Cleaning Memo for November 2020
Visual Residue Limits – Part 1

For this two-part series, we will look at *how to establish visual residue limits* in this first part. In Part 2 we will look at the recent (2018) EMA Q&A that deals with using a visually clean criterion in routine monitoring to establish that a *quantitative* residue limit is being met.

Before I start, here is a little history. Requiring that equipment be visually clean at the beginning of product manufacture is ancient history. The idea that we should require the equipment to be visually clean at the end of a validated cleaning process is a logical extension of that older idea (if it needs to visually clean before I start manufacture, it probably must also be visually clean at the end of the cleaning of the prior product; if it is visually soiled at the end of that cleaning process, in most cases it will not clean itself before I start manufacture of the next product). That the equipment in a validated cleaning process should be visually clean was more or less "solidified" by the Fourman/Mullen 1993 publication, by the FDA Cleaning Validation Guidance of 1993, and by the 1998 PIC/S Cleaning Validation Recommendations. In 2002 I published a paper (with a faulty conclusion) dealing with spiking studies to establish a visual residue limit (VRL). There have been many papers published since that time by scientists such as Richard Forsyth (first when he was with Merck & Co., and later with other affiliations). There are also many Cleaning Memos dealing with "visually clean", but not all deal with VRLs (April 2002, September 2004, July 2010, August 2010, September 2010, January 2015, December 2015, and August 2019).

The general approach in a spiking study is to spike a residue at *different levels*. The spiking is done by dissolving the residue in a volatile solvent, spiking the solution on a coupon of a specified material of construction (MOC), and then drying the spiked coupon under defined conditions. While different companies may specify the spiking levels by the concentration of the residue in the spiking solution or by the concentration of the residue in the extracted swab solution (assuming the calculated limit is for swab sampling), my preference is to define the spiked levels as the *amount per surface area* (such as mcg/cm^2), which corresponds to what I typically call a L3 limit. The spiked, dried coupons are then evaluated under specified conditions of lighting and distance. The evaluation is typically done by several (minimum of three) observers independently.

Now we get to the interesting part: how the end point of the evaluation is defined. Realize that if we spike at a series of levels, we might see some that are *grossly soiled* over the entire spiked area, some that are *lightly soiled* over the entire spiked area, some that are soiled over only *portions* of the spiked area (that is, portion are soiled and portions are visually clean), and some that *visually clean for the entire spiked area*.

So the question arises, how do I define the VRL? The answer to that depends on how we are using the VRL. The most *useful* purpose is to say that the VRL establishes a value (let's call that value X mcg/cm^2) so that if the equipment is visually clean (when

observed under the same lighting and distance), I can be assured that the residue level on the surface is below X mcg/cm^2. I don't necessarily know the exact or precise value of that residue on a visually clean surface, but I know it is *below that VRL value*. Using this criterion, then the VRL is the lowest spiked level where I can see at least some amount of residue across the *entire* spiked surface.

To many this seems counterintuitive; shouldn't we be looking at the other end of the spiking levels, and either select the highest level at which the coupon was completely visually clean or the lowest level at which we can see only a small amount of residue on a portion of the spiked area. Let's look at the first situation (where the coupon was completely visually clean). Let say that spiked level was 0.5 mcg/cm^2; does this mean that any surface that is visually clean has a residue level below 0.5 mcg/cm^2)? Well, the answer to this depends on whether we also spiked at a level of 0.6 mcg/cm^2. If we didn't spike at that level, then perhaps that higher level would also be visually clean; therefore to say that visually clean means it is below 0.5 mcg/cm^2 is a faulty conclusion. Okay, what if we spike at 0.6 mcg/cm^2 and it was in fact *not* visually clean; does this mean we can say any surface that is visually clean is below 0.5 mcg/cm^2? The answer is still "NO". Perhaps if we spiked at 0.55 mcg/cm^2 the surface would be visually clean. This logic can be continued to the point where we spike at a level very close to 0.5 mcg/cm^2, such as 5.1 mcg/cm^2.

There also is a problem with selecting the VRL as the lowest level at which there is at least *some visible residue on a small portion of the spiked area*. The issue is this: If we spike a coupon at a nominal level of 0.5 mcg/cm^2 (as an example), what does it mean if a portion of coupon is visually clean and a portion is not visually clean? Well, it probably means that that the residue is not evenly distributed over the coupon. It might be the situation where the visually clean portion is 0.45 mcg/cm^2 and the visually soiled portion is 0.55 mcg/cm^2. If that were the case, what conclusion can I draw about the spiked level of 0.5 mg/cm^2? How can it happen that we spike at one level and the coupon has different levels of residue? Very easily. Let's say I spill my coffee on a white table, and it forms a natural circle; as it dries, I will typically see a darker portion (higher levels of residue) around the outer portion of the circle. This probably happens because I get different rates of drying on the edges (as compared to the center portion), which could allow for some concentration gradients to form within the spiked solution (this sounds reasonable to me; if there are any physical chemists out there, perhaps they have a better explanation of the phenomenon). So trying to draw a conclusion on spiked coupons which are only partially visually clean is not an acceptable practice.

This is why I advocate setting the VRL as the lowest level where I can see residue across the entire spiked surface (even if I can visually see different levels across the coupon). Remember that this VRL is a level where, if a surface is observed under the same conditions and is visually clean, the surface has a residue value below the VRL.

For clarification, the VRL limit for a given residue is not fixed. It depends on the viewing conditions (including lighting, distance, and angle of viewing). It also depends on the surface MOC; a white residue on Teflon will generally have a higher VRL as compared

to the same white residue on stainless steel. Furthermore, as a practical matter we may initially spike at levels of 0.25, 0.50, 1.0 2.0 and 4.0 mcg/cm^2, and determine that the VRL is 1.0 mcg/cm^2. If our calculated carryover residue limit were to be 0.70 mcg/cm^2, then a VRL of 1.0 mcg/cm^2 would not be adequate to confirm a visually clean surface was below the carryover limit (the best we could do was to say the visually clean surface was below 1.0 mcg/cm^2). However, in that situation we have the option of doing *additional spiking levels* between 0.50 and 1.0 mcg/cm^2, which *might* result in a VRL of 0.70 or even 0.60 mcg/cm^2, resulting in a *useful* VRL; on the other hand, with those additional spiking levels the VRL might be confirmed at a value of 0.80 mcg/cm^2 or above, in which case we could *not* claim that a visually clean surface has residue values below the calculated carryover limit of 0.70 mcg/cm^2. There clearly is an option to only do spiking levels down to a calculated carryover limit; others may choose to drive the VRL value as low as possible to account for possible future changes (that is, lower L3 values) in the calculated carryover limit.

This Cleaning Memo does not have all I teach about VRLs; you might check my other Cleaning Memos for help there. This Cleaning Memo does focus on why the "endpoint" for establishing VRLs should be the *lowest* spiked level at which a residue is visually seen across the *entire* spiked area. It sets the stage for next month, when we will take up the issue of applying VRLs to routine monitoring (that is, monitoring a cleaning process after completion of the validation protocol as part of "validation maintenance").