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The Use of Default Limits

References to default limits such as 10 ppm are included in both the FDA and PIC/S guidance documents (although they are not specifically called default limits in those documents). This Cleaning Memo will address what these default limits are, how they should properly used, and how they are commonly misused.

Default limits are, in a sense, a maximum allowable residue limit should a limit calculated on the standard dose-based calculation (0.001 of the minimum dose of the residue active in the maximum dose of the next product) be above the chosen default limit. The default limit is always given in this context of a comparison to a scientifically justified limit. For example, if the default limit is 10 ppm in the next product, then it is utilized if the dose-based calculation results in a value above 10 ppm. However, if the dose-based calculation results in a value below 10 ppm, then that dose-based limit is selected as the residue limit. It is important to remember this is NOT an "either/or" situation. One does not have the option to arbitrarily select the default limit without first doing the dose-based calculation and comparing that limit to the default limit. This is the most common misuse of default limits - to select the default limit without reference to the dose-based limit.

Is the use of a default limit strictly arbitrary? In one sense the selection of a specific value for the default limit is arbitrary. While 10 ppm in the next product is a common default limit, other default limits such as 5 ppm could also be chosen. This is permissible because the dose-based limit is the "scientifically justified" limit, and provided that the default limit is below that dose-based limit, one can use the lower value. Because of that comparison, the selection of the default value as the limit is justified.

It is also important to remember that the typical default limit of 10 ppm is the default limit in the next product. Sometimes this is applied as 10 ppm in the analytical sample. While one can select a default limit for the value in the analytical sample (based on a dose-based calculation), this is not the conventional way to proceed. The reason is that the value of the limit in the analytical sample can be leveraged, and can be higher or lower depending on the sampling procedure. The dose-based limit in the next product is, on the other hand, solely dependent on how the residue active and the next drug product are dosed.

While 10 ppm is the most common default limit for finished drug product manufacture, the default limit in the next API can justifiably be higher in API manufacture. For example, 100 ppm in the next API is probably a more common default limit for API manufacture. The reason for this is that the residue in the API will be further diluted (typically by a factor greater than 10) as the API is manufactured into a finished drug. Therefore, a limit of 100 ppm in the API will result in less than 10 ppm in the finished drug.

The purpose of this Cleaning Memo is not to recommend default limits, nor to specify certain limits. Rather the purpose is to clarify understanding of the use of default limits, and to help assure that default limits are used appropriately. It should be noted that this Cleaning Memo only focuses on default limits and dose-based limits; it does not cover other issues in setting limits such as allergenic, cytotoxic, or reproductive hazard concerns.