Cleaning Memo for March 2019
Contaminants in API Manufacture

For the past six months the FDA (as well as many other regulatory agencies) has been dealing with recalls of drug products and drug substances contaminated with nitrosamines. Nitrosamines are probable human carcinogens. The products are associated with API manufacture of angiotensin II receptor blockers (ARBs), mainly with valsartan but also including other ARBs. The two nitrosamine impurities that are generally found are N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA). Those two materials are found widely in water and foods, but the FDA has stated that their "presence in drug products is unacceptable".

The safe daily intake amount for the suspect nitrosamines is 0.096 µg/day. The amounts found in *some* tablets of ARB products have ranged from 0.3 µg/tablet up to 20 µg/tablet, clearly above the safe threshold set by the FDA. The FDA has been clear to point out that not all lots of ARB products have unacceptable levels. The FDA has published analytical methods suitable for measuring NDMA and NDEA in valsartan drug products and drug substances, which it believes would be suitable for other ARB products.

The FDA as well as EU agencies are trying to determine the *root causes* of the nitrosamine impurities, as well as to *prevent recurrence* of these problems. The FDA describes its effort as an "exhaustive effort". Two possible root causes being investigated are (a) by-products of the synthesis procedure and (b) reuse of solvents. And the two may be related.

Nitrosamines are generally formed by the reaction of sodium nitrite with secondary amines. While neither are required in the synthesis of valsartan itself, in a *newer* synthetic route sodium nitrite is use to destroy the excess sodium azide used in that newer process. If the DMF (dimethylformamide), which is the solvent used in the ARB synthesis, contained residual dimethylamine, this could lead to the formation of NDMA (a common synthesis of DMF uses dimethylamine as a reactant).

So, why is this important for the *cleaning validation community*? Well, it reminded me of two past problems with API syntheses. The first is the case mentioned in the 1993 FDA Cleaning Validation guideline. It involves a drug product made with a drug active cross-contaminated with an intermediate and/or degradant from the synthesis of an agricultural pesticide product. The cause appeared to be reclaiming and reuse of a solvent without making sure the solvent quality was not inappropriately compromised with residues that could be transferred to the drug substance. This was the event cited by the FDA that increased its awareness of the need for validating cleaning processes.

The second problem was with Roche's Viracept (over ten years ago). In that situation, ethanol was used to clean a storage tank for methane sulfonic acid (MSA), and was apparently not adequately removed (or evaporated) prior to the addition of the MSA reactant. Over time the ethanol and MSA *slowly* reacted to form ethyl mesylate, a known

carcinogen. The reaction of MSA with nelfinavir to produce the desired API (nelfinavir mesylate) occurred in an ethanol solvent, but because of the *short* reaction time the production of ethyl mesylate as a by-product in the reaction step itself was minimal. Only with the continued use of the MSA reactant (now with higher levels of the carcinogenic impurity) did the problem of ethyl mesylate in the API become apparent.

So, either of these two older situations may shed light on possible root causes for the more recent nitrosamine contamination issues with ARB's. And they may point out that prior acceptable limits for "impurities" may not be applicable in all situations, that closer attention may be required to possible by-product reactions to form highly toxic impurities, and that closer scrutiny may be required for the quality of solvents (whether a "virgin" solvent or a reclaimed solvent).

I'm sure there will be further updates from regulatory agencies and from industry. The easiest way to get more (or new) information is to do an internet search for key words like "nitrosamine", "contamination", and "valsartan".