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Review Article

A REVIEW ON PHARMACEUTICAL NITROSAMINE IMPURITIES REGULATIONS AND TIMELINES

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ABSTRACT

The aim of this review is to provide a guidance to pharmaceutical scientist in need of identifying and controlling the nitrosamines in pharmaceutical drug products and drug substances. Nitrosamines are the molecules containing the nitroso functional group. The presence of nitrosamines has been detected recently in several angiotensin II receptor blockers (ARBs) commonly known as 'sartans', ranitidine, nizatidine and metformin. The most commonly found nitrosamines are N-nitrosodimethylamine (NDMA) and nitrosodiethylamine (NDEA) belong to the so-called "cohort of concern", which is a group of highly potent mutagenic carcinogens that have been classified by the WHO's International Agency for Research on Cancer as probably human carcinogens. In 2018, NDMA and NDEA were detected in some valsartan drug substances and the drug products manufactured from drug substances using specific synthetic routes. This observation triggered extensive synthetic route assessments and development of analytical procedures to quantify these two nitrosamine impurities. Since then, US Food and Drug Administration (FDA) is working with global regulatory authorities, sharing information about ongoing investigations, and learning about their findings. As a result of the potential toxicity associated with these impurities, global regulatory bodies recommended to take steps to control and limit their presence in pharmaceutical materials.

Key words: Nitrosamines, cohort of concern, 'Sartans', Ranitidine, Nizatidine, Metformin, FDA, European Medical agency.

Introduction

In March 2018, the FDA issued a guidance for manufacturers that lays out risk assessments that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally harmonized guidance that both regulators and industry have agreed to [1]. The aim of FDA and other regulatory bodies is to limit a possible human cancer risk due to lifetime or less-than lifetime mediations having the trace levels of genotoxic impurities.

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These impurities have potential to cause damage to the DNA which leads to cancer. Nitrosamine impurities are ICH M7 class 1 known mutagenic carcinogen impurities belonging to the so-called "cohort of concern", which is a group of highly potent mutagenic carcinogens that have been classified by the WHO's International Agency for Research on Cancer as probably human carcinogens [2,3]. Now a days almost all the regulatory bodies and pharmaceutical manufacturers throughout the world are working in establish the risk easements, limits for nitrosamine impurities and confirmatory testing in some category of drug products. the most found nitrosamine impurity in pharmaceutical products is N-nitrosodimethylamine (NDMA), which was first found in valsartan, an angiotensin II receptor blocker, in July-2018. Since then, other nitrosamine impurities were subsequently detected in other medicines belonging to the 'sartan' family. More recently nitrosamine impurities have been identified in batches of ranitidine, nizatidine and metformin drug products.

Potential source of Nitrosamines:

Nitrosamines, or more correctly N-nitrosamines, are the molecule containing the nitroso functional group, they are common in water and foods, including cured and grilled meats, dairy products and vegetables etc,. as this food undergoes a process in our body and can form nitrosamines and everyone exposed to some levels of nitrosamines is not atypical in our daily lives. However, the exposure to nitrosamines above acceptable levels as part of lifetime medication can increase the risk of cancer. Presence of this impurities in pharmaceutical drug products is not acceptable. Some potential sources of nitrosamine impurities into drug products been identified and reported that Nitrosamines are formed by 'nitrosation' chemical reactions between amines and nitrous acid that occur during API manufacturing in the presence of some starting materials, intermediates, reactants, reuse of solvents and by-products; also the use of sodium nitrite (NaNO2), or other nitrites, in the presence of secondary or tertiary amines is a potential cause of nitrosamine formation **(Figure 1).** Also, in marketed product they may form through degradation products generated during formulation or improper storage conditions or from environmental contaminants.

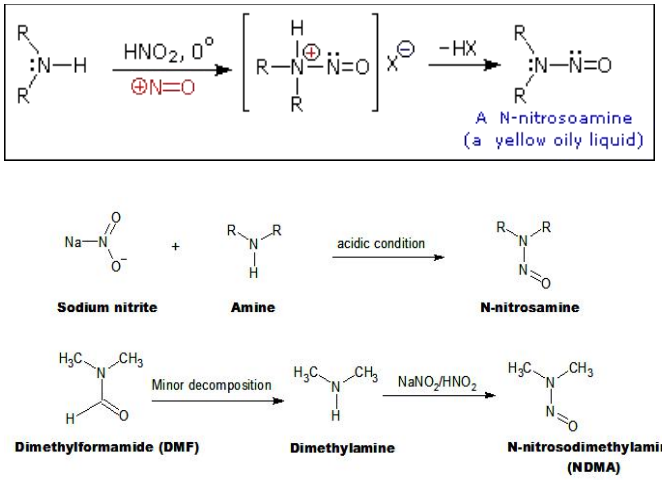

Fig 1: Reaction 1

Additionally, several external factors, such as packaging or storage conditions, can intensify nitrosamine contamination, a new root-cause for contamination of drug products been reported is that the reaction of nitrocellulose in the lidding foil with amine containing printing ink [dimethylamine (DMA) and diethylamine (DEA)] and transferred to the finished product during heat-sealing bottling / blistering process via vaporization and condensation on the finished product.

REGULATORY EXPECTATIONS:

In September 2020, the US FDA issued guidance for industry on detection, prevention, and risk management of nitrosamine impurities in APIs and drug products. For approved or marketed drug products, manufacturers should conclude the risk assessment by March 31, 2021.

Confirmatory testing should start if a nitrosamine risk is identified and conclude immediately on high-risk products. Manufacturers do not need to submit risk assessment documents to the agency, but they should retain these documents so that they are available if requested. [4]

European Medical agency (EMA) issued guidelines to marketing authorization holders (MAHs) to perform a risk evaluation to ascertain whether chemically synthesized active pharmaceutical ingredients (APIs) are at risk for containing nitrosamines by 31 March 2021. The initial evaluations are followed by a second step of confirmatory testing when risk is involved. Step 2 testing should be completed and reported to EMA by 26 September 2022 for chemical APIs and by 1 July 2023 for biological APIs. If a risk is identified for an active substance, marketing authorization holders should submit the step 1 response template and proceed with step 2 confirmatory testing of the finished product. If no risk is identified for an active substance, marketing authorization holders should conduct a risk evaluation of the finished product and submit the outcome of step 1 only when they reach a final conclusion on the active substance and finished product. [5]

Health Canada issued a guideline to prescription and non-prescription pharmaceuticals Market Authorization Holders (MAHs) that they are responsible for testing of their products to determine the presence of nitrosamine impurities. If the outcome of the tests indicates the product is safe, the results should be retained by the MAH. If any impurities are detected during testing, the MAH is required to inform Health Canada immediately to allow proper steps to be taken. Confirmatory testing and any changes to the marketing authorizations be completed within two years, with a deadline of October 1, 2021. Now, as a result of the COVID-19 pandemic, Health Canada has provided an extension and has released an updated timeline. The risk assessments now must be completed by October 1, 2020 and confirmatory tests and any changes to the market authorization must be completed by October 1, 2022.[6]

All the regulatory agencies Guidance provides the following recommendations for manufacturers of APIs and drug products to detect and prevent unacceptable levels of nitrosamine impurities.

(A)RISK ASSESSMENT:

Pharmaceutical manufacturers should review their manufacturing processes and perform risk assessments to identify the potential for nitrosamine impurities. While conducting risk assessment they should refer to the recommendations in ICH M7(R1) and the ICH guidance for industry Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (September 2016) and Q11 Development and Manufacture of Drug Substances (November 2012). The following factors should be considered during process development.

(i) Drug substance risk assessment:

- Evaluate the sources of Nitrosating agents, the possible sources of nitrosating agents are nitrites (e. g. sodium nitrite, $NaNO_2$) and nitrous acid (HNO_2), nitric oxide (NO), nitrosyl halides (e. g. ClNO, BrNO), dinitrogen trioxide (N_2O_3), dinitrogen tetroxide (N_2O_4) and organic nitrites (e. g. t-BuONO).
- Evaluate the potential contamination risk, the possible contaminations are use of recovered materials (e. g. solvents, reagents, catalysts), also cross contamination from shared equipment use.
- Avoid reaction conditions that may cause to generate nitrosamines during process steps and demonstrate that the process is adequately controlled and is capable of consistently reducing nitrosamine impurities through appropriate and robust fate and purge studies.
- Unless otherwise mandate, use bases other than secondary, tertiary, or quaternary amines.
- Replace nitrites with other quenching agents for azide decomposition processes.
- Optimize and consistently controlling the sequences of reactions, processes, and reaction conditions (such as pH, temperature, and reaction time).
- API manufacturers should audit their supply chains and monitor them for any at-risk raw materials, starting materials, and intermediates and their qualification records.
- If a nitrosamine impurity formation risk is identified during process. They should implement changes in the manufacturing process to reduce or prevent nitrosamine impurities.

(ii) Drug Product Risk Assessment:

- Drug product manufacturers should conduct risk assessments in collaboration with API manufacturer and excipients manufacturers to determine the potential for nitrosamine impurities in drug products.
- As an initial evaluation DP manufacturer should check for drug substances those are containing a reactive secondary amine which, if nitrosated, would lead to nitrosamine. Tertiary amines are significantly less reactive than secondary amines, hence, tertiary amines would generally consider as negligible risk. also, few amine excipients that are risk of containing amines (e. g. EDTA salts and triethanolamine).
- Water for formulations is purified as low as < < 0.01 ppm nitrite which is of low risk. [6]
- Solid based formulations are as less risk as the availability of amines within matrix can be substantially lower and trapped within the solid matrix. Whereas in aqueous based formulations, the formulation pH is to be consider as risk, heat also important. It is acknowledged that pH between 3 to 4 is considered optimal for the nitrosation with nitrous acid if pH of the product and entire process is > 7 the risk of nitrosation is considered negligible. The use of flavors and fragrances in drug products are identified as no risk as they are approved food grade materials.
- The key risk assessment of drug product is to understand what limits within a drug product is at risk. Where the risk is identified, safety experts should set the limits as per ICH M7. If an acceptable intake (AI) cannot be calculated an interim acceptable limit of 44 ng/day can be set until a limit set by ICH.
- If any potential risk is confirmed as per ICH M7 class 3 nitrosamine with known carcinogenic potential proceed for the confirmatory testing with a validated analytical method.

(iii) Risk Assessment for Packaging Materials:

- Packaging materials risk is considered very low as observed levels of nitrosamines, when formed have been very low and significantly below. Packaging materials that are currently considered as potential risk are blister lidding foils containing nitrocellulose as printing primer.
- Nitrocellulose is commonly used in blister lidding foil as a print primer, which may react with printing ink to form nitrosamines. To avoid such cases, nitrocellulose free materials are available and can be changed without prior regulatory approval.

(B) Establishment of Limits for Nitrosamines:

The FDA has established the acceptable intake limits (AI) for the following nitrosamine impurities: NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA (table 1) to consider manufacturers in establishing API and drug product limits.

Nitrosamine	AI Limit (ng/day)
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Table 1. AI Limits for NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA in Drug Products

Example Calculations of Nitrosamine Limits:

The AIs in nanograms per day and the maximum daily dose (MDD) of the drug substance (DS) from the drug label in milligrams per day can be used to calculate the maximum nitrosamine concentration limits, in ppm, for individual drug products using the following equation:

Concentration = AI/DSdose

Since the exposure to nitrosamines is related to the MDD of the DS, different concentrations of nitrosamines (ng/g) may be acceptable for each material evaluated. The acceptable concentration in the material can be calculated using the following equation:

Acceptable nitrosamine content = AI/MDD
AI = acceptable intake of the nitrosamine (ng/day)
MDD = maximum daily dose of the drug substance (g/day)

Name	Acceptable Concentration (mg/g)			
Nitrosamine	0.050 (50-mg dose)	0.100 (100-mg dose)	0.250 (250-mg dose)	1.00 (1000-mg dose)
	1.920	0.960	0.384	0.096

Table 2. Example Using an AI of 96 mg/day for the Target Nitrosamine

If more than one nitrosamine impurity is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the acceptable intake for the most potent nitrosamines) based on the maximum daily dose (MDD), FDA requests that the manufacturer contact the agency for evaluation. If nitrosamines without published AI limits are found in drug products, manufacturers should use the approach outlined in ICH M7(R1) to determine the risk associated with the nitrosamine and contact the Agency about the acceptability of any proposed limit.

(C) Confirmatory Testing:

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.
FDA recommends that, to ensure the safety of the U.S. drug supply, confirmatory testing of drug products and submission of required changes in drug applications should be concluded on or before October 1, 2023. EMA article 5(3) call for review to MAHs recommends that if risk is identified MAH should submit the step 1 response template and proceed for step 2 confirmatory testing and should be completed by September 26, 2022.[7]. As per Health Canada regulations Confirmatory Testing and any changes to the market authorization must be finalized by October 1, 2022. [8]. For confirmatory testing, testing should be carried out on the FP, testing of API and raw materials also recommended if the risk evaluation indicates that these materials are a potential source of nitrosamine impurities in the FP. If the source of risk has been identified and impurity levels are expected to be consistent from batch to batch, testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. Methods for determination of various nitrosamines in APIs and drug advanced and sensitive tools to meet regulatory requirements, various nitrosamines in sartans, metformin and ranitidine have already been developed by the Official Medicines Control Laboratories and are available on the European Directorate for the Quality of Medicines & HealthCare (EDQM) website [9]. FDA publishing a general chapter USP <1469> Nitrosamine impurities and providing several analytical methods based on different scientific principles (e. g. HPLC- RHMS; HPLC–MS/MS, GC–MS/MS & GC-MS) [10]. Gas chromatography along with mass spectrometry (GC-MS) is the most efficient method for the qualification of Nitrosamines with lower molecular weight. Many recent publications employed GC-MS, GC–HS/MS or GC-MS-MS methods due to its high selectivity and low detection limit.

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