Mutagenic impurities: a done deal? (part 3)

In the third part of this series on mutagenic impurities, Dave Elder discusses the realities of the EMA’s guidance for manufacturers regarding the processes to prevent nitrosamine impurities.

Interestingly, there are many within the EMA’s own safety working party (SWP) that viewed the “risk avoidance” strategy finally adopted by EMA with concern. The so-called “risk minimisation” group within SWP felt that the established AI strategy defined in ICH M7(R1) employs a conservative risk assessment approach, which is considered suitable if levels are kept below these thresholds. The “risk minimisation” group felt that there were no compelling reasons to deviate from the accepted “risk/benefit balance regulatory practices for handling mutagenic impurities”. This is based on the fact that there are no factual data to demonstrate that “NDMA and NDEA are fundamentally different from other mutagenic carcinogens, which are covered by the TTC framework in ICH M7(R1), besides being more potent”. As such, the higher potency is handled by “defining compound-specific thresholds based on carcinogenicity data and by linear extrapolation”. Thus, there is no requirement for a “no threshold” approach.

The FDA proved to be extremely problematic. Indeed, there was significant concern that an unwillingness to accept even the most infinitesimal risks could “force off the market many substances utilised in agriculture and food processing that are widely regarded as safe when used as intended”.

Currently, the nitrosamine methodologies have ppb limits based on acceptable intakes (AI) for NDMA (Candesartan: 3000 ppb; Irbesartan: 320 ppb; Losartan: 620 ppb; Olmesartan: 2400 ppb; Valsartan: 300 ppb) and NDEA (Candesartan: 820 ppb; Irbesartan: 88 ppb; Losartan: 177 ppb; Olmesartan: 663 ppb; Valsartan: 82 ppb). EMA has indicated that after the transition period a limit of <30 ppb for both nitrosamines would be applicable. However, this confirmatory limit is difficult to justify, as it isn’t based on a specific daily dose of any specified sartan, or on the specific nitrosamine impurity (ie, NDMA or NDEA), or on the AI limits for those specific nitrosamine impurities; it appears to be an arbitrary figure.

The most famous example is the 1958 US Delaney Clause. It states that no human or animal carcinogen, “shall be deliberately added to, or found as a contaminant in food”. However, enforcement by the FDA proved to be extremely problematic. Indeed, there was significant concern that an unwillingness to accept even the most infinitesimal risks could “force