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Control strategy of Nitrosamine impurities in Pharmaceutical Drugs

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***Abstract*:** The carcinogenic properties of nitrosamines have been known for more than 50 years [1] and there are several nitrosamines that have been tested for carcinogenicity and have shown carcinogenic activities N-nitroso-dimethylamine (NDMA), N-nitroso-diethylamine (NDEA), N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitroso-diethanolamine (NDELA), nitroso-morpholine (NMOR), N-nitroso-N-methyl-N-ethylamine, and N-nitrosopyrrolidine (NPYR), being some of the well-known among these [2,3]. There are many more Nitrosamines are considered during the assessment as per ICH M7(R2), EMA guideline (current versions of EMA/369136/2020 & EMA/409815/2020) and Control of Nitrosamine Impurities in Human Drugs (Febuary-2021 Rev-1), as high potency mutagenic carcinogens referred to as compounds that are part of the "cohort of concern" and as such are classified as Class 1 impurities "known mutagenic carcinogens," based on both rodent carcinogenicity and mutagenicity data [4]. In order to ensure that the presence of nitrosamine impurities in the medicinal products is mitigated as much as possible and controlled at or below a limit defined based on ICH M7(R2), EMA guideline (current versions of EMA/369136/2020 & EMA/409815/2020) and Control of Nitrosamine Impurities in Human Drugs (Febuary-2021 Rev-1). This review article reflects calculation for the control of nitrosamine impurities in drugs by considering lifetime daily exposure.

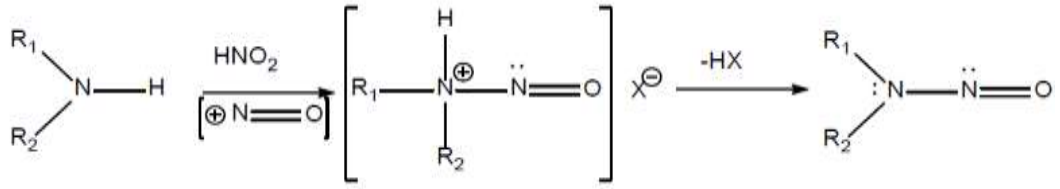
Keywords: N-Nitrosamines, Cohort of Concern, ICH M7, Drugs, exposure

Introduction

Nitrosamines are a group of carcinogens that are formed by the reaction of secondary and tertiary amines, amides, carbamates, and derivatives of urea with nitrite or other nitrogenous agents (including N_2O_3 and N_2O_4) [5]. The common nature of the precursors and the facile nature of the nitrosation reactions under acidic and neutral pH [6] have made nitrosamines a common and an unwelcomed guest in the world of foods, consumer goods, and pharmaceuticals.

The term nitrosamine describes a class of compounds having the chemical structure of a nitroso group bonded to an amine (R1N(-R2)-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. Representative Reaction to Form Nitrosamines



Nitrosamines are present in pharmaceuticals. Two well-known, efficacious anti-tumor drugs, carmustine and lomustine, have nitrosamines in their chemical structures. are also known to form endogenously based on the structure of certain drugs. Nitrates that we consume produce nitrites and other oxides of nitrogen in vivo, mediated by reductase enzymes and nitric oxide synthase (NOS) [7,8] may cause nitrosation of amines. Elimination of NDMA and N-nitrosoproline (NPRO) in human urine is evidence of endogenous nitrosation [9]. There are numerous approved drug products (DP) like amitriptyline, clomiphene, clomipramine, dextropropoxyphene, diphenhydramine, disopyramide, erythromycin, mepyramine, methapyrilene, penicillin G procaine salt, procaine, tamoxifen, trimeprazine, tripelennamine, minocycline, and aminopyrine that are known to undergo endogenous nitrosation and generate volatile nitrosamines like NDMA in vivo. [10,11].

Nitrosamines have once again become a focus of global regulatory agencies, including FDA, due to the discovery of trace amounts of these compounds in a class of drugs known as angiotensin II receptor blockers (ARB), frequently referred to a “sartans.” The “sartan” molecules involved include Valsartan, Losartan, Irbesartan, Azilsartan, Olmesartan, Eprosartan, Candesartan, and Telmisartan. Valsartan and Losartan were the most severely affected due to their market share when several lots were recalled [12]. Subsequently there were recalls of other histamine H –receptor antagonists like ranitidine and nizatidine, which were found to contain NDMA as both a process impurity and degradant [13]. In addition, FDA, European Medicines Agency (EMA), and other global authorities have confirmed the presence of NDMA in metformin and pioglitazone, which are used widely for Type II diabetes [14]. In February 2020, FDA posted results of analysis of metformin products, which showed no detectable to low levels of NDMA in the lots tested. However, in May 2020, FDA recommended that several lots of metformin extended-release tablets be withdrawn from the market due to the presence of trace amounts of NDMA [15].

The assessment, testing, and remediation related to nitrosamine impurities in the sartans, ranitidine, and other drugs has required significant additional resource allocation from the pharmaceutical industry, as well as from Regulatory Authorities.

This situation has created uncertainty for FDA, industry, and consumers. It has shaken consumers’ confidence in the safety of the medications they have come to trust and depend on to maintain the quality of their lives. The impact on the generic pharmaceutical industry has been especially disconcerting, as most of the affected drugs are genericized. Generics represent, by volume, 90% of all prescriptions dispensed in the U.S. There are more than 15,000 approved generic prescription products listed in the active section of the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Cumulative Supplement, Version November 2019 [16].

Methodology

ICH M7(R1) guideline defines N-nitrosamines as substances of the "cohort of concern" for which limits in medicinal products refer to the so-called substance-specific acceptable intake (AI) (the Threshold of Toxicological Concern, TTC, value of 1.5 ug/day cannot be applied) which is associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure). The calculation of AI assumes a lifelong daily administration of the maximum daily dose of the medicinal product and is based on the approach outlined in the ICH M7(R1) guideline as well as the principles described in relation to the toxicological evaluation in the assessment report of the CHMP's Article 5(3) opinion on nitrosamine impurities in human medicinal products.

The 'less than lifetime' (LTL) approach should not be applied in calculating the limits as described above but can only be considered after consultation with competent authorities as a temporary measure until further measures can be implemented to reduce the contaminant at or below the limits defined above.

For products intended for advanced cancer only as defined in the scope of the ICH S9 guideline, N-nitrosamine impurities should be controlled according to ICH Q3A(R2) and ICH Q3B(R2) guidelines, as specified in the Q&A document to ICH S9 guideline. If the active substance itself is mutagenic or clastogenic at therapeutic concentrations, N-nitrosamine impurities should be controlled at limits for non-mutagenic impurities according to ICH M7(R1).

The same risk approach is applicable to all routes of administration. Corrections to limits are generally not acceptable unless route-specific differences are justified by data.

Calculation of the limit when a single known nitrosamine is identified

Table 1: The following Acceptable Intake (AI) limits have been established for some specific N-nitrosamines and should be applied:

***N*-Nitrosamine (CAS number)**	**ng/day (AI)**
N-Nitrosodimethylamine, NDMA(62-75-9)	96.0
N-Nitrosodiethylamine, NDEA(55-18-5)	26.5
N-Nitrosoethylisopropylamine, EIPNA(16339-04-1)	26.5
N-Nitrosodiisopropylamine, DIPNA (601-77-4)	26.5
N-Nitroso-*N*-methyl-4-aminobutyric acid, NMBA (61445-55-4)	96.0
1-Methyl-4-nitrosopiperazine, MeNP (16339-07-4)	26.5
N-Nitroso-di-*n*-butylamine, NDBA (924-16-3)	26.5
N-Nitroso-*N*-methylaniline, NMPA (614-00-6)	34.3
N-Nitrosomorpholine, NMOR (59-89-2)	127
N-Nitrosovarenicline, NNV	37.0
N-Nitrosodipropylamine, NDPA (621-64-7)	26.5
N-Nitrosomethylphenidate, NMPH, (55557-03-4)	1300
N-Nitrosopiperidine (100-75-4)	1300
N-Nitrosorasagiline	18
7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3-a]pyrazine	37
N-Nitroso-1,2,3,6-tetrahydropyridine, NTHP (55556-92-8)	37
N-Nitrosonortriptyline	8
N-Methyl-*N*-nitrosophenethylamine, NMPEA (13256-11-6)	8
N-Nitrosodabigatran	18
4-(Methylnitrosoamino)-1-(3-pyridinyl)-1-butanone (NNK)	100

***N*-Nitrosamine (CAS number)**	**ng/day (AI)**
N-nitrosoduloxetine	100
N-nitroso-fluoxetine	100
N-nitrosoparoxetine	1300
N-nitroso-diphenylamine NDPh (86-30-6)	78000
N-nitroso-mefenamic acid	78000
N-nitroso-pyrrolidine NPYR (930-55-2)	1700
N-nitroso-diethanolamine NDELA (1116-54-7)	1900

The conversion to a specification limit in ppm for a particular medicinal product is calculated by dividing the respective above limit (ng) by the maximum daily dose (mg).

$$\text{Acceptable limit [ppm]} = \frac{\text{AI}\left[\frac{\text{ng}}{\text{day}}\right]}{\text{maximum daily dose}\left[\frac{\text{mg}}{\text{day}}\right]}$$

EMA/409815/2020 Rev.15 [17] article helps to understand "Calculation of limit when more than one nitrosamine is identified in the same product"

Let's say for Example, there are three possible Nitrosamine Impurities in the drug substance. NDMA, NDEA, N-Methyl-N-nitrosophenethylamine (NMPEA).

If NDMA (AI: 26.5 ng/day), NDEA (AI: 96 ng/day), N-Methyl-N-nitrosophenethylamine (NMPEA) (AI: 8 ng/day) are detected at or above 10% of their respective AI in a finished product with maximum daily dose of 300 mg.

Limits for individual impurities will be

NDMA	0.088 ppm
NDEA	0.320 ppm
NMPEA	0.027 ppm

There are **three approaches** for the control of more than one nitrosamine impurities in the Specification.

Option-1

Limits for individual N-nitrosamines can be defined but are not necessarily needed

NDMA	NMT 0.088 ppm (Optional)
NDEA	NMT 0.320 ppm (Optional)
NMPEA	NMT 0.027 ppm (Optional)
Total Nitrosamine Impurity.	**NMT 0.027 ppm**

Limit of Most Potent Nitrosamine impurity.

<table>
<tr><th colspan="2"><u>Option-2 (Fix Approach)</u></th><th colspan="2"><u>Option-3 (Flexible Approach)</u></th></tr>
<tr><td colspan="2">The limit for each N-nitrosamine should be set at a percentage of its AI limit such that the sum of the % AI limits for each specified nitrosamine does not exceed 100%.</td><td colspan="2">Each N-nitrosamine should be specified at its AI limit and an additional limit for total N-nitrosamines is required.</td></tr>
<tr><td>NDMA</td><td>NMT 0.035 ppm (40% of AI)
(i.e. 0.088 ppm x 0.4)</td><td>NDMA</td><td>NMT 0.088 ppm</td></tr>
<tr><td>NDEA</td><td>NMT 0.032 ppm (10% of AI)
(i.e. 0.320 ppm x 0.1)</td><td>NDEA</td><td>NMT 0.320 ppm</td></tr>
<tr><td>NMPEA</td><td>NMT 0.013 ppm (50% of AI)
(i.e. 0.027 ppm x 0.5)</td><td>NMPEA</td><td>NMT 0.027 ppm</td></tr>
<tr><td>Total Nitrosamine Impurity.</td><td>Not Required.</td><td>Total Nitrosamine Impurity.</td><td>Not more than 100% (Based on Actual analysis result)</td></tr>
<tr><td colspan="2">Distribution of % for individual impurities we can decide based on actual data</td><td colspan="2">$$\sum_{i=2}^{n} \frac{Xi}{AIi} \; x \; 100\% \; \leq \; 100\%$$
Xi = Amount of Individual Nitrosamine (in ppm) (Actual analysis result)
AIi = Acceptable intake (limit) of Individual Nitrosamine (in ppm)</td></tr>
</table>

Conclusion

This approach for the controlling N-Nitrosamine impurities in pharmaceutical drugs is based on scientific understanding and it ensures the quality of drugs with highest safety standards determined by the regulatory authorities.

References

1. Preussmann R. Carcinogenic N-nitroso compounds and their environmental significance. Naturwissenschaften. 1984;71(1):25-30. doi:10.1007/BF00365976
2. Park JE, Seo JE, Lee JY, Kwon H. Distribution of Seven N-Nitrosamines in Food [published correction appears in Toxicol Res. 2018 Oct;34(4):371]. *Toxicol Res*. 2015;31(3):279-288. doi:10.5487/TR.2015.31.3.279
3. Yang C.S., Smith T.J. (1996) Mechanisms of Nitrosamine Bioactivation and Carcinogenesis. In: Snyder R. et al. (eds) Biological Reactive Intermediates V. Advances in Experimental Medicine and Biology, vol 387. Springer, Boston, MA.
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; "ICH Harmonised Guideline - Assessment and Control Of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7(R1)"; March 31, 2017.
5. Loeppky, R., N.; "Nitrosamine and N-Nitroso Compound Chemistry and Biochemistry: Advances and Perspectives"; ACS Symposium Series, 1993, 553, Chapter 1, pp. 1-18. doi:10.1021/bk-1994-0553.ch001.

6. Challis BC, Edwards A, Hunma RR, Kyrtopoulos SA, Outram JR. Rapid formation of N- nitrosamines from nitrogen oxides under neutral and alkaline conditions. IARC Sci Publ. 1978;(19):127-142.
7. Brambilla G, Martelli A. Update on genotoxicity and carcinogenicity testing of 472 marketed pharmaceuticals. Mutat Res. 2009;681(2-3); pp.209-229
8. Heinrich TA, da Silva RS, Miranda KM, Switzer CH, Wink DA, Fukuto JM. Biological nitric oxide signalling: chemistry and terminology. Br J Pharmacol. 2013;169(7):1417-1429. doi:10.1111/bph.12217
9. Leaf CD, Wishnok JS, Tannenbaum SR. Mechanisms of endogenous nitrosation. Cancer Surv. 1989;8(2):323-334.
10. Mirvish SS. Formation of N-nitroso compounds: chemistry, kinetics, and in vivo occurrence. Toxicol Appl Pharmacol. 1975;31(3):325-351. doi:10.1016/0041- 008x(75)90255-0.
11. Brambilla G, Martelli A. Update on genotoxicity and carcinogenicity testing of 472 marketed pharmaceuticals. Mutat Res. 2009;681(2-3):209-229. doi:10.1016/j. mrrev.2008.09.002
12. U.S. Food and Drug Administration; "FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan"; https://www.fda.gov/ drugs/drugsafety/ucm613916.htm;
13. FDA Updates and Press Announcements on NDMA in Zantac (ranitidine), https://www.fda.gov/drugs/drug-safety and availability/ fda-updates- and -press announcements- ndma- zantac- ranitidine
14. Update on nitrosamine impurities: EMA continues to work to prevent impurities in medicines, 26th April, 2019, https://www.ema.europa.eu/en/documents/press-release/update-nitrosamine-impurities-ema-continues-work-preventimpurities-medicines_en.pdf
15. FDA Updates and Press Announcements on NDMA in Metformin, https://www.fda.gov/drugs/drug-safety-andavailability/fda-updates-and-press announcements-ndma-metformin
16. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, https://www.accessdata.fda.gov/scripts/cder/ob/
17. Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-marketing-authorisation-holders/applicants-chmp-opinion-article-53-regulation-ec-no-726/2004-referral-nitrosamine-impurities-human-medicinal-products_en.pdf

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