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Addressing nitrosamine and related impurities in pharmaceuticals

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Nitrosamine impurities may be formed during API processing under certain processing conditions

Recently, a concern raised by regulatory agencies on the presence of nitrosamine impurities observed in drugs such as angiotensin II receptor blockers (ARBs) viz. Valsartan, and other class of drugs (e.g. Ranitidine, Nizatidine, and Metformin) that has created a havoc in pharma industry as this compelled the pharma companies to recall many lots of Finished Goods from the market.

Nitrosamine is a class of compound having N-nitroso (R1-N (-R2)-N=O) functional group as a part of their chemical structure. These molecules are potent genotoxic and are classified as probable human carcinogens by the International Agency for Research on Cancer (IARC). Very small exposure of these impurities can lead to cancer.

Although they are also present in some foods and drinking water supplies, their presence in medicines is nonetheless considered unacceptable.

European Medicine Agency (EMA) has finalised a review under Article 5(3) of Regulation (EC) No 726/2004 in June 2020 to provide guidance to marketing authorisation holders on how to avoid the presence of nitrosamine impurities in human medicines.[1]

FDA has also issued guidance on “Control of Nitrosamine Impurities in Human Drugs” which recommends steps that should be taken by API and Drug Products manufacturers to detect, reduce or prevent the presence of nitrosamine impurities in APIs and finished drugs.[2]

Potential Source of Nitrosamine Impurities:

Nitrosamine impurities can originate from different sources related to the manufacturing process (including raw materials, reagents, reactants and solvents used in the process), chemical processing reaction conditions, use of recycled solvents and

the chemical structure of the API.

Additionally, several external factors, such as packaging or storage conditions, can intensify nitrosamine contamination.

Potential root cause for the formation of Nitrosamine impurities:

Nitrosamine impurities may be formed during API processing under certain processing conditions and in the presence of some types of raw materials, starting materials, and intermediates. These impurities may not be fully purged in subsequent steps of the API manufacturing process and get incorporated into the drug substances or drug product.

- Nitrosamine impurities are generally formed when secondary amines, tertiary amines, or quaternary amines react with nitrite under acidic reaction conditions. Nitrite salt under acidic conditions forms nitrous acid which can react with an amine to form nitrosamine. The use of sodium nitrite ($NaNO_2$), or other nitrites, in the presence of secondary or tertiary amines (used as reactant / reagent) is a potential cause of nitrosamine formation.

- Amide solvents (such as N,N-dimethylformamide, N-methylmorpholine, tributylamine, N-methylpyrrolidone, N,N-dimethylacetamide and N,N-diethylacetamide etc) which are susceptible to degradation under certain reaction conditions (such as high temperature for an extended reaction period) can degrade into secondary amine, which can react with nitrous acid to form N-nitrosamine impurities.

- Secondary amines could also be present as impurities in amide solvents. For example, dimethylamine, which can react with nitrous acid to form NDMA, may exist as an impurity in N,N-dimethylformamide.

- Use of outsourced Starting Materials or intermediates may pose a risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are produced in other processes.

- Sodium nitrite is a known impurity present in some starting materials. If nitrites are present in raw materials, and or Starting materials (such as sodium azide), they could react with amines under acidic conditions to form nitrosamines. The amount of nitrite impurity that can be tolerated is process dependent and should be determined by each API manufacturer.

- Use of recovered materials (such as recovered solvents and catalysts, may pose a risk for nitrosamine formation due to the presence of amines in the solvents or catalysts sent for recovery and the subsequent quenching of these materials with nitrous acid to destroy residual azide without adequate removal. Independent recovery facilities may co-mingle solvents/catalysts from various customers or not perform adequate cleaning of equipment between customers.

Risk assessment and mitigation:

API and Drug Products manufacturers should perform a comprehensive risk assessment for already approved /marketed products, and pending for approval applications to identify the potential for nitrosamine impurities. If a risk of nitrosamine impurities is identified, confirmatory testing of batches should be conducted using sensitive and appropriately validated methods. If the risk assessment determines that there is no potential for nitrosamine impurities, there is no need to take further action.

If a nitrosamine impurity is detected, API manufacturers should investigate the root cause. They should implement changes in the manufacturing process to reduce or prevent nitrosamine impurities.

A risk-based approach can be adopted to prioritize the evaluations followed by confirmatory testing (if the risk evaluation

would indicate that testing would be required). Following factors should be considered for prioritization:

- Maximum daily dose taken
- Duration of treatment
- Therapeutic indication
- The number of patients treated

Following factors should be considered during risk assessment:

- Potential risk of formation of nitrosamine impurities during its synthetic process due to reagents, solvents, catalysts and starting materials used, intermediates/impurities /degradants formed and reaction conditions (such as temperature, pH, carbon treatment, chemical reduction or excess of alcohol etc.) forming or suppressing nitrosamines.

Purging factors, if known, can be useful to review the risk

- Potential risk of nitrosamine contamination from recovered materials (such as solvents, reagents catalysts), inadequate cleaning of equipment, degradation, starting materials or intermediates) as well as nitrosating agents, nitric acid, nitrites, amide solvents and reagents containing secondary and tertiary amino group.
- Potential risk for the presence of nitrates and nitrites in water used in the manufacturing. NDMA can occur in drinking water as it is a by-product of several industrial processes and can also be formed as a by-product of anion-exchange treatment of water.

Finally, absence of nitrosamine impurities should be verified by testing a representative number of samples of the relevant starting material, intermediate, API or finished product and the number of batches/samples tested should be scientifically justified. Any API batch containing a nitrosamine impurity above the interim acceptable limits should be recalled, if distributed, or dispositioned as not suitable for use in DP.

Corrective Actions for mitigation:

If presence of nitrosamine impurities is confirmed, then API / Drug product manufacturers are required to modify the processes so they do not produce any nitrosamine impurities. Following can be considered for change in process:

- Use of amide solvents (like DMF, DMA, NMP etc.) to be discouraged and should be replaced with non-amide solvents (if possible)
- Use of sodium nitrite as a quenching agent for azide group to be replaced with another quenching agents
- In-process controls for testing of raw materials that may introduce nitrite to be performed
- Using bases other than secondary, tertiary, or quaternary amines (when possible)
- Be extra-careful with recycling of solvents

- Routine testing of the API for nitrosamines and their levels “not measurable (< 0.03 ppm)”, irrespective of nitrosamine and API

Limits for Nitrosamine impurities

The Acceptable Intake (AI) limit for nitrosamine is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure. The conversion of AI limit into ppm varies by product and is calculated based on a drug’s maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

Test methods to be developed should be sensitive enough to detect these impurities at very low levels. Limits proposed for some of the nitrosamine impurities in Valsartan and their LOD achieved through different test methods are provided below:

		LOQ achieved by Test method	
Nitrosamine Impurity	Limit in Valsartan		
		UHPLC/MS/MS	GC/MS/MS
NDMA	0.3ppm	0.2ppm	0.08ppm
NDEA	0.08ppm	0.04ppm	0.04ppm

AI Limits for Nitrosamine impurities in Drug Products are provided below:

Nitrosamine Impurity	Acceptable intake (AI) Limit (ng/day)
NDMA	96
NDEA	26.5
NMPA	26.5
NDIPA	26.5

- For drug products with a Maximum Daily Dose (MDD) of less than 880 mg/day, a recommended limit for total nitrosamines of 0.03 ppm is not more than 26.5 ng/day and is considered acceptable.

- For drug products with an MDD above 880 mg/day, the limit for total nitrosamines should be adjusted so as not to exceed the recommended limit of 26.5 ng/day

Analytical Test Methodology for nitrosamine impurities:

API and Drug Product manufacturers are responsible for developing and using suitable methods to detect and limit

unacceptable nitrosamine impurities, including any new impurities that may arise when they make changes to their manufacturing processes.

The typical tests for API purity, identity, and known impurities are unlikely to detect the presence of a nitrosamine impurity. Further, each failure mode could result in different nitrosamines, different amounts, or undetectable amounts of nitrosamine impurities in different batches from the same process and API producer.

Analytical methods developed by FDA and EDQM for determination of nitrosamine impurities in sartans can be used as a starting point for the development and validation of analytical methods appropriate for other APIs.

The following technical aspects should be considered during development of analytical methods:

- Interferences caused by presence of trace amounts of nitrosamines in testing materials used (e.g. water, airborne sources, plastics products, rubber/elastomeric products)

- In situ formation of nitrosamines

Recommended Timeline for Risk Assessment, Confirmatory Testing, and Submission of Required Changes:

For Approved / Marketed Products:

Drug Product manufacturers should conclude a risk assessment of approved or marketed products within 6 months of publication of this guidance (Sep 2020). Confirmatory testing should start as soon as the risk of nitrosamine is identified from the risk assessment and should begin immediately for products considered at high risk.

For Pending Applications:

Applicants should conduct a risk assessment for nitrosamine impurities in APIs and drug products and conduct confirmatory testing if needed, and changes to the DMF or application should be submitted as quickly as possible.

If confirmatory testing finds nitrosamine levels above the LOQ but is within the AI limit, the applicant should amend the application as appropriate. The Agency will work with the applicant to resolve issues during the review cycle or immediately after approval, and before distribution, if determined to be necessary by the Agency.

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[1] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions

[2] https://www.fda.gov/media/141720/download