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What's a "Dose" for Calculating Limits?

The traditional formulation for finished drug product residue limits for an active involves something like "no more than 0.001 of a minimum dose of the active in the maximum dose of the next drug product". The question sometimes arises as to how that dose is calculated; is it a single dose or a daily dose? Before that is answered, it is important to emphasize that the first dose (the minimum dose) is the dose of the active itself. The second dose is the dose of subsequently manufactured drug product (not the drug active). In fact, using this calculation it doesn't matter what the active is in the next product, what its level is in its drug product, or at what level it is dosed (except insofar as the dosing of the active determines the dosing of the drug product itself).

To answer the question, it may be helpful to recall what this type of calculation is trying to do. It is basically trying to determine at what level residues of the active could be therapeutically active if present in the subsequently manufactured product. It does this by first calculating the minimum amount of that residue active that could be a therapeutic dose, and then determining the maximum amount of the subsequent drug product that could be dosed (this maximum amount of the subsequent drug product would constitute the situation in which the maximum amount of residue active could be dosed). A "safety" factor of 0.001 is applied to that level to arrive at a maximum acceptable level.

Therefore, in calculating doses it is necessary to compare the same situation. If both have a daily dose, then using a daily dose is a preferred method. If the first drug is dosed once daily and the second drug product is dosed twice a day, a calculation based on a single dose would understate the risk. If both are dosed twice daily, then a calculation based on a single dose and one based on a daily dose would give the same result.

Where this becomes complicated is when each is dosed for a different time period. One example would be where one is dosed once a week and the other is dosed once daily. If the first product is dosed once a week and the second product is dosed once a day, then a calculation based on a weekly dose of each would be appropriate (it would stretch the "acceptable" residue level of the first active over a seven day period). If the opposite is the case, and the first is dosed daily and second is dosed weekly, then a calculation based on a weekly dose may not be appropriate (Note: is getting an "acceptable" residue level once daily the same as getting seven times that level once a week? In some cases it may be of no significance, but in others it may be a risk.). In a situation like this (where the first is dosed daily and the second is dosed once a week), it may be appropriate to err on the side of safety and use the daily dose of the first drug active and the weekly dose of the second drug product.

Another situation arises when dosing is by different routes of administration, for example, one orally and another topically. This is not likely in many facilities because these products are usually manufactured in different types of equipment. However, in the manufacture of API's (which may be formulated into finished drugs with multiple routes of administration) or in clinical manufacturing settings, this may be an issue. The key is to determine whether there is any dosing information on the first drug (the potential residue) when administered by the same route of administration as the second drug product. In there is, then that information should be utilized because it addresses the potential risk if that first drug active were administered by the route of the second. If there is no information on the dosing of that active by the other route of administration, then

the use of toxicity information by that same route of administration may be appropriate. The determination of "dose-based" limits for products without a dose is discussed in the May 2001 Cleaning Memo.

It should be remembered that a dose-based calculation is not necessarily the only consideration in setting residue limits for cleaning validation. Other criteria, such as visual cleanness and concerns about effects (such as allergenic, cytotoxic, and reproductive effects) other than a therapeutic dose should also be considered.

This Cleaning Memo is designed to stimulate thought about the meaning of "dose" in dose-based calculations. It does not proscribe nor prescribe any residue limit calculations, but rather is meant to assist manufacturers as they consider the appropriate residue limits for cleaning validation in their individual situations.