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What's a Contaminant?

At recent FDA Basic Drug School, I was asked the question whether allowing a specified level (such as 0.001 of a therapeutic dose of a previous active) of residue in a manufactured product was, in fact, allowing manufacturers to produce and release drug products which were "contaminated". My answer at the time was related to the fact that with newer analytical methods, we were able to measure residues at even lower levels, so that it was not feasible to specify that no "residues" of previous products appear in any other product. In giving this more thought, my answer would be slightly different. Rather than concede that any measured residue is a "contaminant", I would now answer that question by stating that a contaminant is defined by both the presence of a "foreign" substance as well as the level of that substance in the drug.

This is related to the argument that "the dose makes the poison". For example, selenium is considered a poison at doses of 500 micrograms, but is necessary in human diets at levels of about 50 micrograms (and in fact is included in some vitamin and dietary supplement formulations at around 100 micrograms). Now this analogy doesn't apply directly to residues in drugs, because for the most part we are not considering substances that may have beneficial effects at extremely low levels.

However, it is easy to think of situations where it is only certain levels of a certain substance in a drug that render it to be classified as an objectionable contaminant. For example, bioburden in a non-sterile drug product can be present at levels of certain levels (such as 75 CFU per gram) and not be considered objectionable. However, if those 75 CFU were *E. coli*, then one would readily conclude that the material was objectionably contaminated. It is both the nature of the substance and the level that are important.

This suggests that perhaps we should be more precise in our language as we discuss acceptable levels of residues. Thus, we should avoid phrases like "acceptable level of a given contaminant", because in some cases it is the level that makes the "residue" a "contaminant". Therefore, to say that a drug contains a residue of a previous drug at a given level is not to state that it is necessarily contaminated (or even adulterated).

This should not be used as an excuse to be sloppy in our cleaning efforts, and say that any residue is okay as along as it is below the acceptance criterion. We should be conscientiously applying good manufacturing practices in our cleaning procedures so that any potentially contaminating residue is kept as low as practical.

This is also not to be interpreted as saying that for any substance, some measurable amount may be acceptable. Consistent with the PIC/S cleaning validation guide, for certain allergens and cytotoxic substances, any residue should be below the limit of detection by the best available analytical technology. In such a case one must still concede that a possibility exists that the drug has a small, but not measurable (with current technology) residue of the allergen or cytotoxic material.

Nor is it to ignore the fact that, with new information, levels that we believe are acceptable today may become objectionable in the future. However, this is one of the trade-offs we live with in trying to advance medical care.