Cleaning Memo for February 2021
What's a "Worst Case"?

I commonly hear companies say that they use a "worst case" approach for their cleaning validation program. My first question is usually "*Which* worst case aspect are you referring to?" The term "worst case" could cover a variety of different things for cleaning validation. For example, there are worst case aspects that may be used for setting limits, for grouping (matrixing) approaches, for sampling, analytical methods, and for sampling recoveries. I will cover examples in each of these categories. However, before I do that, I need to remind you that in some cases "worst cases" are things that I generally *must* do, and in other cases they are things that I *may* do (but am not required to do) based on good science and logic. The reasons for choosing "worst cases" in the latter category might be to simplify my validation, to make my validation more robust, or just because a corporate policy requires it. So, when a worst case is chosen, it may be appropriate to consider the reasons for choosing it. Now, let's discuss some specific examples; the examples I give will generally be with drug product manufacture, but will also apply to API manufacture with appropriate adjustments.

"*Worst cases*" for Determination of a Limit

1. The first example is for a typical carryover calculation (what a lot of companies call a MAC calculation), where for a given residue (such as the active or API), the limit depends on two characteristics of any possible *next* product made in the cleaned equipment. In doing such calculations, one approach is to look at the *ratio* of batch size to maximum daily dose for the next drug product. The *lowest ratio* for any possible next product made on the same equipment should be used in carryover calculation. This will insure that, as long as the list of possible next products (along with their batch sizes and maximum daily doses) does not change, I can safety make the drug product with that those other products being possible next products. This is clearly an example of something I must do; if I don't, I will end up with a situation where, based on the order of manufacturing, I may cross-contaminate a possible next product.

2. The second example is similar to the first, but in this case I may choose to use as my "worst case" for the carryover calculation *both* the smallest batch size of any possible next product *and* the largest maximum daily dose of any possible next product (realizing that the smallest batch size may be for one next product and the largest maximum daily dose may be from a *different* next product). Clearly this calculation will result in a calculated limit either the same or lower than what would be calculated in Example 1 above. Therefore, it is something I could do from a compliance perspective. I might also choose this option because in the future I might have a *new* next product which would have a batch size and maximum daily dose which would drive a calculated limit lower; by setting the limit lower than what is required by the lowest ratio for a single product (as

given in Example 1), I may be able to avoid revalidating because of future new products. So this approach is a "may use, but not required".

3. This third example continues with issue of carryover calculations, but only applies to situations where limits for the active in the cleaned product are set based on the minimum daily dose of that active. The standard approach is based on 0.001 of a minimum *daily* dose of the active. Some companies may choose to use a worst case of a minimum *single* dose of the active. That approach provides a lower limit as compared to the minimum daily dose if the drug product is dosed twice a day as the minimum (but the limit is the same if the minimum daily dose is a single dose). Note, however, that use of a minimum single dose is probably not applicable if the cleaned product is dosed *once a week* and the next product is dosed *daily*; that is a case where both products should be considered based on the same dosing frequency (either both daily or both weekly).

4. The fourth example deals with the shared surface area. The most accurate approach is to use the surface area only for equipment that is *actually shared* between the two products (between the cleaned product and the next product). What this means is that the shared area between Product Q and Product R may be different from the shared area between Product Q and Product S (due to the fact that one or more equipment items may not be used for all three products). This approach *must* be used. To simplify determining the exact shared area, some companies will use as the "shared" area in a carryover calculation the *largest equipment train area of any single product*. In this way, the value for the shared area used in the denominator of the carryover calculation will be either exactly the same as the actual shared area or somewhat greater than the actual shared area (with the latter resulting in lower limits, and therefore a worst case). A slightly different worst case is, when determining the shared area *between two products*, using the lower of the two equipment train areas. This will result in the value for the shared area used in the denominator of the carryover calculation being either exactly the same as the actual shared area or somewhat greater than the actual shared area (with the latter resulting in lower limits, and therefore a worst case).

5. This fifth example deals with situations where companies calculate carryover limits by several methods, and then use the lowest limit value for protocols. For example, this might involve limits based on a PDE value of the active, based on 0.001 of a minimum daily dose of the active, and a 10 ppm value of the active in the next drug product. If your company guidelines call for doing that, then clearly the worst case (the lowest of the three surface area limits, or what I typically call L3) should be used. On the other hand, if your company's documents only specify *one way* to set limits (such as PDE only), and then there is no worst case in this example.

"Worst Cases" for a Grouping Approach

6. This sixth example deals with selecting the "most difficult to clean" product in a grouping/matrixing approach. My purpose here is not to get into how that "most difficult to clean" product is chosen, but merely to say that the "most difficult to clean" product should be the "worst case" product utilized for the validation protocol as a representative for all other products in the group. This is a "must" for a product grouping approach.

7. This seventh example deals with the limits set for that worst case ("most difficult to clean") product. The most logical approach is to make sure that the limit for the most difficult to clean" product is not set at its calculated limit as if it were being validated separately apart from all other products in the group, but to utilize the lowest limit of *any product in the group*. This approach, as compared to the older approach of doing separate protocols on *both* the "most difficult to clean" product and on the product with the lowest limit, provides more assurance that all possible manufacturing sequences are adequately covered. Since I have taught and written extensively on this, I will not go into detail for the rationale.

"Worst cases" for Swab Sampling

8. When swab sampling location are chosen, it is mandatory that "worst case" locations be selected. What makes a swab location a worst case? It may be a location that where the amount of soil on the surface is greater at the beginning of the cleaning process; therefore, other things being equal in the cleaning process, it is *more likely* that the location will have a larger amount of residue at the end of the cleaning process. It may be a location where the nature of the soil on the surfaces is different (such as being compacted, dried on, or baked on), such that at the end of cleaning it is *more likely* that the location will have a larger amount of residue at the end of the cleaning process. It may be a location that because of the geometry of the equipment surfaces, it is more difficult to have physical contact of the cleaning solutions under specified parameters (as compared to flat surfaces). It may be a location where for manual cleaning the location is such that appropriate physical action (such as brushing or impingement) may be lessened. It may be a location where, based on previous engineering studies, residues after cleaning are found to be higher. It is likely that some worst case location may involve several of these conditions that lead to it being considered a worst case.

   It should be noted that worst case swabbing locations for a residue of an active may be different from worst case locations for swabbing for bioburden, particularly for swabbing for a clean hold time study (in which locations where water may "pool" should also be considered based on the greater probability of bioburden proliferation).

   It should also be noted that it may be possible to design a cleaning process so robust that all locations of the equipment may have essentially the same low

residue value when swabbing is actually performed. However, we should still select worst case locations based on the likelihood of *possible* failures if the cleaning process were not carried out correctly.

"Worst cases" for Analytical Methods

9. We don't ordinarily think of TOC (Total Organic Carbon) as a *worst case* analytical method. Typically, we think of it as an "easier" analytical method because analytical method development and validation are more straightforward. However, in another sense TOC is a worst case. Assuming that I could measure residues of an active by either HPLC or by TOC, then I am more likely to report higher residue levels with the use of TOC. This is because (in most situations) I will have significant contributions to the TOC value due to organic carbon sources other than the active (such as from excipients). Assuming that the calculated residue limit for the active is the same, I am more likely to report a higher, and possibly failing, residue value with TOC as the analytical method as compared to with HPLC as the analytical method. In that sense, TOC is a worst case as compared to HPLC. However, it is *not* a worst case that must be used.

10. Another worst case for analytical methods is one that more often involves TOC (rather than specific methods like HPLC). This involves the practice of *not* subtracting a blank value from the protocol sample. By not subtracting the blank value (such as a rinse blank that accounts for the "background" TOC in the sampling water and in the collection vial). Subtracting the blank value in that situation gives a value more accurately representing the organic carbon from the sampled surface. However, by not subtracting the blank value, the reported residue values will be a higher value and therefore more likely to give failing results. So, in this sense not subtracting out the blank represent a worst case that could be used, but a worst case that is *not* mandatory.

"Worst cases" for Sampling Recovery Studies

11. This example is the reverse of the worst-case in Example 10. This involves use of a proper blank for sampling recovery studies involving TOC as the analytical method. For a recovery study utilizing TOC, it is *critical* that a blank value be subtracted from the experimental test sample result. If the blank is not subtracted, the resultant recovery percentage will be *higher* than the "true" value, and therefore represents an inappropriate practice. In fact, in the situation of a laboratory recovery study the TOC blank should include the TOC contribution from a cleaned, unspiked coupon. In this situation, the subtracting of the blank should be considered a *mandatory* "worst case".

I'm sure these examples do not exhaust all possible situations where a "worst case" either should be used or could be used. In any case, a careful evaluation should be done to clarify whether the worst case is mandatory or is just an acceptable option.