Cleaning Memo for February 2015
What's a Potent Active?

There seems to be at least two ways people in the pharmaceutical industry refer to potent actives. This is further confounded by the references to both "potent" and "highly potent" actives. This can lead to some confusion if we are not clear in how we use the terms.

One use of the term refers to actives having *therapeutic* activity at very low levels. Traditionally, *potent* actives are those having a therapeutic dose of less than or equal to 10 mg/day. In other words, an active given at a dose of 25 mg/day would not be considered potent. However, an active dosed at 3 mg/day would be considered potent. Depending on the reference, a *highly potent* active would have a therapeutic dose of less than or equal to 1 mg/day. Note that this classification depends on the therapeutic dose. There are at least two consequences of an active being potent or highly potent. One is the effect on residue limits, in that potent actives will have lower limits that non-potent actives (this will generally be true whether the limit is based on the traditional 0.001 of a minimum dose or on an ADE/PDE). The second consequence is that there will be more worker safety concerns due to possible exposure, and therefore generally more practices to avoid and/or minimize worker exposure. (Note that practices to minimize worker exposure may also reduce the likelihood of cross-contamination into the next drug product.)

A second use of the term refers not to therapeutic doses, but rather to worker exposure (safety or toxicity). The basis for the use of the term in this way is the OEL (Occupational Exposure Limit). An OEL is generally given in mass units per cubic meter of air for an 8-hour worker exposure. An example of units is micrograms per cubic meter (or $\mu g/m^3$). It is generally assumed a human adult breathes 10 cubic meters of air in an 8-hour period. Many companies will have a 'banding" systems for OEL values. A typical system may have four or more bands, covering certain ranges of OEL values. Those bands may just be referred to as a "potency" or "toxicity" category, or certain bands may actually have a designation such as "potent" or "highly potent". For example, bands in the range of 10 $\mu g/m^3$ down to 1 $\mu g/m^3$ might be in the "potent" category, and bands in the range of 100 ng/m^3 up to 10 $\mu g/m^3$might be considered "highly potent". The company's procedures will then specify what must be done appropriately for an active in each category.

Note there while it may be possible in certain situations to directly compare banding based on both OEL and therapeutic doses, they are inherently measures of two different things. One is related to the therapeutic effect via a defined mode of administration (oral, dermal, parenteral) for a specified patient population. The other is related to the safety/toxicity generally for healthy adults with breathing as the exposure mode. It is generally assumed that if the active is in contact with the lungs, there is essentially 100% systemic availability. Clearly judgment is required to compare the two measures.

It should also be noted that for some drugs, the primary toxicity (the critical effect) is related to the therapeutic effect. For some drugs, particularly those where there is a significant toxic effect apart from the therapeutic effect (what I have referred to elsewhere as "highly hazardous" actives), there may be a significant divergence between

a classification based on therapeutic dose and a classification based on an OEL. In such cases, it is most likely the case that OEL values will produce a more stringent classification.

This Cleaning Memo is designed to cover some of the issues in terminology we use when we refer to drug actives as potent and/or highly potent. It is certainly not the case that every company defines those terms the same. However, it is important that within a given company, these terms be well-defined and used consistently in various documents for both cleaning validation and for EHS purposes. If a distinction is made between different potency categories (or bands), then it is critical to specify the various practices that are appropriate for each category/band.

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Note: This Cleaning Memo corrected in September 2015 to fix typo; a potent active is less than or equal to 10 mg/day, not 10 µg/day.