Cleaning Memo for October 2019
Limits for "Product A to Product A"

Typically the greatest concern in limits for drug actives is when moving from one drug product to a *different* drug product. This is sometimes expressed as limit "ProdA to ProdB". For this Cleaning Memo we will cover the situation where the *same* product follows the cleaned product; that is, it will be a "ProdA to ProdA" situation. In discussing this, we will cover limits set on HBEL's as well as limits set on a 0.001 dose criterion. Note in this discussion, we will stop at the L1 limit, because beyond L1 there is nothing significant or different in the A → A situation as compared to the A → B situation (for those unfamiliar with my shorthand way of expressing limits – L0, L1, L2, etc. - please see my Cleaning Memo of September 2012). Furthermore, we'll use drug product manufacturing for examples, and not drug substance manufacturing (although the principles apply there as well). Furthermore, this discussion focuses on situations where there is *validated* cleaning between the two batches of ProdA.

We'll cover the dose-based situation first. The L1 limit (the limit in the next product) for the A → B situation is typically calculated based on allowing no more than 0.001 of the *minimum* daily dose of the active in ProdA in a *maximum* daily dose of the drug product *ProdB*. Why is it a matter of *minimums and maximums*? A simple answer might be that it represents a worst case (a lower limit) because the minimum value is in the numerator and the maximum value is in the denominator. But, as I regularly teach, there are some worst cases that must be used, and there are some worst cases that *could* be used, but are *not* required by good science or sound logic. In this example (going from one product to a different product), why *must* the worst case be used?

The rationale is that the carryover concern is based on what will be the effect the residue of the active in ProdA on the patient taking ProdB if that residue of ProdA is present in ProdB. Clearly, assuming a fixed concentration of the residue of active of ProdA in ProdB, the worst case (the maximum taken on a daily basis) is if that patient takes the *maximum* dose of ProdB. The question then becomes "On what basis is the safe amount of the active of ProdA set?" It may be that some patients who are taking ProdB might, if they were prescribed ProdA at the same time, would be prescribed ProdA at the *minimum* dose of ProdA, while some other patients might be prescribed at the *maximum* dose of ProdA (and perhaps some an in-between dose). However, there is *no way of consistently knowing* which dose of ProdA would be *relevant (*and therefore applicable) for each person taking ProdB. Therefore, a worst case assumption is made that for patients taking ProdB, the relevant safe amount of the active of ProdA is based on the *minimum* dose of the active of ProdA. Note that in this situation, patients taking lower daily doses of ProdB will receive lower daily amounts of the active of ProdB (as compared to those patients where ProdB is taken at the maximum daily dose).

Now we'll move from that situation (based on ProdA and ProdB being two *different* products) to the situation where both the cleaned product and the next product are the *same* product (ProdA → ProdA). The question sometimes arises as to whether in this

situation the limit should be based on 0.001 of the minimum daily dose of the active in ProdA in a maximum daily dose of the drug product ProdA. I assume the logic behind this is that if the minimum/maximum calculation works for two different products (where it is a required *worst* case), shouldn't it also be applicable if we are going from one product to the *same* next product. I think *not*. In this situation, *we do know* exactly what the relevant dose is for a given patient. Let's say that the possible doses for ProdA are 1, 2 and 3 tablets per day. Suppose a patient takes 3 doses per day of ProdA. If the safe level of the active of ProdA is 0.001 of a dose *for that patient*, then the *relevant* dose of the cleaned product for that particular patient is based on 3 tablets. In that case, both the numerator and denominator are based on a dosage of 3 tablets. At the other extreme, suppose a given patient only takes 1 tablet per day of ProdA. If the safe level of the active of ProdA is 0.001 of a dose, then the *relevant* dose of the cleaned product for that particular patient is based on 1 tablet. And in that case, both the numerator and denominator are based on a dosage of 1 tablet. Therefore, where both products are ProdA, the *use of minimum and maximum is not relevant* to the potential effect on patient safety for the person taking only ProdA.

Another way to look at this situation of both products being the same product is to evaluate the effect of one active getting carried over to a different batch of the same product at a level of 0.001 of concentration of the active (which is essentially the consequence of not using the minimum/maximum formulation in the carryover calculation). Let's say a tablet nominally contains 20 mg of active. If an amount of active corresponding to 0.001 is carried over to a next batch, it will increase the amount of drug active in that next batch by 0.02 mg, thus making the total amount of active in that next batch 20.02 mg. This change in active level would ordinarily be considered an insignificant change not affecting the therapeutic effect or the product quality of that drug product.

Okay, let's change the focus and assume limits are set based on a HBEL (such as a PDE or ADE) of the active of the cleaned product. In that case, if we are considering a "ProdA to ProdB" scenario, then the L1 value is the HBEL value of the active of ProdA divided by the maximum daily dose of ProdB. There is no need to consider minimums *and* maximums (only the maximum of ProdB is relevant). The rationale for using the maximum daily dose of ProdB should be fairly obvious.

Bu, what happens if we are in the "ProdA to ProdA" situation and we are using HBEL values for limits of the active? Do we say nothing changes, and we still use the HBEL value in the maximum daily dose of ProdA? That is possible, but the issue is that I am not adding a *foreign* residue by carryover of the active; I am merely changing the concentration of the active in the subsequent batch. I would argue that it makes more sense to just use the criterion of 0.001 of active concentration as the L1 value. This provides a consistency in terms of assessing the possible changes of the active concentration in the next batch. Otherwise, depending on the ratio of the HBEL to the daily dose, there could be cases with much more than a 0.1% concentration change or with much less than a 0.1% concentration change in the level of the active in next product.

This Cleaning Memo is not to say that this is the only way to set limits for active in a ProdA to ProdA situation. Depending on the specifics of product manufacture and the manufacturing/cleaning process, some companies might just use a “default” L1 limit of 10 ppm, while other might just require that the equipment be visually clean. Furthermore, it should be clear that in a “ProdA to ProdA” scenario, the issue of carryover of cleaning agents and bioburden still require consideration in just the same manner as would be used in a “ProdA to ProdB” scenario. Furthermore, if the active degrades or if there are cleaning process degradants, further assessment of cleaning limits is required.