Available online on 15 Mar, 2024 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with RAPS & Delhi Pharmaceutical Sciences & Research University

Review Article **Open Access**

Nitrosamine Contamination in Pharmaceuticals: Regulatory Perspectives and Control Strategies of USFDA, EMA & HC

Nidhi Pardeshi*, Vijay Satapara, Kajal Patel

Isazi Pharma and Techno Consultancy Private Limited, D345, Siddharth Excellence, Opp. D-Mart, Vasna Road, Vadodara, Gujarat, India – 390007.

Abstract

Various regulatory authorities were notified the presence of nitrosamine impurities in human medicines including angiotensin II receptor blockers (ARBs), ranitidine, nizatidine and metformin in 2018. The presence of nitrosamines led manufacturers to assessed their products by any means that might inadvertently lead to nitrosamine content and taking steps to mitigate these risks after issuance of safety alerts, recall and withdraw certain batches of these drugs. Importantly, global cooperation by regulatory authorities triggered the investigation of synthetic route, rapid development of analytical procedures and publication of guidelines. This article highlights mainly on risk assessment and control strategies adopted by United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA), and Health Canada (HC) regulatory bodies. Additionally, compare the acceptable intake (AI) values recommended by these regulatory authorities which will help the manufacturer to either limit or eliminate nitrosamines impurities in their medicines because nitrosamines are probable or possible human carcinogens, hence, it is recommended that the potential causes of nitrosamine formation as well as any other pathways observed and evaluate the risk for nitrosamine contamination or formation in their APIs and drug products. Manufacturers should prioritize evaluation of APIs and drug products based on factors such as maximum daily dose, duration of treatment, therapeutic indication, and number of patients treated for the products which are under pre approval stage and already marketed products.

Conclusion:

As nitrosamine contamination affects patients worldwide, in case the levels of nitrosamines exceed acceptable limits, or more than one nitrosamine is observed, such products should not be commercialized. All the international regulatory agencies continuing to work with to propose various analytical methodologies to determining nitrosamine content in the API or FPP, risk assessment evaluation and control strategies, extrapolation of toxicological data and various confirmatory test for mutagenicity detection. Due to this rapid action taken by global authorities will help manufacturer to design their manufacturing process to be more robust so that they will timely register their products and reduce the additional cost require for its complete analysis by taking care of consumer's safety as well.

Keywords: Nitrosamines, Acceptable intake (AI), United States Food and Drug Administration (USFDA), European Medicines Agency (EMA), Health Canada (HC), Risk assessments.

Article Info: Received 10 Nov 2023; Review Completed 19 Jan 2023; Accepted 30 Jan 2023

Cite this article as:
Pardeshi N, Satapara V, Patel K. Nitrosamine Contamination in Pharmaceuticals: Regulatory Perspectives and Control Strategies of USFDA, EMA & HC. Int J Drug Reg Affairs [Internet]. 2024 Mar 15 [cited 2024 Mar 15]; 12(1):1-8. Available from:
http://ijdra.com/index.php/journal/article/view/624

DOI: 10.22270/ijdra.v12i1.624
*Corresponding author

1. Introduction

Nitrosamines are a class of compounds having the chemical structure of a nitroso group bonded to an amine ($R^1N(-R^2)-N=O$), as shown in Figure 1. The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions).

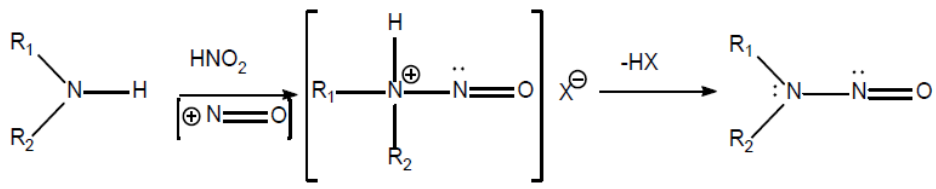


Figure 1. Formation of Nitrosamines (1)

There are mainly seven nitrosamine impurities that theoretically could be present in drug products: NDMA, N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and N-nitrosomethylphenylamine (NMPA). (1)

Nitrosamines are probable human carcinogens, and five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have been detected in active pharmaceutical ingredients (APIs) or drug products.

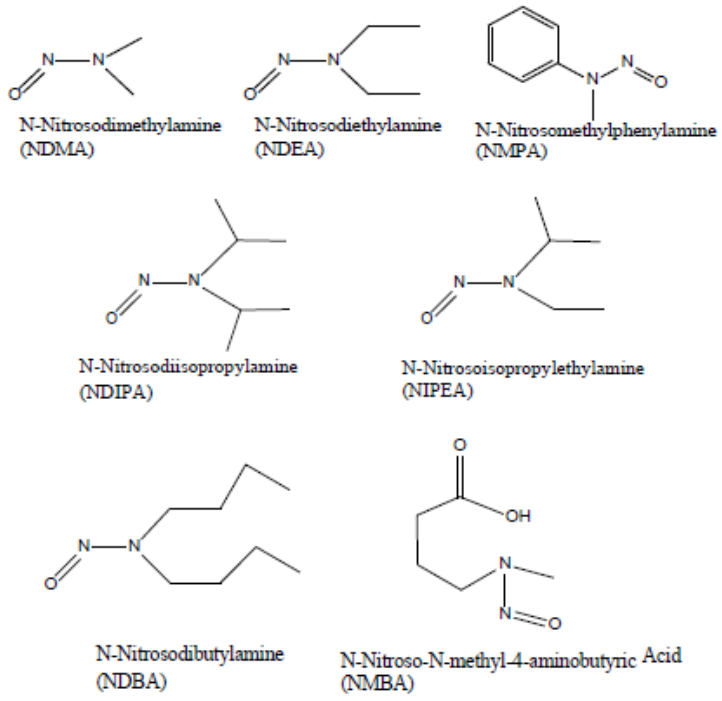


Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products (1)

2. Occurrence of N-nitrosamines in different areas are: (3)

i. Environment:

N-nitrosamines occur and are formed in the environment. In the air they form mainly by combustion processes and in water by biological processes in trace amounts. Control strategies are according to the as low as reasonably achievable (ALARA) or as low as reasonably practicable (ALARP) principles. Concentrations are considered to be higher in areas with less control and high air and water pollution.

ii. Food and Drinking Water

In food products formation of *N*-nitrosamines mainly occurs by reaction of nitrite and nitrosatable amines in meat, fish and other products at higher temperature.

Regulations to minimize formation of *N*-nitrosamines in food, beverages and beer aim to minimize exposure and are based on the ALARA principles.

In Germany, control limits for NDMA in drinking water are 10 ng/l and considered as health-based according to the German Umweltbundesamt (UBA) for lifetime and less than lifetime exposure. California has set a public health goal of 3 ng/l for drinking water and New Jersey 0.7 ng/l for NDMA and 5 ng/l for NDPA in groundwater. The Environmental protection Agency (EPA) set health reference levels for NMBA (30 ng/l), NDEA (0.4 ng/l), NDMA (0.6 ng/l) etc.

iii. Presence and formation of *N*-nitrosamines in human medicinal products

The detection of nitrosamines in some types of drug products led the international regulators to conduct a detailed analysis of these impurities in affected APIs and drug products.

Nitrosamine impurities can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions). Both high temperatures and low pH contribute to nitrosamine formation.

3. Identified sources of nitrosamines (1,3)

The probable already identified root causes for **nitrosamine contamination** are:

- Sodium nitrite (NaNO2), or other nitrosating agents, in the presence of secondary, tertiary amines or quaternary ammonium salts within the same or different synthesis step in which these compounds are carried over due to incomplete depletion or in combination with reagents, solvents and catalysts, from which secondary or tertiary amines are generated by degradation reactions.

- Contaminated raw materials (solvents, reagents, catalysts) in the API production process.
- Recovered materials (solvents, reagents, catalysts), in particular when reprocessed by third parties using equipment not dedicated for this purpose.
- Contaminated starting materials and intermediates from suppliers whose manufacturing processes or the starting materials may generate nitrosamine.
- Cross-contamination between different manufacturing processes on the same production line that are not clearly allocated and operator-related errors.
- Degradation processes of starting materials, intermediates and finished products, including those induced by inherent reactivity in combination with carry-over of sodium nitrite, which could occur also during finished product formulation or storage.
- Impurities in the container–closure system for the finished drug product, which may include impurities capable of forming nitrosamines, especially if associated with materials containing amines and potential sources of a nitrosating agent (e.g., nitrite, nitrocellulose).

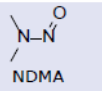
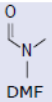
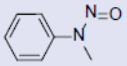
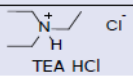
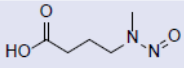
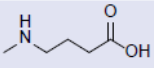
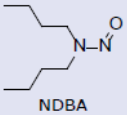
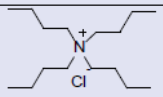
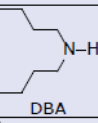
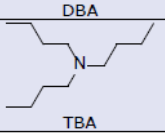
N-Nitrosamine	NOX Source	Amine Source	Amine nitrosated by NOX	Critical Compound Combination
 NDMA	$NaNO_2$	 DMF	 DMA	reagent/solvent
 NMPA	$NaNO_2$	 *N,N*-DMA	 *N,N*-DMA	reagent/solvent
 NDEA	$NaNO_2$	 TEA	 DEA	reagent/reagent
		 TEA HCl	 TEA	reagent/catalyst
 DIPNA	$NaNO_2$	 DIPEA	 DIPEA	reagent/reagent
 EIPNA	$NaNO_2$	 DIPEA	 DIPEA	reagent/reagent
 NMBA	$NaNO_2$	 NMP	 MBA	reagent/solvent
 NDBA	$NaNO_2$	 TBAB	 DBA	reagent/catalyst
			 TBA	

Figure 3. Critical Compound Combinations responsible for N-nitrosamine formation in Sartans (3)

4. Risk associated with nitrosamine impurities (1-3)

Nitrosamine impurities are probable human carcinogens. At present, there are insufficient data on carcinogenic potency of nitrosamines in humans. The potential risk for humans is based on animal studies and due to long-term exposure to a level above what is considered to be safe may increase the risk of cancer.

There is no immediate health risk associated with the use of medications containing low levels of a nitrosamine impurity. Foods such as meats, dairy products and vegetables as well as drinking water may also contain low levels of nitrosamines.

Generally, we don't expect that a nitrosamine impurity will cause harm when exposure is at or below the acceptable level. The actual health risk varies from person to person. The risk depends on several factors, such as:

- the daily dose of the medication
- how long the medication is taken
- the level of the nitrosamine impurity in the finished product

Patients should always take advice from health care provider before stopping a prescribed medication.

5. Guidance from health authorities on nitrosamines: (1-4)

- FDA – Control of nitrosamine impurities in human drugs
- EMEA – Nitrosamine impurities in human medicinal products
- Health Canada – Nitrosamine impurities in medications: Overview
- ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

Each of these guidance documents provide specific details about acceptable levels, possible sources of nitrosamine impurities, formation of nitrosamine impurities, analytical procedures for detection and possible ways to control and `mitigate.

To better understand this global issue, all regulatory health authorities are cooperating and sharing information among international regulators and manufacturers to control and eliminate nitrosamine impurities as much as possible. Therefore, it is now crucial for pharmaceutical companies and manufacturers to adhere to these guidelines and speed up the risk assessment and control strategies as per latest requirements.

Table 1. Comparison of Acceptable Intake limits (AI) between USFDA, EMA and Health Canada (1-3, 5)

N – Nitrosamine	CAS number	Acceptable Intake limits (AI) (ng/day)		
		USFDA	EMA	Canada
N-nitrosodi-methylamine (NDMA)	62-75-9	96.0	96.0	96.0
N-nitrosodi-ethylamine (NDEA)	55-18-5	26.5	26.5	26.5
N-nitrosodi-propylamine (NDPA)	621-64-7	-	-	26.5
N-nitrosodi isopropylamine (NDIPA / DIPNA)	601-77-4	26.5	26.5	26.5
N – Nitrosamine	**CAS number**	**Acceptable Intake limits (AI) (ng/day)**		
		USFDA	**EMA**	**Canada**
N-nitrosoethyl isopropylamine (NEIPA / EIPNA)	16339-04-1	26.5	26.5	26.5
N-nitrosodi-butylamine (NDBA)	924-16-3	-	26.5	26.5
N-nitrosomethyl-amino butyric acid (NMBA)	61445-55-4	96.0	96.0	96.0
N-nitrosomethyl-phenylamine (NMPA / PMNA)	614-00-6	26.5	-	-
N-nitrosomorpholine (NMOR)	59-89-2	-	127.0	127.0
1-methyl-4-nitrosopiperazine (MNP)	16339-07-4	-	-	96.0
N-nitroso varenicline (NNV)	-	-	37.0	37.0

This acceptable intake data shows similarity in the limit of nitrosamine impurities among USFDA, EMA and HC which are calculated based on ICH Guidance M7(R1).

6. USFDA Perspectives and Control Strategies:

Manufacturers of APIs and drug products should take appropriate measures to prevent unacceptable levels of nitrosamine impurities in their products. (1,6)

Nitrosamine risk assessments—development of a control strategy (6)

Below is the flow chart for the ease to understand risk assessment.

High level process for development of a nitrosamine impurity control strategy. (Refer to Table 1; P1, P2, P3 = Process 1, 2, 3; D1, D2 = Decision 1, 2) In all cases, if nitrosamines are predicted in the risk assessment or confirmed to be present through testing in the drug product, the control strategy should define the approach to ensure that the nitrosamine levels comply with the established interim AIs.

6.1 Manufacturers steps to deal with Nitrosamines impurities:

6.1.1 Commercial Products

As per FDA guidance if the products are approved or marketed, it is recommended to perform an immediate risk assessment with respect to the potential presence or formation of nitrosamines in which involves assessing all raw materials, carefully monitoring of finished product manufacturing process and stability programme.

If this risk assessment indicates the possibility of nitrosamine presence or formation, the product should be tested to confirm the absence of such impurities.

The FDA had recommended completion of the primary risk assessment within seven months of the original September 2020 guidance publication (i.e., by March 31, 2021). Confirmatory testing, if required, should begin immediately for products considered at high risk. Both confirmatory testing and submission of any required changes in drug applications for mitigation purposes should be concluded on or before October 1, 2023. (1)

6.1.2. Under Development Products

In case of pending application before submission of an original dossiers, FDA also recommends that applicants conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products and conduct confirmatory testing as needed. However, it can be submitted in an amendment if the studies are not completed at the time of the original submission filing as early as possible to avoid any delay in application assessment timeline. (1)

Nitrosamine risk assessments—development of a control strategy (5)
Below is the flow chart for the ease to understand risk assessment.

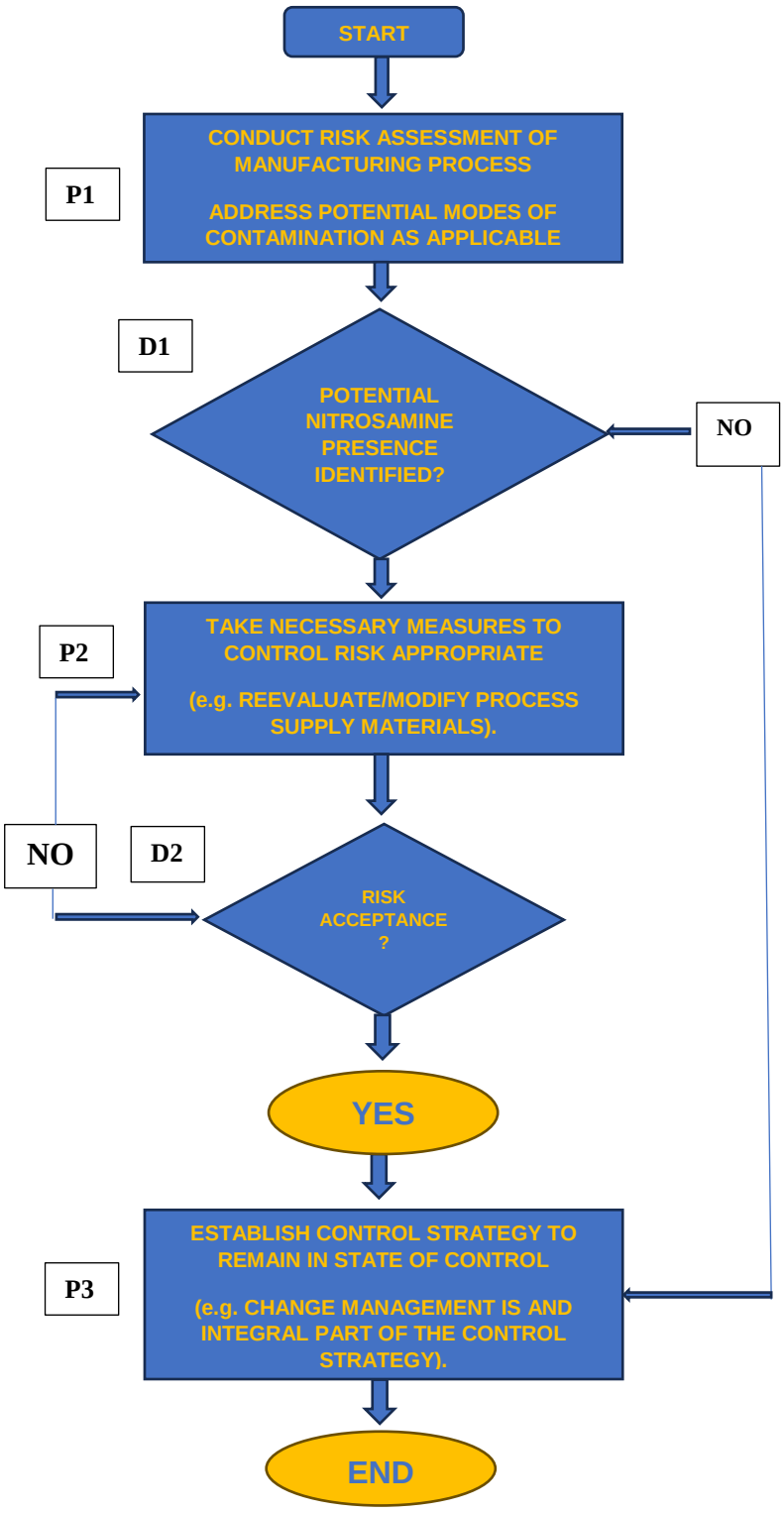


Figure 4. Nitrosamine risk assessments-development of a control strategy

High level process for development of a nitrosamine impurity control strategy. (Refer to Table 1; P1, P2, P3 = Process 1, 2, 3; D1, D2 = Decision 1, 2) In all cases, if nitrosamines are predicted in the risk assessment or confirmed to be present through testing in the drug product, the control strategy should define the approach to ensure that the nitrosamine levels comply with the established interim AIs.

Applicants should conduct the risk assessment and inform FDA if confirmatory testing finds nitrosamine levels above the AI limit. If a nitrosamine impurity is detected above the LOQ but is within the AI limit, the applicant should amend the application as appropriate for all under approval products. The Agency will get time to resolve issues during the review cycle itself or immediately after approval, and before distribution. (1)

7. European Perspective and Control Strategies

The EU reviewer have identified a number of root causes leading to the presence of nitrosamines in medicines due to chemical reactions of primary and secondary amines, linked with water, solvents, reagents, catalysts, raw materials etc.

The presence of N-nitrosamines in human medicinal products shall be avoided or controlled at or below a limit based on ICH M7(R1) principles for substances of the "cohort of concern" defined in the EMEA guideline and calculated considering a lifetime daily exposure.

The various limits of N-nitrosamines as considered are based on analytical capability led to lowest possible limit than those based on ICH M7 (R1) approach, based on toxicology data, based on ALARP methodology, Polypharmacy factors etc. All drug products and manufacturing processes are not similar so it requires thorough assessment in every step to know from where these impurities are arising. Hence, the manufacturers can take various steps either to control it or alternatively put measures to remove it. The various completion deadlines are: (3,7)

7.1. Risk assessment

- Products containing chemically synthesized API: Latest by March 31, 2021
- Products containing Biologicals API: Latest by July 1, 2021

7.2. Confirmatory Test

1. Products containing chemically synthesized API: Latest by September 26, 2022
2. Products containing Biologicals API: Latest by July 1, 2023.
3. The deadline for the submission of any changes required to Marketing Authorisations is by October 1, 2023.

   Require MAH to submit variations demonstrating implementation of effective risk mitigation measures where nitrosamines presence is confirmed. (3)

8. Canada Perspective and Control Strategies

The Health Canada's initiated to evaluate the risk of the presence of nitrosamine impurities after issuance of letter in October – 2019 onwards this includes:

- prescription and non-prescription (over-the-counter) drug products
- chemically synthesized excipients and raw materials used in the manufacturing of drug products
- drug products that have been approved but are not yet marketed
- approved drug products with a DIN status reported as "dormant"
- biological and radiopharmaceutical products for human use.
- All non-prescription products with a DIN, such as topical antiseptic products, grooming and personal hygiene products and sunscreens, are within the scope of products for assessment if they contain a chemically synthesized or semi-synthetic API. This is irrespective of the route of administration or any cosmetic properties.

The antimicrobial agents, veterinary products (including veterinary health products) and natural health products. Disinfectant products for use on hard surfaces are out of the scope of products for assessment at this time. (2)

8.1 Timelines for completing risk assessments

The drug products containing chemically synthesized and semi-synthetic APIs, action steps relating to nitrosamines are expected to be completed as follows:

- Step 1: risk assessments by March 31, 2021
- Step 2: confirmatory testing by October 1, 2022
- Step 3: changes to the market authorization by August 1, 2025

For biological and radiopharmaceutical products, action steps relating to nitrosamines are expected to be completed as follows:

- Step 1: risk assessments by November 30, 2021
- Step 2: confirmatory testing by November 30, 2023
- Step 3: changes to the market authorization by August 1, 2025

Whenever possible for APIs and drug products that are under development, manufacturing processes should ensure that the formation or introduction of nitrosamine impurities should be avoided. If it is unavoidable than it should be reduced the levels of nitrosamine impurities below the AI.

For drug products that are planned for submission or have already been submitted, then manufacturer should proactively undertake a risk assessment for the potential presence of nitrosamine impurities and communicate to the agency.

The applicant will submit the risk assessment in section 3.2.P.2 of the CTD.

Confirmatory testing results and updated control strategy should also be included in following sections like 3.2.S.2, 3.2.S.4, 3.2.S.7, 3.2.P.3, 3.2.P.4, 3.2.P.5, 3.2.P.8).

For under review application risk assessment and confirmatory testing results must be part of assessment procedure. Other risk management considerations (for example, the availability of alternative medications on the Canadian market).

Manufacturers should test a representative number of batches of the drug product as appropriate based on the risk assessment.

If the root cause for nitrosamine risk has been identified and consistent, testing should be conducted on 10% of annual batches, or 3 per year, whichever is highest. Testing should include both newly produced batches as well as retained samples of batches still within the expiry date. If fewer than 3 batches are manufactured annually, then all batches within the expiry date should be tested.

For NDSs, ANDSs, Supplements and Notifiable at least 6 pilot or 3 commercial-scale batches should undergo confirmatory testing. A higher number of batch results including minimum of 6 months of accelerated and long-term stability data in the proposed container closure system(s) should be submitted for assessment where the risk of nitrosamine presence is high. (2)

9. Post Approval Changes Assessment related to Nitrosamine/Mutagenic impurities:

Post-approval submissions involving the drug substance synthesis, manufacturing, and controls require an evaluation of the associated potential risk with mutagenic impurities due to changes to the route of synthesis, reagents, solvents, or process conditions after the starting material, supplier change, manufacturing site change which are likely to be the source of generation of Nitrosamine impurities which might be mutagenic, hence, the drug must be evaluated to determine if the changes result in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities.

However, this also applicable to the drug product (e.g., change in composition, manufacturing process, dosage form). Reevaluation of the drug substance related with drug products is not required if there are no changes to the drug substance. Changing the site of manufacture of drug product do not require a reassessment of mutagenic impurity risk.

Changes to the clinical use of marketed products that can also require reevaluation of the mutagenic impurity limits include a significant increase in clinical dose, an increase in duration of use (in particular when a mutagenic impurity was controlled above the lifetime acceptable intake for a previous indication. Therefore, it is anticipated that the impurity assessment applies to products in clinical development. (4)

Table 2. Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (4)

Class	Definition	Proposed action for control
1	Known mutagenic carcinogens	Control at or below compound- specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non- mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

TTC-based Acceptable Intakes

The TTC-based acceptable intake of 1.5 µg/day is considered to be protective for a lifetime of daily exposure.

Table 3. Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 – 12 months	>1 – 10 Years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

The TTC-based acceptable intakes should be applied to each individual impurity. When there are two Class 2 or Class 3 impurities, individual limits apply. When there are three or more Class 2 or Class 3 impurities specified on the drug substance specification, total mutagenic impurities should be limited as described in Table 4 for clinical development and marketed products. (4)

Only specified Class 2 and 3 impurities on the drug substance specification are included in the calculation of the total limit. However, impurities with compound-specific or class-related acceptable intake limits (Class 1) should not be included in the total limits of Class 2 and Class 3 impurities. Also, degradation products which form in the drug product would be controlled individually and a total limit would not be applied. (4)

Table 4. Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	≤ 1 month	>1 – 12 months	>1 – 10 Years	>10 years to lifetime
Daily intake [µg/day]	120	60	30	5

10. Conclusion:

As nitrosamine contamination affects patients worldwide, in case the levels of nitrosamines exceed acceptable limits, or more than one nitrosamine is observed, such products should not be commercialized.

All the international regulatory agencies continuing to work with to propose various analytical methodologies to determining nitrosamine content in the API or FPP, risk assessment evaluation and control strategies, extrapolation of toxicological data and various confirmatory test for mutagenicity detection. Due to this rapid action taken by global authorities will help manufacturer to design their manufacturing process to be more robust so that they will timely register their products and reduce the additional cost require for its complete analysis by taking care of consumer's safety as well.

Acknowledgments

We would like to express my sincere gratitude to Mr. Vijay Satapara (CEO of Isazi Pharma & Techno consultancy Pvt. Limited) for his great support and inspiration.

We wish to acknowledge my colleagues, friends for interesting discussions, inspiration, moral support and giving me the power to believe in myself. And last not the least, we would like to express our sincere gratitude to IJDRA Journal for publishing our work.

Financial Disclosure statement

The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Control of Nitrosamine Impurities in Human Drugs, Revision 1 [Internet]. FDA; 2021 Feb [cited 2023 Apr 03]. Available from: https://www.fda.gov/media/141720/download
2. Nitrosamine impurities in medications: Guidance [Internet]. Canada.ca; 2022 Apr [cited 2023 May 02]. Available from: https://www.canada.ca/en.html
3. Assessment report: Nitrosamine impurities in human medicinal products [Internet]. EMA; 2020 Jun [cited 2023 Apr 10]. Available from: https://www.ema.europa.eu/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf
4. ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk [Internet]. European Medical Agency; 2023 Jul. [cited 2023 Nov 05]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m7r2-guideline-assessment-and-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential-carcinogenic-risk-step-5_en.pdf
5. The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk [Internet]. FDA; 2018 Mar [cited 2023 Feb 12]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf)
6. USP General Chapter <1469> Nitrosamine Impurities, 2021, Issue 3 [Internet]. USPPF; 2021 [cited 2023 Nov 09]. Available from: https://online.usppf.com/usppf/document/GUID-C97F817C-A383-4693-8E0C-2F0A0A371977_10101_en-US?highlight=1469 © 2020 USPC
7. Ruepp R, Frötschl R, Bream R, Filancia M, Girard T, Spinei A, Weise M and Whomsley R (2021) The EU Response to the Presence of Nitrosamine Impurities in Medicines. Front. Med. 8:782536. doi: 10.3389/fmed.2021.782536