The clear majority of drug substance manufacturers, both innovator and generic, were aware of the problem and had in place robust, risk-based processes to assess the potential for mutagenic impurity formation and control. However, in mid-2018, the EMA announced that they were “reviewing medicines containing valsartan from Zhejiang Huahai following the detection of an impurity”. The recall involved nearly 2,300 batches that were sent to Germany, Norway, Finland, Sweden, Hungary, the Netherlands, Austria, Ireland, Bulgaria, Italy, Spain, Portugal, Belgium, France, Poland, Croatia, Lithuania, Greece, Canada, Bosnia and Herzegovina, Bahrain and Malta. The EMA indicated that the impurity was “a result of a change in the manufacturing process.”

What caused so much surprise and concern across the industry was the identity of the impurity – the known carcinogen, N-nitrosodimethylamine (NDMA). To the best of my knowledge, this was the first instance of a product recall being initiated on the basis of an impurity that was a member of the so-called “cohort of concern” class.

During the evolution of the ICH M7 guidelines, the authors had introduced the concept of the threshold of toxicological concern (TTC). The TTC defined an acceptable intake (or risk) for any unstudied chemical that would pose “a negligible risk of carcinogenicity or other toxic effects”. A TTC value of 1.5μg/day, which corresponded to a theoretical 10^-5 excess lifetime risk of cancer, was deemed to be acceptable. However, some structural groups were deemed to be of such high carcinogenic potency that even intakes below the default TTC of 1.5μg/day, would still be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens was referred to as the “cohort of concern” and was comprised of aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds. However, it had always been the industry’s contention that the “cohort of concern” reflected structural classes that were very unlikely to be encountered during the synthesis of pharmaceutical drug substances. Delaney indicated that the TTC was, “(a) unduly influenced by many classes of potent carcinogens of historic concern, which would be impossible to generate unknowingly as pharmaceutical impurities, and (b) that the majority of reactive chemicals that would be useful to synthetic chemists are among the least potent carcinogens in the underpinning supportive analyses”.

Against this background, a product recall based on a “cohort of concern” impurity, ie, NMDA that appeared to be “unknowingly generated”, was very worrying. The EMA3 recall was quickly followed by FDA recalls (“FDA announces voluntary recall of several medicines following detection of an impurity”) and recalls in India (“India launches probe as China co-recalls BP drug”). Subsequently, questions have been received from multiple regulatory agencies and the scope of the questions is now focused on all sartans that contain a tetrazole ring and any source of secondary amine. Several observers have asked the key question, “How did NDMA get into Valsartan?”.

It would appear that impurities in the solvent DMF (dimethylformamide), ie, dimethylamine and subsequent reaction with sodium nitrite (NaNO2), would yield NDMA. Regulatory questions now appear to be focused on this possibility and the presence of dimethylamine in dimethylformamide has been reported in the literature.

It would appear likely that probable bi-products, especially those arising from impurities that are generated during the synthesis, will feature prominently in future regulatory questions in the field of mutagenic impurities.