protocols? Clearly the answer is, based only on water activity of the product, that I cannot skip bioburden measurements in protocols. If I leave microorganisms behind on equipment surfaces after cleaning (or after the clean hold time), those microorganisms can transfer to the next manufactured product. Even if that next product is a dry product with low water activity (realizing that liquid products can also have low water activities), those microorganisms could survive, but not grow or proliferate, in the product itself. Remember that USP discusses limits for non-aqueous oral dosage products (with typical limits of 1000 CFU/g for the Total Aerobic Microbial Count). I want to control the contribution to that bioburden from the equipment surfaces (realizing that equipment surfaces are just one of the contributors to bioburden in a drug product).

Furthermore, I may also be concerned about objectionable organisms left on equipment surfaces which could potentially transfer to the next product. How would I know whether I had any objectionable organisms unless I preformed bioburden sampling and identification? For these reasons, it is prudent to measure bioburden as part of a cleaning validation protocol.

What about the issue of bioburden during the clean hold time? Well, that's a different matter. I am still concerned about proliferation of bioburden and transfer to the next manufactured product. However, the water activity of the next manufactured product has little impact on the proliferation of microorganisms during the clean hold time. And that is particularly so if the equipment is stored wet. Furthermore, if I perform a clean hold study, I am going to have to measure bioburden at the end of the hold period (note that I might also measure bioburden at the beginning of the hold period, which is also the end of the cleaning process itself).

The bottom line is that a low water activity of the next product may prevent growth in the product itself, but it

is not a substitute for controlling and measuring bioburden in the cleaning protocol and/or the clean hold study. Another way to think of this is to suppose I have a product with a high water activity, but with a preservative. Because it has a preservative, am I allowed to not control and measure bioburden in the cleaning process? Of course not! The USP is very specific in this regard, in that it states that preservatives in the product are not a substitute for good control during the manufacturing (remember that for most applications, the preservative is designed to deal with possible microbial contamination during product use by the consumer or patient).

One last thought. This does not mean that I must always measure bioburden in a protocol. There may be situations where there is no aqueous processing and where microorganisms would not be present. For example, in small molecule API synthesis, where all reactions are with organic solvents and where cleaning is with organic solvents, I might provide a risk analysis with a rationale for not measuring bioburden in a cleaning protocol. Or, in finished drug product manufacture where the final rinse is with 70% isopropanol, I might write a similar risk analysis. For clean hold studies, I might do the same thing if I can establish that the equipment is dry (at the end of cleaning and throughout the clean hold period). However, these rationales have nothing to do with water activity of the next manufactured product.

This is not to say water activity is not an important consideration in the control of microbial contamination of drug products. However, it is not a substitute for effective microbial control during the cleaning process itself and during the clean hold time.