Nitrosamines

How to address these unwelcome guests in the pharmaceutical world

Nitrosamines are a family of carcinogens which are formed by the reaction of secondary amines, amides, carbamates, derivatives of urea with nitrite or other nitrogenous agents with the nitrogen in the +3 state.[1] The common nature of the precursors and the facile nature of the nitrosation reactions under acidic pH have made nitrosamines one of the common and unwelcome guests in the world of consumer goods and pharmaceuticals—the one who comes uninvited, consumes our resources, and will simply not go away.

The carcinogenic properties of nitrosamines have been known for over 50 years[2] and there are several nitrosamines that have been tested for carcinogenicity and have shown activities, nitrosodimethylamine (NDMA) and nitrosodiethylamine (NDEA) and N-nitroso-N-methyl-4- aminobutyric acid (NMBA) being the well-known amongst these.[3] Nitrosamines are classified by the ICH M7(R1) Guideline as Class 1 impurities, "known mutagenic carcinogens," based on both rodent carcinogenicity and mutagenicity data.[4] They are categorized by the International Agency for Cancer Research (IARC) as 2A – Probable Carcinogens5 based on data on a number of species studied. These two classifications (ICH M7(R1) versus IARC) should not be confused as they address the carcinogenicity from different angles. The ICH M7(R1) Class 1 finding limits the safety assessment approach/control options, which requires these to be at or below a compound-specific acceptable limit. The limits for nitrosamines in pharmaceuticals can be derived only from rodent study cancer potency data as the threshold of toxicological concern (TTC) approach is not acceptable to most regulatory agencies in the world.[4]

Nitrosamines have recently re-surfaced in the pharmaceutical world due to FDA and other international agencies finding traces of these compounds in the angiotensin II receptor blockers (ARBs), commonly known as the "sartans." The drugs involved are Valsartan, Losartan, Irbesartan, Azilsartan, Olmesartan, Eprosartan, Candesartan and Telmisartan.[6] As of now, Valsartan and Losartan are the worst affected and several lots of these products have been recalled.[7] Also, all pharmaceutical companies which have FDA approved "sartans" have been sent requests to evaluate the presence of nitrosamines in their products and communicate their findings to FDA.[7] In addition, FDA has been working towards addressing the issue of nitrosamines in "sartans" and keeping the public informed about the actions being taken.[7] FDA's actions have included recalls of several lots of ARBs, providing of acceptable limits of the nitrosamines in the ARBs and also providing the sponsors with sensitive analytical methods for analysis.[8] Following ICH M7(R1), safe levels of NDMA and NDEA have been calculated using the TD50 values from rodent carcinogenicity studies adjusted to represent a cancer risk of one excess cancer per 100,000 people exposed on a daily basis over a lifetime. FDA has currently provided safety limits for NDMA at 96 ng/day and NDEA at 26.5 ng/day.[6] For NMBA, which was identified more recently, the safety level is determined at 96 ng/day.[6]

However, for Losartan, FDA is currently accepting an interim specification of NMBA at 9.82 ppm versus 0.96 ppm, which would be the limit based on the TDI (total daily intake) of 96 ng/day.[6] The basis of the acceptability of NMBA at levels up to 9.82 ppm for a limited time is based on the agency's finding that the interim specification presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm.[6] The expectation is that this interim specification will prevent a shortage of Losartan and will also give sponsors a few months to develop a process to assure that they can provide the American public with NMBA-free losartan. Overall, the unexpected finding regarding the nitrosamines in ARBs has increased the work load of the pharmaceutical industry, especially API manufacturers as well as FDA, exponentially. It has also left the consumers wondering about the safety of the blood pressure medications they have been taking, sometimes for many years.

While the entire pharmaceutical industry is holding its breath and waiting to see how nitrosamines in ARBs

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are eventually handled, questions have also arisen as to how a situation of this kind could be anticipated and possibly avoided in the future. Based on the structure of the "sartans" and the nature of the nitrosamines found in them, it can be concluded that the sources of the nitrosamines are not the degradation or the manufacturing process of the "sartans." The sources lie in the impurities that may be present in the reagents and solvents used in the manufacturing of most of the "sartans" and, in some cases, the improper recycling of the solvents, which in turn can give rise to impurities.[7] Sodium nitrite is a common agent used in the manufacturing of most of the "sartans."

As mentioned before, sodium nitrite undergoes a facile reaction under acidic pH with any amines, amides etc. that may be present impurities in the solvents, recycled solvents and reagents, to form the nitrosamines. Thus, it is imperative that manufacturers understand the possible source of nitrosamine formation in their manufacturing process and add proper controls to reduce the possibility of formation of these carcinogenic impurities. The pharmaceutical industry needs to look beyond the obvious and understand that the quality of the reagents and solvents, even those used relatively upstream in the manufacturing process, are critical for assuring the quality of the final drug substance.

The questions that arise with nitrosamines and other mutagenic impurities in drug substances are what to do and where to start in order to anticipate and prevent these situations. In the case of nitrosamines, the following are examples of proactive steps that the drug substance manufacturers can take during the manufacturing of drug substance, which could lower the possibility of the presence of nitrosamines as impurities significantly:

- Whenever the drug product is a secondary amine or any of the intermediates or impurities in the drug substance are secondary amines, it is beneficial to look for corresponding nitrosamines during the manufacturing process development.
- When sodium nitrite is used in any step of the manufacturing process of a drug substance, an extensive evaluation should be done for all possible nitrosamines based on the starting materials, reagents and solvents. If sodium nitrite is used upstream in the manufacturing process, steps should be taken to make sure that it is very efficiently washed out.
- When solvents such as DMF (dimethylformamide), DMA (dimethylacetamine), or DEA (diethylacetamide) are used in the manufacturing of a drug substance, it would be prudent to look for potential nitrosamines like NDMA and NDEA.
- When a reagent has a secondary amine structure (e.g., diethanolamine or its derivatives are used as linkers in many synthetic process), it would be prudent to look for nitrosamines related to these amines.[9]
- N-alkyl amides, carbamates can be nitrosated.[1] So, one should be cognizant of the possibility of nitrosamines being formed, in case amides and carbamates are used as reagents or generated as intermediates in the synthetic scheme of the drug substance.
- If a late-stage intermediate is considered a Regulatory Starting Material (RSM) and bought from an external vendor, it should be verified whether sodium nitrite has been used in any step of the manufacturing process of the RSM.

As of now, it seems like an uphill task for the pharmaceutical industry to understand when and where nitrosamines may become present in drug products. However, with better understanding of their precursors and the conditions which facilitate their formation, the industry may be able to reach a point where it can curtail or even eliminate the possibility of nitrosamines appearing in pharmaceutical products. **CP**

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