Cleaning Memo for March 2016
Meeting EMA Requirements for Existing Products

An industry working group has published a paper (A. Teasdale et al, "EMA Guideline on Setting Health-based Exposure Limits", *BioPharm International*, 29:1, January 2016; also published in *Pharmaceutical Technology*, 40:1, December 2015) proposing a streamlined way to prioritize meeting the EMA requirement for limits in shared facilities for *existing products*. The EMA date for compliance for *human* health products "already produced in shared manufacturing facilities" (I assume the "already produced" is as of November 20, 2014) is November 20, 2015 (several months ago). The authors were from the following large pharma companies: Astra-Zeneca, Merck & Co., Pfizer, Bristol-Myers Squibb, Lilly, and GlaxoSmithKline.

The rationale for the proposed approach was the consumption of "significant resources" to do formally documented ADE/PDE monographs or equivalent safe threshold values for existing products for which the key safety concern was the therapeutic effect (or the pharmacological activity). Essentially the proposed approach for these actives was to determine an *estimated* ADE/PDE value based on the value a company has for OEL (Occupational Exposure Level) values or for OEB (Occupational Exposure Band) values. Those are values used for EHS purposes to determine the safe air exposure for production workers. The OEL is generally given in values such as $\mu g/m^3$ in air for an eight (8) hour exposure. Since actives taken by the inhalation route are generally close to 100% available systemically, these are viewed as a worst case. A typical value for air volume breathed in eight hours is 10 m^3. Therefore, multiplying the OEL (or OEB) value by 10 m^3 provides an estimate of a health-based ADE/PDE value.

For those actives where the primary safety concern is the therapeutic effect, this estimate of the ADE/PDE (or safe threshold value, if you prefer that terminology) is compared to the dosed-based limit (such as 0.001 of a minimum dose) previously used in cleaning validation studies. If the ADE/PDE estimate is greater than the value for the dose-based limit (within a reasonable safety margin), then the authors suggest that these actives can be given a lower priority in terms of implementing more formal compliance with the EMA guidance.

The authors also provide an example for estimating the OEL if it is not known, so read that section carefully. The approach in the example given is to start with the minimum therapeutic dose and covert it to an OEL value. For an oral drug, that is done by multiplying the minimum dose by 0.3 (to account for the 30% bioavailability of the oral drug) and dividing it by 30 (as the composite uncertainty factor as given in Risk-MaPP) and also dividing it by 10 m3 of air. Here is where you have to reads carefully, because in the equations in the printed article, there is no line separating the numerator from the denominator (I guess this is called "reading between the lines"). Then after calculation of that OEL estimate, the OEL estimate is multiplied by 10 m^3 to give the estimated ADE/PDE value. Note that the composite uncertainty factor of 30 is only given as an

example; the authors give the rationale for the selection of uncertainly factor for the example given.
Note that this approach is only taken to *prioritize* achieving compliance. Obviously, priority for *more formally documented* approaches for determination of ADE/PDE values should be given to highly hazardous actives (those that are mutagenic, have reproductive hazards, and the like) made in shared equipment/facilities, or for any new actives made in shared facilities.

The authors also address large molecules (biotech proteins). Other than to point out that the EMA guideline does state that use of PDE values of the intact active *may not* be required for biotech products which are degraded by the cleaning process, nothing new is suggested for providing further clarity in setting limits in biotech manufacturing where the active is degraded and deactivated.

I highly recommend getting a copy of this publication and reading it carefully. To be clear, it does not say that OEL values can be used for determining ADE/PDE values (although others may argue that that approach is sound). It merely suggests using PDE/ADE *estimates* based on OEL (or OEB) values as a tool for prioritizing so that efforts are focused on the largest risks. Realize, in addition, that statements in this Cleaning Memo are my interpretation of what the authors present.

One final comment (I had to get it in). If the gist of this argument is that 0.001 of a minimum dose is a safe value to use for cleaning validation limits where the primary safety concern is the therapeutic effect, why have we wasted the last five years fretting over compliance for these actives. What has changed from the Risk-MaPP assertion that limits based on 0.001 of a dose are not scientific? Did we not know this information five years ago? This is particularly relevant because one of the authors (a toxicologist) of this publication was a co-chair of Risk-MaPP. I'm sure I'll hear some criticism for this last paragraph, but it is in essence no different from what I have been saying for the last five (or more) years.