Available online on 15 Jun, 2023 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

Recent Regulatory Scenario of Nitrosamines Impurities in Regulated Market US, Europe and Canada

Richa Trivedi[a], Ankit Trivedi[b], Vinit Movaliya[a], Khushboo Vaghela[a], Niranjan Kanaki[a], Shrikalp Deshpande[a], Maitreyi Zaveri*[,a]

[a] *K. B. Institute of Pharmaceutical Education and Research, Sector-23, Gandhinagar, Gujarat*
[b]*Sr Team Lead, Syneos Health Ltd.*

Abstract

Unexpected finding of cancer causing, DNA damaging impurities called nitrosamine impurities which are mostly likely to present in structures containing nitroso group as per EMA and also according to ICH M7 is a member of "cohort of concern "class of high potency mutagenic carcinogens. In year 2018 it was first detected in sartans by USFDA after that it found in found in antacid like nizatidine, ranitidine and in anti-diabetic drugs like metformin, pioglitazone. There are nearly more fifteen types of impurities detected in products like NDMA, NDEA, EIPNA, NMBA, NDBA, and MeNP. Thousands of batches were recalled in countries like USA, Europe and all around world. Regulatory bodies of like USFDA, EMA and Health Canada has published stringent guidelines and documents to control carcinogenic impurities and given timelines for submission of risk assessment and confirmatory test and submission of other documents if change in process to mitigate its level and suggested changes in manufacturing process like change in ROS ,Control strategy etc. Along with the Q&A, roots cause for presence of impurities .Immediate submission of the amount of Nitrosamine impurities when detected in product and if negligible amount is present no need to submit report.

Keywords: Nitrosamines Impurities, NDMA, NDEA, EIPNA, NMBA, NDBA, Root Cause, USFDA, EMA, Health Canada.

Article Info: Received 16 Feb 2023; Review Completed 28 Mar 2023; Accepted 13 Jun 2023

Cite this article as:
Trivedi R, Trivedi A, Movaliya V, Vaghela K, Kanaki N, Deshpande S, Zaveri M. Recent Regulatory Scenario of Nitrosamines Impurities in Regulated Market US, Europe and Canada. Int J Drug Reg Affairs [Internet]. 2023 Jun 15 [cited 2023 Jun 15]; 11(2): 30-36. Available from: http://ijdra.com/index.php/journal/article/view/581

DOI: doi.org/10.22270/ijdra.v11i2.581
*Corresponding author

1. Introduction

Nitrosamines are a well-known group of highly potent, mutagenic impurities formed by the reaction of secondary amines with nitrite under acidic conditions. *N*-Nitrosamines are a class of chemical compounds with the general structure .The essential feature of *N*-nitroso compounds is the N–N=O structure; the R1 and R2 groups attached to the amine nitrogen may range from a simple hydrogen (H) atom to more complex chemical substituents (including ring structures that incorporate the nitrogen atom). There are around 15 different kind of nitrosamine found *N*-Methyl-*N*-nitro-*N*-nitroso-guanidine, *N*-Nitrosodi-*n*-butyl amine, *N*-Nitroso-diethanolamine, *N*-Nitrosodiethylamine , *N*-Nitrosodi-*n*-propylamine, *N*-Nitroso-*N*-ethylurea etc. Some are shown below Figure: 1

Contamination of carcinogenic impurities has been vexing problem since 2018 when it was firstly announced by USFDA in Sartans (which are used in hypertension). NDMA impurity was detected in Valsartan, and after that agency found unacceptable level of impurities in other sartans and requested manufactures to recall batches. In September 2019, It was also found in antacid like ranitidine, and nizatidine and their after in anti-diabetic drugs like metformin, pioglitazone. Agency has requested all the manufactures to detect level of impurity by analytical methods given in guideline and report and stop release of the impurity if it is above the acceptable intake limits given by the agency. List of all recalled batches is mention in the website of the FDA.

EMA also announced to recall nitrosamine impurity containing batches after Valsartan Manufactured by Zhejiang Huahai Pharmaceutical (Zhp) was found contaminated With NDMA (Nitrosodimethylamine).In 2019 several other impurities like NDEA, NMPA were found in other sartans, antacids, anti-diabetic and anti-histaminic. Around 2300 batches were recalled but no recall history is mentioned in the site of EMA. European Medicines Agency recommended all the drug product/ APIs manufacturer to analyze their product and report

the amount of impurity to EMA with root cause of its presence. (1-4)

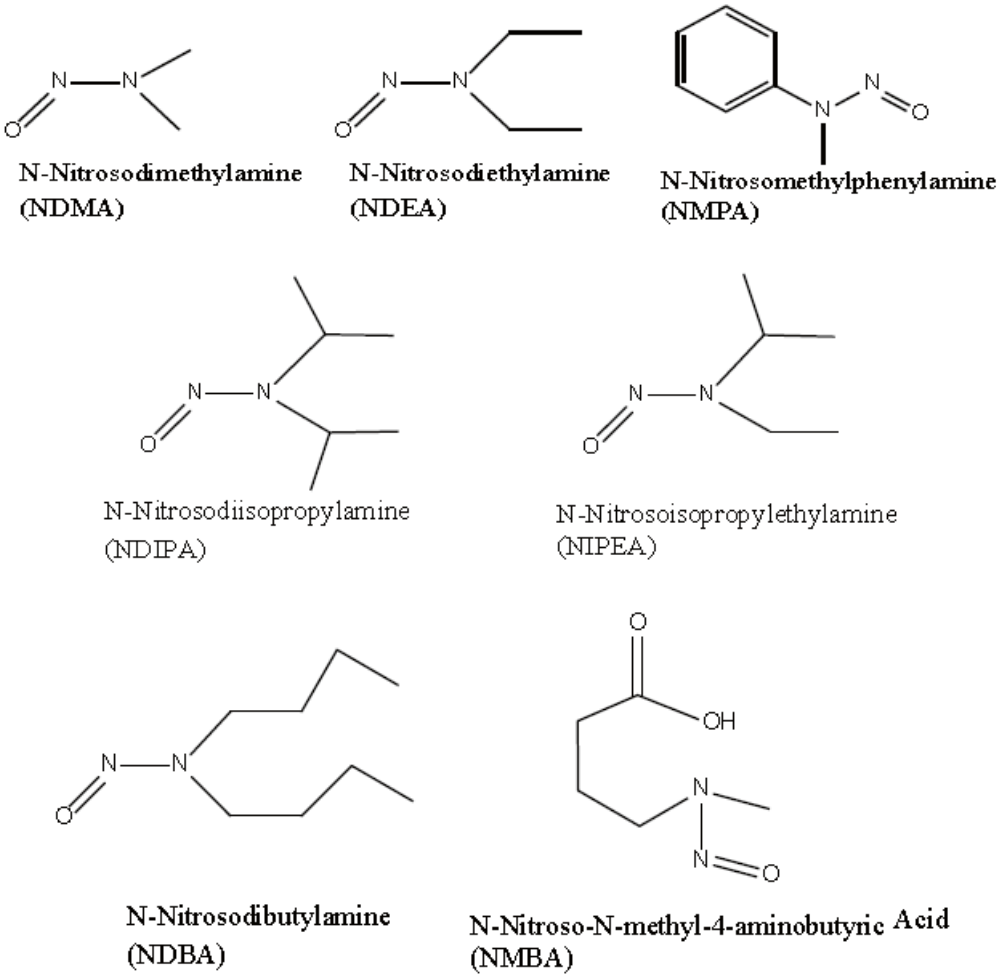

Figure 1. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products (4)

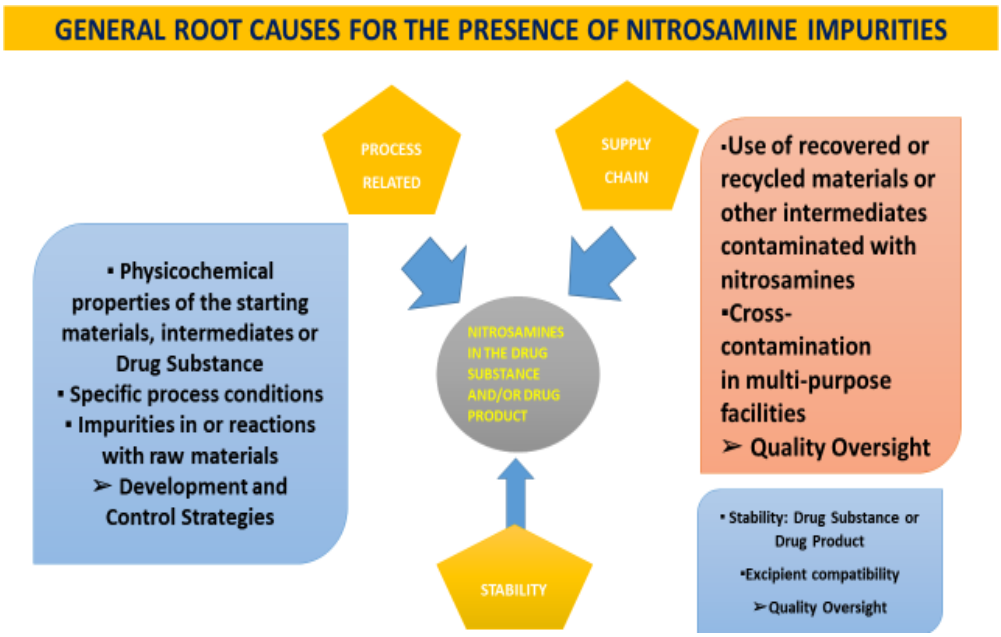

Figure 2. General Root cause of the presence of impurity in product

Health Canada continues to work closely with international regulatory partners including the FDA and the EMA to share information and coordinate efforts on inspections, risk assessments and public

communications. Health Canada has provided a method that has been developed to detect and quantify the Nitrosamine impurities NDMA and NDEA in angiotensin II receptor blockers (ARBs).Recall history is mention in website of health Canada.

USFDA ,EMA and Health Canada has mentioned root cause for the presence of carcinogenic impurity and given recommendation to the manufactures to make changes in manufacturing process, audit supply chain , Avoid use of primary, secondary or tertiary amines . Manufactures should refer to ICH M7 (R1), ICH Q7, Q11.Regulatory bodies recommended to perform risk assessment of products and report it in the CTD and eCTD and also confirmatory test if the impurity is present.

Root Cause of the impurity: Possibility of presence of nitrosamine impurity in drug substance or drug product could be basically through following sources shown in the **figure 2.** (5)

2. Recommendation

2.1.Food and Drug Administration

FDA recommends that manufacturers consider the potential causes of nitrosamine formation

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. Manufacturers should refer to the ICH guidance for industry Q9 Quality Risk Management (June 2006) for details related to quality risk identification, analysis, and management. Manufacturers of APIs and drug products should take appropriate measures to prevent unacceptable levels of nitrosamine impurities in their products. FDA has given acceptable intake (AI) limits for the nitrosamine impurities NDMA, NDEA, NMBA, NMPA, NIPEA, and NDIPA (Table 1). Limits are applicable only if a drug product contains a single nitrosamine. If more than one of the nitrosamine impurities identified in Table 1 is detected and the total quantity of nitrosamine impurities exceeds 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD), the manufacturer should contact the Agency for evaluation. (1)

2.2. European Medicines Agency

The *N*-nitrosamines with a TD50 below 1.5 mg/kg/day belong to the cohort of concern as defined in ICH M7 (R1) and are: NMPEA, NDEA, NDMA, NMEA, NNK, NNN, NMOR, NMA, NDPA, NDBA, NPYR, MNNG, NMBA, and NPIP**.** Total risk level of the sum of more than one detected N-nitrosamine cannot be kept below a 1 in 100,000 life-time risk, the MAH should submit to the relevant competent authorities forthwith an investigation report including the potential/identified root cause(s), preventive/corrective actions and a thorough discussion on the impact on the benefit/risk balance including all relevant considerations. MAHs should implement a control strategy regarding N-nitrosamines for their active substances and finished products, which should include current and prospective measures to minimize the risk of generation /contamination with any nitrosamine (e.g. change of manufacturing process, introduction of appropriate specifications and development of appropriate methods, measures related to the premises and equipment e.g. cleaning procedures, environmental monitoring), and control any future change that may impact on this risk (e.g. change of supplier, change of manufacturing process, change of packaging). Manufacturer should carry out risk evaluation/risk assessment of manufacturing processes of API (route of synthesis, starting materials, intermediates, raw materials) in view of potential formation of or contamination with N-nitrosamines, taking into account potential and confirmed root causes for the presence of N-nitrosamines in APIs and also carry out risk evaluation/risk assessment of finished product (degradation of API, primary packaging material, excipients, etc.), taking into account the root-causes for the presence of *N*-nitrosamines in finished products. (2,3)

2.3. Health Canada

MAHs should complete robust risk evaluations using a holistic approach with a detailed assessment of all stages of the product life cycle. This would include an appropriate level of documented root cause analysis, evaluation of manufacturing controls and conditions for the medicinal ingredients, non-medicinal ingredients (excipients) and the drug product, the potential interactions with the container closure system, and the potential of increased risks over the retest period for the API or the shelf life for the drug product. MAHs are responsible to ensure that the risk assessments have been conducted by personnel with acceptable qualifications and expertise (e.g., relevant training, knowledge, and practical experience). To enable this robust risk assessment, information should be made available by API, excipient, and drug product manufacturers to the MAH. Comparison of the recommendation given by different regulatory bodies is mention in Table 1.

Table 1. Recommendation given by regulatory bodies (1-6)

SR.NO	TITLE	USFDA	EMA	HEALTH CANADA
1.	Guidelines	ICH guidance for industry Q9 Quality Risk Management , ICH Q3B(R), Q3A(R), ICH Q3C, ICH Q3D	Q10 :limit of nitrosamine Q12: mitigate risk of nitrosamine impurity	ICH's M7(R1) guideline, and ICH Q9 guidelines together with Health Canada's GMP Guides 0001 and 0104,
2.	AI Limits	NDMA 96, NDEA	NDMA* (62-75-9) 96.0	(NDMA) 96.0, (NMBA)

		26.5. NMBA 96 NMPA 26.5 ,NIPEA 26.5, NDIPA 26.5	,NDEA*(55-18-5)26.5 ,EIPNA**(16339-04-1) 26.5,DIPNA**(601-77-4) 26.5,NMBA**(61445-55-4)96.0,MeNP**(16339-07-4) 26.5 ,NDBA**(924-16-3)26.5	96.0,(MNP) 96.0, (NDEA) 26.5, (NEIPA) 26.5,(NDBA) 26.5
3.	Suggestions	1.optimize the design ROS 2. quenching steps 3.avoid cross-contamination 4.analyze nitrite and nitrosamine levels in water, exogenous sources 5.audit their supply chains	Minimize the risk of generation/contamination with any nitrosamine (e.g. change of manufacturing process, introduction of appropriate specifications and development of appropriate methods, measures related to the premises and equipment e.g. cleaning procedures, environmental monitoring,…) and control any future change that may impact on this risk (e.g. change of supplier, change of manufacturing process, change of packaging…)	1.Risk Assessment 2.ConfirmatoryTesting 3.Changes to the Marketing Authorization
4.	Timelines	1.Before March 31, 2021 2. October 1, 2023	1.Chemically synthesized products- 31st march 2021 2.Biologically synthesized products- 1stjuly 2021 2. 1.Chemically synthesized products- 26thsept 2022 (FOR STEP 2 & 3) 2.Biologically synthesized products- 1stjuly 2023(FOR STEP 2 & 3)	o Step 1 - Completion of risk assessments by March 31, 2021 Step 2 - Confirmatory testing by October 1, 2022 o Step 3 - Changes to the market authorization by October 1, 2022.

3. Reporting of Impurity

3.1. Food and Drug Administration

Drug manufacturers must report changes implemented to prevent or reduce nitrosamine impurities in accordance with FDA regulations (21 CFR 314.60, 314.70, 314.96, and 314.97). FDA published "interim acceptable limits" for these nitrosamine impurities in ARBs. ARB DS or DP with levels of impurities exceeding these interim limits were recommended for recall from the market. Applicants report to FDA a summary of the testing performed, as requested above, for the presence of any nitrosamine impurities in batches distributed in the US or exported from the US that are within their labeled expiration, even if recalled. Reporting of Nitrosamine impurity is mentioned in **Figure1.**We request a table is submitted to each application, if not already provided in previous correspondence to the application, with the following information for each batch number that is sampled and tested:

- product name (identify whether API or DP batch)
- labeled strength (if DP batch)
- date of manufacture
- labeled expiration date
- Name of test method
- Amount and type of nitrosamine detected, if any, or "none detected."
- Data should be submitted to the application as a "General Correspondence;" the words "nitrosamine-related" should be prominently displayed on the cover letter.
- Marketing authorization holders should review their manufacturing processes for all products containing chemically synthesized or biological active substances to identify and, if necessary, mitigate the risk of presence of nitrosamine impurities. The European medicines regulatory network encourages marketing authorization holders to submit the outcome of step 1 before the deadlines if they complete the risk evaluation or identify a risk in their products. Marketing should inform the national competent authorities for nationally authorized products or EMA for centrally authorized products as soon as possible if tests confirm the presence of nitrosamine, irrespective of the amount detected. They should also assess the immediate risk to patients and take appropriate action to avoid or minimize the exposure of patients to nitrosamines. At all steps, timelines should be shortened and marketing authorization holders should immediately inform authorities if findings indicate an immediate risk to public health. Reporting impurity in EMA is mention in the flow chart given below (Figure 4) (6-9)

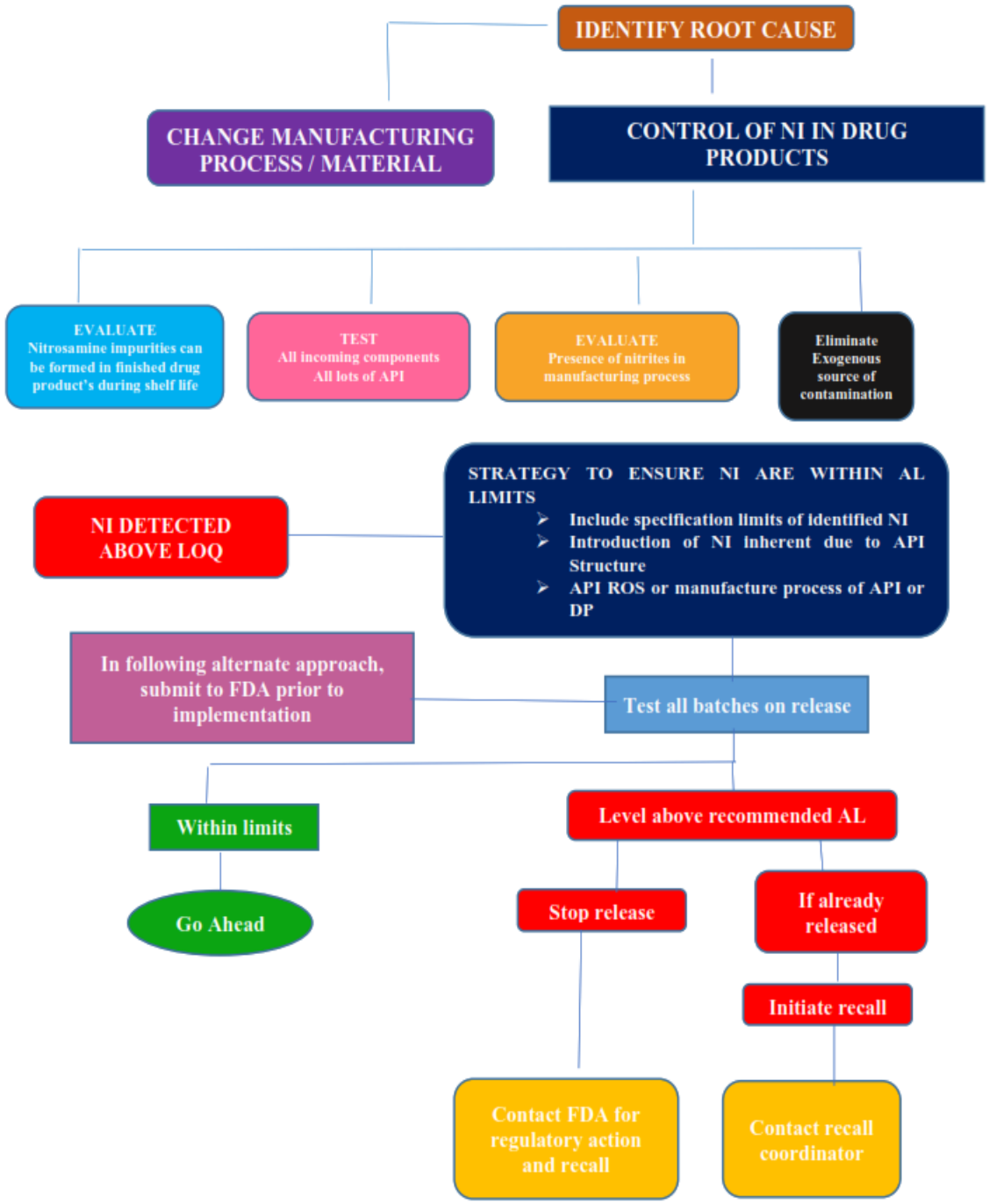

Figure 3. Reporting impurity in USA (1)

3.3. Health Canada

Health Canada has shared potential root cause of the impurity. Agency has asked manufacturers to find the amount of impurity through analytical method. The acceptable intake limit is provided by the regulatory if the value is above the mentioned value than manufactures are requested to report the amount of impurity and root cause of it and further proceed to confirmatory test and report the data to health Canada immediately, in case of no impurity the MAH has to retain the data .The priorities and order in which product should be reviewed. Principles set out in the ICH's Q9 guideline on Quality Risk Management; Maximum daily dose of the drug product; Route of administration; Duration of use; Indication and considerations of special populations such as pregnant women and children; Toxicological profile of the API.ICH's M7 (R1) guideline, and ICH Q9 guidelines together with Health Canada's GMP Guides 0001 and 0104, should be consulted for further information concerning mutagenic impurity considerations and quality risk management principles, respectively. Reporting of the impurity in Canada is mentioned in form of flow chart (figure 5). (10-13)

3.2. European Medicine Agency

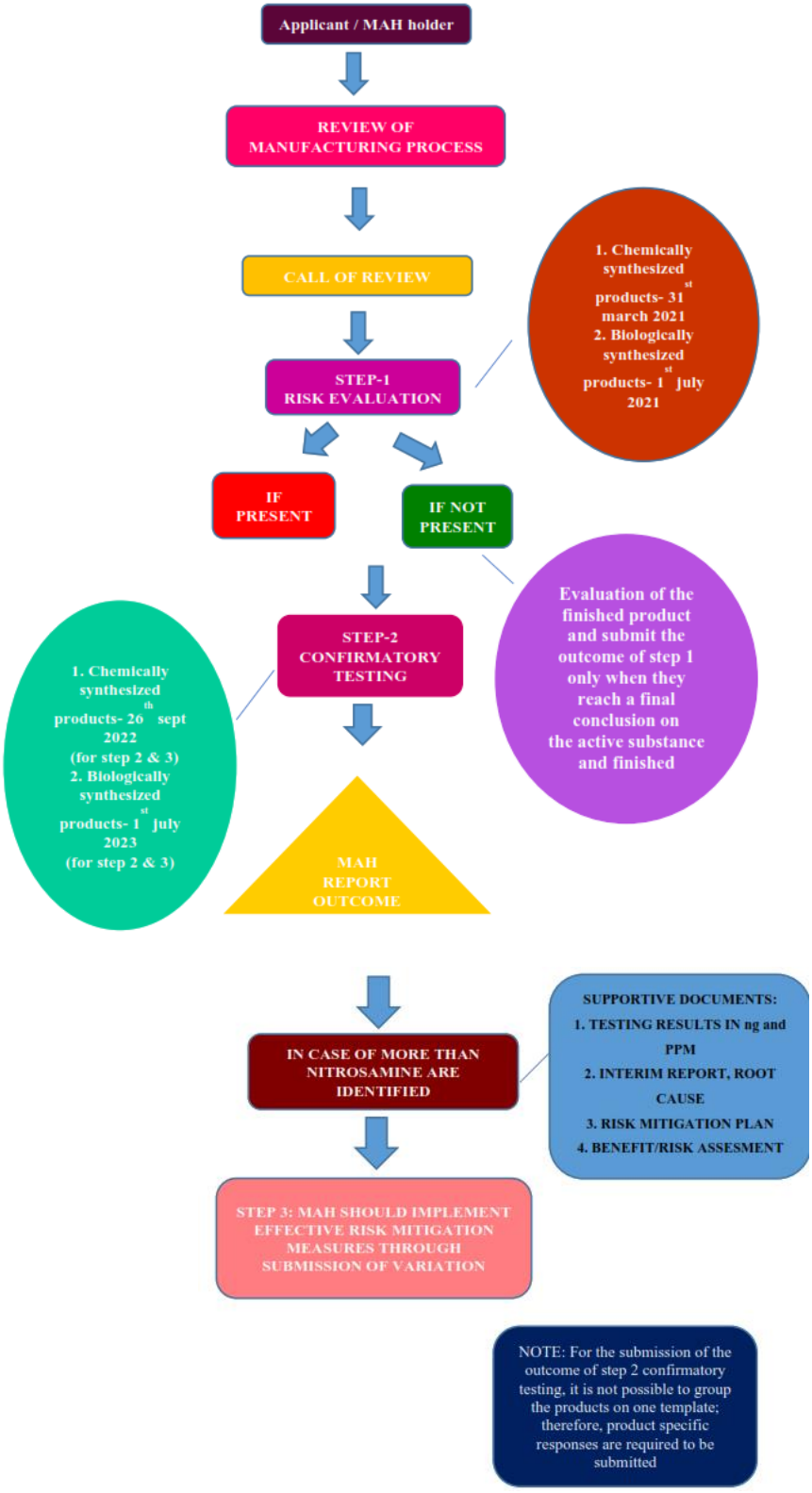

Figure 4. Reporting of impurity in EMA

4. Conclusion

As for all impurities, and especially for highly potent, mutagenic carcinogens, risk assessments should be conducted routinely during drug substance and drug product development. The outcome of the risk assessment and the justification for the proposed control strategy with respect to such impurities should be made available for assessment in the drug submission. ICH's guidance documents M7(R1) and Q9 should be consulted for further information concerning mutagenic impurity considerations and quality risk management principles, respectively.

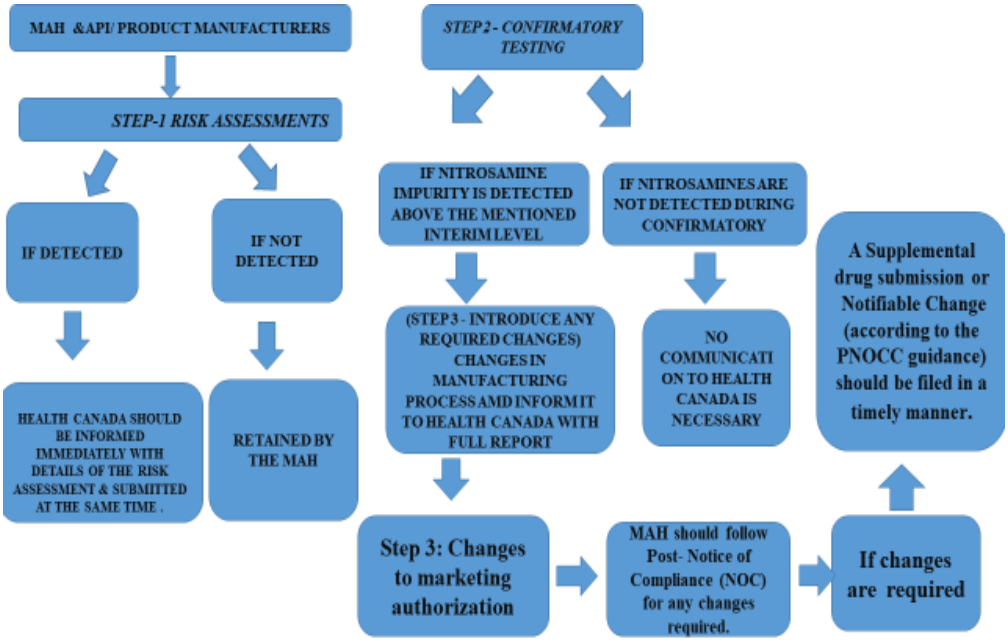

Figure 5. Reporting of nitrosamine impurity in Canada

Acknowledgements

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 [Internet]. FDA; 2021 Feb [cited 2023 Jan 01]. Available from: https://www.fda.gov/media/141720/download
2. Nitrosamine impurities in human medicinal products [Internet]. European Medicines Agency; 2020 Jun [cited 2023 Jan 01]. Available from: https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf
3. The EDQM's Response to Nitrosamine Contamination [Internet]. The European Directorate for the Quality of Medicines & HealthCare [cited 2023 Jan 01]. Available from: https://www.edqm.eu/en/edqms-response-nitrosamine-contamination
4. WHO Information Note: Update on Nitrosamine impurities [Internet]. World Health Organization; 2020 Apr [cited 2023 Jan 01]. Available from: https://www.who.int/docs/default-source/substandard-and-falsified/informationnote-nitrosamine-impurities-april2020.pdf
5. European Medicines Agency. Assessment report: Nitrosamine impurities in human medicinal products. 2020;5(June):1-90.
6. Byrn, S., & Stowell, J. Impurities in Drug Substances and Drug Products. Validation of Active Pharmaceutical Ingredients, Second Edition. 2001 Dec;2(1):271–292. https://doi.org/10.1201/b14415-10
7. Lijinsky W. Health Problem with Nitrites Associated and Nitrosamine. Ambio. JSTOR. 1976; 5(2): 67-72 http://www.jstor.org/stable/4312174.
8. Karuna, K. & Balamuralidhar, V. Nitrosamine impurities: The European policy review. Drug Invention Today. 2020 Jun;13(6):1–2. http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=09757619&AN=143462594&h=kHiRCJPOcDe3X4BUk3yBp0A%2BCo98WUPXkzm%2FETCiUGqwWTsTmoxxMG47zeipx5%2FJ6y6c7jnA8HuTWevf4VgVlg%3D%3D&crl=c
9. Iram M. From Valsartan to Ranitidine: The Story of Nitrosamines So Far. Indian Journal of Pharmacy Practice.2020;13(1):01–02 https://doi.org/10.5530/ijopp.13.1.1
10. European Medicines Agency. Lessons learnt from presence of N-nitrosamine impurities in sartan medicines. [Internet]. European Medicines Agency; 2020 [cited 2023 Jan 08]. Available from: https://www.ema.europa.eu/en/documents/report/lessons-learnt-presence-n-nitrosamine-impurities-sartan-medicines_en.pdf
11. Request To Evaluate the Risk of the Presence of N - Nitrosamine Impurities in Human [Internet]. European Medicines Agency; 2021 Apr 12 [cited 2023 Jan 09]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities
12. Leistner, A., Haerling, S., Kreher, J. D., Becker, I., Jung, D., & Holzgrabe, U. Risk assessment report of potential impurities in cetirizine dihydrochloride. Journal of Pharmaceutical and Biomedical Analysis. 2020;189: 113425. https://doi.org/10.1016/j.jpba.2020.113425
13. Dobariya U, Chauhan N, Patel H, Pardeshi N. Nitrosamine Impurities: Origin, Control and Regulatory Recommendations. Int J Drug Reg Affairs [Internet]. 2021 Jun.17 [cited 2023 Jan. 26];9(2):77-0. Available from: https://ijdra.com/index.php/journal/article/view/472