Cleaning Memo for July 2018
The EMA Q&A on Routine Analytical Testing

As discussed last month, the EMA issued it clarifying Q&A on limits in shared facilities on April 19, 2018. Last month we focused on HBELs and "historically used" limits. This month we'll focus on Questions 7 and 8 dealing with *routine analytical testing*.

The question in Q7 is as follows: "Is analytical testing required at product changeover, on equipment in shared facilities, following completion of cleaning validation?" The answer starts off with the following: "Analytical testing is expected at each changeover unless justified otherwise via a robust, documented Quality Risk Management (QRM) process." That answer continues with three things that should be considered *at a minimum* as part of the QRM process: (a) the repeatability of the cleaning process (manual vs. automated), (b) the residue hazard, and (c) "whether visual inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the HBEL".

It makes sense to do a risk assessment to determine what should be done for analytical testing on routine cleaning after completion of the validation protocols. The key items in the list of three minimum considerations is the third relating to whether visual inspection is adequate to determine meeting the limit calculated using the HBEL. Is that a reasonable expectation? Well, it is a reasonable expectation that the equipment be visually clean at the end of the cleaning process. However, most companies do not assume that being visually clean means you are meeting the calculated limit (whether it is the "historically used" limit based on dosing or a limit based on a HBEL).

The question arises as to whether this is a guideline prescription or recommendation or an option. If it is something that must be done to minimize or avoid analytical testing for routine manaufacture, it is adding a whole new layer of testing to support the assertion that the HBEL is being met. After all, the purpose of cleaning validation is to demonstrate that if the cleaning process is carried out correctly, equipment will be cleaned to the applicable residue limits. The proposed "visual limit" type of testing usually involves laboratory spiking studies to determine levels that would indicate passing results in comparison to the calculated limit (typically in $\mu g/cm^2$). It may be possible, however, to avoid laboratory tests if the HBEL-calculated residue limit is *significantly* above values of 1-4 $\mu g/cm^2$ typically cited for this type of evaluation. That is, if my calculated HBEL limit were to be 15 $\mu g/cm^2$, could I avoid doing spiking studies? While that seems like a reasonable approach, will we then proceed to start arguing about where that cut-off level should be, because we want a "science-based" cut-off level?

Let me also point out that the answer to question 7 appears to say that visual cleanness must be shown to correlate in a certain way with a limit calculated by using the HBEL, and not necessarily with a cleaning validation limit which many be more stringent than the HBEL limit (consistent with the answer provide to question 6).

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Before we leave this topic, Question 8 and its answer adds another element to this determination of what visually clean means. The question in Question 7 is: "What are the requirements for conducting visual inspection as per Q&A 7?" The answer is that "manufacturers should establish the threshold at which the product is readily visible as a residue." This should be interpreted carefully, particularly what the applicability of "threshold" might be. Many that are performing visual limit spiking studies spike with decreasing level of residue to determine the amount that allows for the entire spike surface to be visually clean, and then uses that level (or one level above that level) to establish a "visual detectability limit". I don't think that is a good practice. Why? In any spiking study it is next to impossible to spike a surface so that the residue is evenly dispersed across the surface. Part of the reason for that is how the residue (in solution) is applied and part is that as the residue dries, not all areas dry at the same rate so there may be some degree of "migration" across the surface. What happens is that *at low levels*, the spiked surface may be visually clean in some or most areas, but will have spots where residue is clearly visible.

Let's say that I spike at nominal levels of 0.1 and 0.2 $\mu g/cm^2$. When I view the 0.1 spike, it is visually clean under defined viewing condition, but when I view the 0.2 spike I see a few specks of residue scattered on the surface. What does that mean? If my HBEL residue limit is 0.4 $\mu g/cm^2$, does this mean that with a visually clean surface that I am meeting my HBEL limit? My answer is "not necessarily". When I spike at the 0.2 level and only see scattered spots, the concentration of residue *at the locations of those scattered spots* is not 0.2, but is likely somewhat higher. So I would not be using sound science to say that visually clean would mean that residue must be below 0.4. It might be, but might not be.

The approach I usually recommend (see the Cleaning Memo of April 2002) is to spike the surface at a level equal to the calculated limit. In the example given, I would spike the surface at a level of 0.4 $\mu g/cm^2$ and observe it after drying. If it is visibly soiled (that is, not visibly clean) across the *entire* spiked surface, then I could logically conclude that if a surface is visibly clean, it would be at a residue level below that 0.4 value. Note that in this type of evaluation, there would be some areas of the spiked surface that would be below that 0.4 value and some areas above that spiked value. But, since even those lower values must be visibly soiled, I can conclude that the amount of the residue would be below that 0.4 value if a surface observed under the same viewing conditions in a protocol were visibly clean. I also like this type of evaluation since it is more straightforward. Note that if my residue limit were 0.4, I might do my spiking at 0.3 or even 0.2. If these lower levels also were visibly spoiled across the entire surface, that would be an indication of the robustness of such a visual observation.

Now, I don't think a use of visibly clean for routine monitoring *in this manner* is helpful. Don't get me wrong here; it is still appropriate for routine monitoring to perform visual examination to the extent it is practical. But it should not be required to correlate a visually clean state with meeting the HBEL calculated limit. And for most situations doing any extensive "dismantling" of equipment (as suggested in the EMA Q&A) to gain access for viewing probably poses an additional and unnecessary risk of adulteration or

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contamination of the next manufacture product. The situation that should be of most interest for the EMA recommended approach is for highly hazardous actives, and it is precisely those actives which are more likely to have very low residue limits. And with those very low residue limits it is likely the case that equipment could be visually clean and still have unacceptable levels of residues. That is one of the reasons why I would generally recommend for highly hazardous actives that a more appropriate *routine monitoring* approach is to perform rinse sampling with a specific analytical method for the highly hazardous active (or a swab sample where rinse sampling is not practical).

Okay, now for two editorial comments. One of the proposed advantages of moving to HBELs (such as ADE/PDE values) was that there could be considerable simplification and cost savings. Now, I believe this is true for highly hazardous active where it is no longer required that they be made in dedicated equipment. I'm not so sure that advantage has panned out for actives where the therapeutic effect is the main concern for patient safety. For those latter products, the introduction of HBELs has only made cleaning validation more complex and costly. The advice from EMA about what to do for analytical testing for routine cleaning only further complicates things (unnecessarily in my opinion).

My second editorial comment relates to how these Questions 7 and 8 were added to the EMA 2018 Q&A document. There was *nothing* in the 2017 draft document that in any way relate to the issues brought up in these two questions, namely routine analytical testing and using visual limits to document that HBEL limits are being achieved. I would have thought that if the EMA wanted to bring up totally new issues, they would have solicited comments on these two questions. [Note: It may be the case that question 5.5 of the ICH Q7 Q&A (2015) is the basis for these EMA questions. However, EMA added some constraints that unnecessarily complicated things.]

As it stands, it appears that HBELs are with us to stay. However, my position on their use as limits has not changed, at least since the December 2013 Cleaning Memo. I am still an advocate that for *all actives* companies use the most stringent of (a) a HBEL calculated limit, (b) a dose-based calculated limit, and (c) a limit calculated based on 10 ppm in the next product.

Next month's Cleaning Memo will address some final issues in the EMA 2018 Q&A document.

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