

Cleaning Memo for September 2020

Avoiding “Visually Dirty” Observations

A frequent question I get is “What is the most common FDA (or another regulatory body) finding in an inspection?” Well, I certainly haven’t seen them all, and don’t have any clear data. However, based on my experience one of the most frequent observations I see is that in an inspection some item of equipment (which could be “product contact” or “non-product contact”) is *visually soiled*. Why is that the case? It might be that such an observation is an “easy” one. If equipment *should be* visually clean, and if it *is not*, that is an easy finding. After all, it not like seeing the calculations that are done for limits of an active ingredient, where there are all sorts of terms in an equation, and where every company (while using the same principles) expresses those limits in a slightly different way. It takes a lot more effort to see problems in such calculations as compared to looking at equipment and saying “It’s not visually clean”.

In the Cleaning Memo we will look *first* at what we can do to avoid situations where equipment is visually soiled. And after that we will discuss what should be done in response, either in an inspection or at any other time, if we find ourselves in a situation where we have visually soiled equipment that *should be visually clean*.

The obvious answer for avoiding visually soiled equipment is to make sure it has been cleaned appropriately, and then that it has been examined and documented that it is visually clean. This means that we have *designed* our validated cleaning procedures (and other cleaning procedures too) well, including the frequency of use of the cleaning procedure. By this I mean it may not be an expectation within a campaign (where batch to batch “minor” cleaning is done) that the equipment be visually clean, but for cleaning at the end of a campaign visually clean equipment is usually an expectation. Furthermore, to avoid situations where equipment is documented to be visually clean but where it clearly is *not* visually clean during an inspection, it is critical that those operators doing the visual inspection be appropriately trained. This includes not only *what to look for*, but also *how to look* (with flashlights/torches, at what distance, and the like), *how to document* the visual examination, and *what to do if the equipment is not visually clean*.

Clearly there may be cases where the equipment was visually clean at the end of cleaning, and where the visually “clean state” was appropriately documented, but where the “visually soiled” condition occurred *after* the cleaning and *after* visual examination. We’ll discuss how to investigate any visually dirty situation later. However, the “take home” lesson here should be what to do *before* a planned inspection. Certainly we prepare so that relevant documents that might be called for by the inspectors are readily accessible, as well as perhaps to review them to make sure they are “inspectable”. At the same time, it would be prudent to have a *pre-inspection walk-through* to identify any items that might need attention from a “visually clean” perspective. This could include dirty equipment, improperly stored cleaning tools, and/or inaccurate “status” labels. Those would be easy citations. If there is equipment that is “permanently stained” with colors or surface anomalies, be prepared before the inspection itself to address those,

preferably with an appropriate rationale or justification. Of course, if things are done 100% right in the first place, then there would be no such problems. If you do find such situations, certainly *make corrections*, but also *take corrective actions* to prevent reoccurrences.

Either in a pre-inspection situation or during an inspection (or for that matter at any time), what should be done if I find equipment that *should be* visually clean but clearly *is not*. Avoid the temptation to *immediately* clean it. What I would prefer to do is an investigation to determine the nature of the residue (or soil) on the surface. Determining the type of residue can not only help me determine how to clean it as part of my correction, but also can help me determine any possible product safety/quality impact if there is a possibility that the residue could have transferred to a manufactured product. In addition to determining the nature of the residue, I want to investigate the *root cause* of why it is there (assuming that with proper cleaning, it should *not* be there). Was it operator technique in a manual cleaning process? Was it a problem with the tools used for cleaning? A problem with the cleaning agent used? A problem with the temperature of cleaning? Ideally a root cause should be identified, and corrective/preventive actions should be identified and implemented. This might include a change in the cleaning parameters. From manual cleaning this might also include changes in the written procedures to better describe what should be done, as well as retraining of operators.

A key initial question is whether the soil is present throughout the equipment, or only on certain locations. Those certain locations may help you identify the root cause. Furthermore, whether the soiled areas have distinctive, sharp edges suggestive of improper manual scrubbing can be important. The identification of the type of soil (or residue) may include its *physical* nature, its *chemical* nature, and its *microbial* nature. For a physical examination, is the soil particulate or present as a continuous “film”? What color is it? Is it transparent or opaque? Is it highly adherent or loosely adherent to the surface? This may require scraping the surface with a metal or plastic spatula. As you do a physical examination, consider taking samples for chemical analysis. Chemical analysis may include Infrared, HPLC, and UV. As you prepare samples for analysis, observing the solubility of the material in different solvents (aqueous and organic) may be beneficial. Although micro-organisms are not likely to be the problem (if you have a visible microbial mass, you *really* have a problem!!), residues may also be characterized for bioburden and/or endotoxin. These characterizations may help you identify not only the correction needed to get the equipment back to its baseline cleanliness, but also what caused the problem. In an investigation, an evaluation of whether this visually soiled condition is a *recurring* problem should be part of looking for a root cause.

Realize there may be a tension between those want to quickly do a correction (so that the equipment can be safely used again for manufacturing) and those wanting to do the investigation (to *clearly* identify the root case so that corrective/preventive actions can be taken). As with many things in life, a balance (and patient understanding) is helpful.

If the problem is seen before subsequent use of the equipment, then provided appropriate correction is done, the impact on a subsequently manufactured product is minimal (other

than perhaps delaying the production schedule). If the problem is only identified after product has been made (which should be less likely on product contact surfaces), then the impact on subsequently produced products should be explored. This may involve estimating the total amount of soil (residue) that may have been left in the equipment. Then the levels of residues in the next product can be estimated assuming that the residue was *uniformly* mixed in the next manufactured product. That estimated level is then compared to an acceptance limit in the product itself. If the residue could transfer but be *non-uniformly mixed* in the next product, the situation is different, but some adjustments can be made to estimate the impact. This exploration may also involve analysis of final manufactured product for the suspect residue in that product. This can be more of a challenge, because of the need to have an analytical method that can measure the specific residue in the presence of large amounts of excipients and actives in that next product.

Thinking about all these issues *in advance* and preparing approaches to dealing with “visually dirty” equipment (if it were to occur) is a prudent consideration.