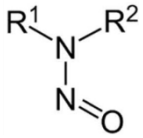
Nitrosamine Analysis in Active Pharmaceutical Ingredients and Finished Drug Products

Nitrosamine impurities became a focus for authorities in July 2018 following recalls of angiotensin II receptor blocker medicines, known as sartans, due to the presence of the nitrosamine N-nitrosodimethylamine (NDMA). Of the sartans, valsartan and losartan were the worst affected with several lots of each needing to be recalled.

Since then, more cases of drug substances and drug products contaminated with nitrosamines have been observed. In the US, there was a recall of drug products containing the drug ranitidine. The EMA has urged manufacturers to test drug products containing pioglitazone and metformin for nitrosamines. Recalls and further reviews are being carried out by several national authorities in Canada, Switzerland and Singapore.

Although nitrosamine impurities have been found in only a few drug products, nitrosamine impurities might exist in other active pharmaceutical ingredients (APIs) and drug products due to the use of common processes and materials that may produce nitrosamines.

Nitrosamines



Nitrosamines are a family of carcinogenic impurities which are formed by the reaction of secondary amines, amides, carbamates, or derivatives of urea with nitrite or other nitrogenous agents with the nitrogen in the +3 state.

In addition to the nitrosamine NDMA discussed above, the FDA is also concerned with the possible presence in drugs of the following nitrosamines:

- N-nitrosodiethylamine (NDEA)
- N-nitrosoethylisopropylamine (NIEPA)
- N-nitrosodiisopropylamine (NDIPA)
- N-nitrosodibutylamine (NDBA)
- N-nitrosomethylamino-butyric acid (NMBA)
- N-nitrosomethylphenylamine (NMPA)

This list represents the most likely nitrosamines to be present but is not intended to be exclusive. If other nitrosamines are present in an API or drug product, they could present similar risk to the patient and should also be evaluated.

Sources of Nitrosamines

Nitrosamines can be formed as synthetic by-products in the manufacturing of the API or drug product excipients. For example, the NDMA found in sartans formed during synthesis as a result of a reaction involving the tetrazole ring on the sartans. The use of nitrosating agents like sodium nitrite in any synthetic process has also been shown to lead to the formation nitrosamine by-products.

A second source of nitrosamines is from contamination. This occurs when the raw materials or solvents are already contaminated with trace levels of nitrosamines upon receipt. Cross-contamination can also occur from other processes at the manufacturing site.

Similar to synthetic by-products, degradation of the raw materials, intermediates and final drug substance can also give rise to nitrosamines over time.

The final source of nitrosamines is by leaching from the manufacturing equipment or packaging materials. Any piece of the manufacturing equipment or packaging materials that come in direct contact with a raw material, intermediate or final product can be a potential source of nitrosamines depending upon the material of construction.

Risk Assessment

A thorough, risk based evaluation of the entire manufacturing process should be performed to determine which nitrosamines are at risk and the likelihood of any nitrosamine being present in the final drug product. This risk assessment will at a minimum evaluate the manufacturing process, the likelihood of nitrosamines being formed in the synthesis or as a result of degradation based upon the structure of the drug, and the risk of nitrosamines leaching into the product from the process equipment or packaging components.

Nitrosamine Analysis

Following the risk assessment, the API and drug product should be tested for the targeted nitrosamines identified in the risk assessment. The analytical methods used will either be GC-MS or LC-MS depending upon the targeted nitrosamines. Methodologies using GC-MS and LC-MS have been proposed by the FDA for specific nitrosamines and are used as a guidance for the analysis. Once the analytical method has been demonstrated to be appropriate for the targeted nitrosamine(s), the method must be validated for the targeted nitrosamine(s) in the specific API or drug product.

Toxicological Assessment

If a nitrosamine is observed in the drug product, a toxicological assessment is required to determine the acceptance limit for the nitrosamine. The observed level of the nitrosamine is then compared to this acceptance limit to determine if the nitrosamine will present a risk to the patient.

Conclusion

Nitrosamines are a class of carcinogenic compounds that have drawn the concern of the FDA and other regulatory bodies. A thorough evaluation of the risk of nitrosamines followed by analytical analysis is required to address this concern.

Pine Lake Laboratories Can Help

At Pine Lake Laboratories, we have the required expertise to meet this challenge. Our materials expert has the experience to identify the potential sources of nitrosamines during the risk assessment. Once the targeted nitrosamines have been selected in risk assessment, our GMP analytical team has experience in developing and validating sensitive GC-MS and LC-MS methods for nitrosamines in a variety of API and drug products. Finally, we can support the final results with a toxicological risk assessment when needed.

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