Cleaning Memo for January 2017
A Critique of the APIC Guideline

The APIC "Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants" was revised in September 2016. This guide is one of the few that specifically addresses issues with cleaning validation in small molecule API facilities (those that manufacture API's by chemical organic synthesis, usually in solvents). While some of the concepts may apply to bulk biotechnology manufacture, the guide does not seem to be oriented to that type of manufacture.

The focus of the 2016 revision is to incorporate the terminology of PDE (Permitted Daily Exposure) from the EMA health-based limits guideline, in addition to the ADE (Acceptable Daily Exposure) terminology which was used in the prior (May 2014) version. Most other things survive from the 2014 version. However, I have not critiqued the 2014 version in a Cleaning Memo, so I will take this opportunity to do so now with this updated version.

First, the positive. This guide (as in the past) focusses on what is different and unique in small molecule API synthesis. The issues related to how to handle intermediates and how to handle "clearance" are a highlight of this guidance. Yes, ICH Q7 says a little about these issues, but provides little specific guidance. If you manufacture small molecule APIs and you have not read this or earlier version of this APIC guide, you should do so now (on the other hand, if you are not familiar with this guide, this Cleaning Memo will probably not make sense to you).

My critiques are for the most part relatively minor, and are basically there to further clarify some issues that are not explained fully (but which should be considered in applying this guide, or considered in future revisions of this guide). I will refer to them by section number.

For clarification, the term MACO as used by APIC is equivalent to the expression L2 that I typically use. The term MAXCONC is the concentration the next product L1 limit that I typically use.

<u>Daily Dose Definition</u>

In the MACO calculation based on therapeutic daily dose (in Section 4.2.2), the "Standard Therapeutic Daily Dose" for both the cleaned product (in the numerator) and for the next product (in the denominator) is used. Typically for carryover calculations, the *minimum* therapeutic daily dose is used for the *cleaned* product and the *maximum* therapeutic daily dose is used for the *next* product. It is unclear why this minimum/maximum is not used here. This same comment applies to the health-based calculation in 4.2.1 and the LD_{50} calculation in section 4.2.3, although in these cases it is only the terminology (or definition) of the daily dose of the *next* product (in the denominator) that is relevant.

Safety Factors for LD_{50} Calculations

In section 4.2.3 the identification of the "way of entry (IV, oral, etc.)" for the LD_{50} testing is specified. Then an empirical factor (2000) and a safety factor is applied to that LD_{50} to take it down to a safe level. Those safety factors are:

Topicals	10-100
Orals	100-1,000
Parenterals	1,000-100,000

While it is certainly possible to use different safety factors for different routes of administration, the critical element is whether the LD_{50} route matches the route of administration of the next product. This may be implicit in this section, but it should be explicit. In other words, if my LD_{50} is oral and the next product is a parenteral, my safety factor should be greater than if the next product is an oral.

Note that this issue of matching routes of administration for what is in the numerator and the denominator of a MACO calculation is also relevant to the *dose-based* calculation in Section 4.2.2. If the cleaned product is an oral dose and the next product is a parenteral, I probably need an additional safety factor. Yes, the guide states that 1,000 is "normally" used, but it would be beneficial to state when it is *not* used. While this matching of the cleaned product and the next product is needed in *some* API manufacturing situations, it is not likely that the same facility and equipment would be used for different routes of exposure in a *finished* drug product manufacturing facility.

Finally, this comment does not apply to the health-based limit MACO in 4.2.1.By the traditional definitions, ADE/ PDE values are by *any* (meaning all?) route of administration. In this case, the ADE/PDE is based on parenteral use (more or less 100% available systemically). Unless the ADE or PDE is for a defined specific route of administration (see the Cleaning Memo of August 2015), then this concern is not relevant.

General Limit

There are two minor but possibly confusing things in Section 4.2.4. First is the use of the term "MACOppm". What this means (I think) is the MACO calculated on a MAXCONC value in ppm. My first reading of this was that the MACO was expressed as ppm, which is not the case since MACO is in mass units such as mg. While the APIC authors used the same "MACO" for MACO calculated by either the health, dose or LD_{50} calculations, it seems unnecessary (and possibly) confusing to add the "ppm" to the acronym for the use here. It also seems confusing because MACOppm is used in the equations, but just the term MACO (without the "ppm") is used in the example given following the equation.

In this same section, MAXCONC is the maximum concentration in the next product. Concentration is given as "kg/kg or ppm". It is unclear whether this is an option (you can express it as either kg/kg or as ppm, or whether this is a typo and that it should read "mg/kg or ppm". Either is possible. My guess is that it is a typo, because if the MAXCONC is in kg/kg, then either MACO is expressed as kg (resulting in a value with lots of decimal places), or else an additional conversion factor has to be used to convert

that kg to something smaller, like µg or g or mg. Furthermore, in the definition of MACOppm, it is stated that it is "Calculated from general ppm limit", which seems to imply that the MAXCONC units would be ppm (or mg/kg).

In this same section is Equation 4.2.5-II, giving a value for "CO", the "True (measured) total quantity" calculated from the swab results. (I think CO refers to the "CarryOver". However, I'm unclear what the distinction is between CO used here and M used in Section 4.2.6, except that one refers to the total actual carryover for swab sampling and the other refers to total actual carryover for rinse limits. The idea in this equation is that based on actual swab results (measured in a protocol, for example), it is possible to calculate the total carryover, and compare that value to the total carryover allowed (the MACO). While there are certain circumstances where that is possible, the conditions under which it can be used are not given. This equation can only be used if I assuming an approach much like described in previous Cleaning Memos related to "stratified sampling" (March, April, and May 2010). If I only take one swab sample for a given vessel, and multiply that actual value in µg/dm^2 by the surface area of the vessel (in dm^2), I can get a value for the total carryover in µg. This assumes, of course, that I have selected the worst case swabbing location. However, it is more likely to be the case that I would choose multiple swabbing locations as worst cases. Unless I multiply only the highest swab value by the total equipment surface area, or else use a stratified approach, I may understate the total carryover.

Why this equation (and calculation) is confusing is that the calculation gives a summation of different swab values. This summation is correct if it involves, for example, a series of different pieces of equipment, and I multiple the swab results by the area of that specific piece of equipment, and then I add the values for different pieces of equipment together. Where I have seen this misused is where within one piece of equipment, the different swab locations are multiplied by the area sampled, not by the what is given in the guide as Ai, or "Area for the tested piece of equipment # i". Ai is to be the total equipment area, not the specific area sampled for that swab result.

If there are multiple swab locations for one piece of equipment, and if those specific swab locations can be linked to a certain *segment* of the overall area of that piece of equipment (use of the "stratified sampling" approach), then it may be possible to use that approach when there are multiple swabbed locations for a given piece of equipment.

A final minor point is that the definition of "m_i" is given as "quantity in µg/dm^2". This could be better expressed as "value in µg/dm^2". When I hear the word "quantity", I usually think of an amount in mass (for example), not a concentration or an amount per surface area. I may be being overly picky for this last point, however.

Rinse Limit

In section 4.2.6, equations are given for determining the acceptability of the rinse limit. The requirement is given as "M < Target value." As defined M is an "amount of residue in the cleaned equipment in mg" and the "Target value" is a concentration (in mg/L) in

the rinse sample. Obviously it is *not* appropriate to compare one value in mg to another with units of mg/L. I think what is intended is that "Requirement: M < MACO." That way, both values are amounts in mg.

Confusing Terminology

In Section 8.0 (on "Determination of the Amount of Residue", relating to analytical methods used), the term "Mper" is introduced and used several times without clearly identifying what it refers to. The first use is in 8.1 where the "carryover acceptance limit" is referred to as Mper. I think, but it is not stated, that Mper refers to the *permitted* value of M. That same section then refers to M as the "actual amount of residue" left in the equipment (which is consistent with the use of M in section 4.2.6).

Section 8.2.4 introduces the term Mres, which is the *measured* amount of residue by the analytical method, which is then divided by the recovery (expressed as decimal) to give M, which is the *true* amount of residue. I suspect that the "res" suffix for M is derived from "result" (meaning the analytical result), and not "residue" (my original *incorrect* assumption).

Section 8.2.5, dealing with analytical method validation for a range, gives MperMin (the lowest foreseen acceptance limit) and MperMax the "highest limit". Once I understood what Mper was (for the longest time I incorrectly thought it referred to "M *per* equipment"), I could follow the meaning of these new terms. However, while validating an analytical method from the upper permitted limit down to the lower permitted limit is acceptable, what this actually means is that for the situation where I am measuring residue in the minimum situation, I really just have a pass/fail test. Most companies in that situation would want to extend the validated range significantly *below* the MperMin in order to demonstrate the robustness of their cleaning procedure. For example, if the minimum *permitted* M is X, I would prefer to have an analytical method that could measure down to situations where the *measured* M was closer to 0.1X.

Swab Sampling Equation

Equation 6 in Section 8.3.1 gives an equation for calculating the total "true" carryover (M) based on averaging the individual results of each swab sample (in units such mg/dm^2), and then multiplying that value by the total equipment surface area and adjusting for the sampling recovery factor (or recovery rate). This is *not* acceptable *unless* a stratified approach is used (see the earlier discussion in "General Limit"). For example, if I could use this equation, I would just sample a large number of easy to clean locations, with the result that any high values in worst-case locations would be effectively averaged down to an acceptable value. Also, when I measure *more than one* worst case location in a given piece of equipment, how do I know what part of the total surface area each worst case sampled area actually represents? As I stated earlier, unless the highest value of an equipment swab sample is used for the total area, or else stratified sampling is used for segments of a given equipment item, this Equation 6 should be avoided.

There are other minor typos in the document, such as a reference to Example 1 (and not Example 4) in the Example 5 discussion in the Annex 1 examples following Section 4.2.7. However, this guide is valuable for and is the best available for small molecule API synthesis. Use it, but as suggested, use it fully understanding how it applies to your specific situation.