7TH ADVANCED
GMP WORKSHOPS 2022

IPA
INNOVATION. QUALITY. GLOBAL REACH.

Nitrosamine and other ICH M7 impurities

(GROUP 2)

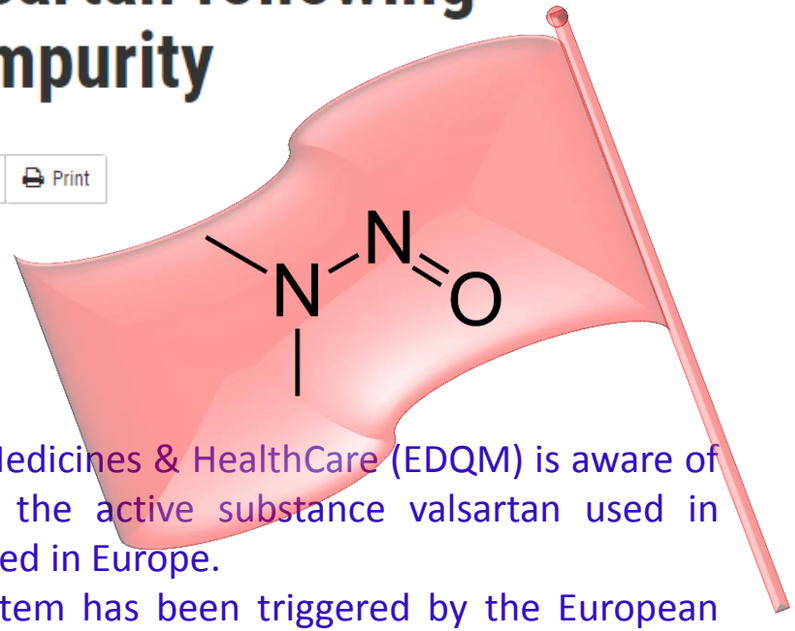
Red Flag & Compliance actions by Regulators

FDA NEWS RELEASE

FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

- First recognized in July-2018 by USFDA.
- "Probable cancer causing chemical".

Share | Tweet | LinkedIn | Email | Print



For Immediate Release: July 13, 2018

CERTIFICATION OF SUITABILITY (CEP) API NEWS
27 JULY 2018 STRASBOURG, FRANCE

- The European Directorate for the Quality of Medicines & HealthCare (EDQM) is aware of a quality defect related to an impurity in the active substance valsartan used in medicines to treat high blood pressure marketed in Europe.
- Earlier this month, a pan-European alert system has been triggered by the European Medicines Agency (EMA) in order to assess the extent of this incident and to establish remedial action plans.
- The EDQM is part of this pan-European alert system and is actively working with the EMA and national competent authorities to better understand the potential impact of this impurity and the extent of the issue.

✓ **Compliance action by Regulators**

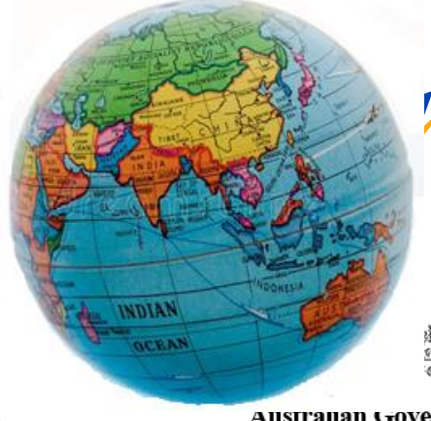
edqm

Health Canada Santé Canada

FDA U.S. FOOD & DRU ADMINISTRATION

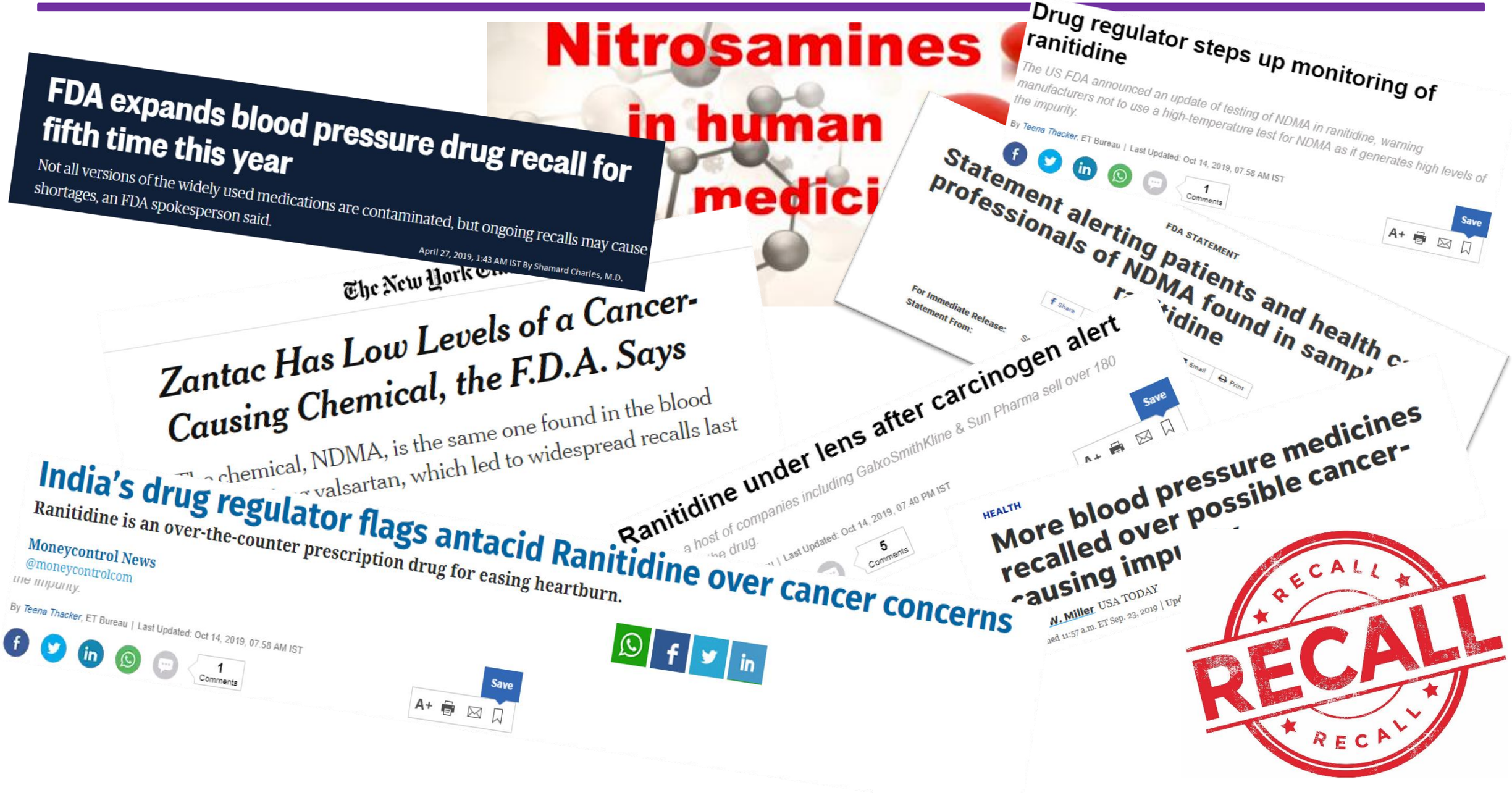
HSA Health Sciences Authority

EUROPEAN MEDICINES AGEI SCIENCE MEDICINES HEA



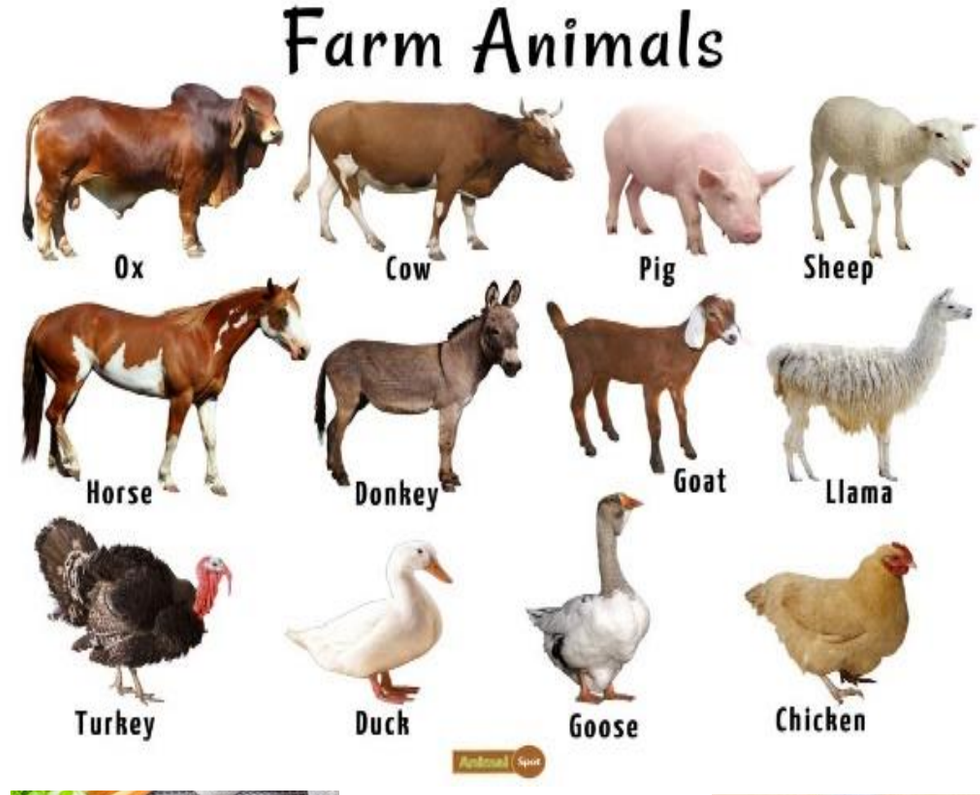
pmda

Australian Government
Department of Health
Therapeutic Goods Administration


Nitrosamines in human medici
FDA expands blood pressure drug recall for fifth time this year
Not all versions of the widely used medications are contaminated, but ongoing recalls may cause shortages, an FDA spokesperson said.
April 27, 2019, 1:43 AM IST By Shamard Charles, M.D.
Drug regulator steps up monitoring of ranitidine
The US FDA announced an update of testing of NDMA in ranitidine, warning manufacturers not to use a high-temperature test for NDMA as it generates high levels of the impurity.
By Teena Thacker, ET Bureau | Last Updated: Oct 14, 2019, 07:58 AM IST
1 Comments
Save
A+
Statement alerting patients and health professionals of NDMA found in samp idine
FDA STATEMENT
For Immediate Release:
Statement From:
Share
Email
Print
The New York
Zantac Has Low Levels of a Cancer-Causing Chemical, the F.D.A. Says
chemical, NDMA, is the same one found in the blood
valsartan, which led to widespread recalls last
Ranitidine under lens after carcinogen alert
a host of companies including GalxoSmithKline & Sun Pharma sell over 180
the drug.
Last Updated: Oct 14, 2019, 07.40 PM IST
5 Comments
Save
A+
India's drug regulator flags antacid Ranitidine over cancer concerns
Ranitidine is an over-the-counter prescription drug for easing heartburn.
Moneycontrol News
@moneycontrolcom
the impurity.
By Teena Thacker, ET Bureau | Last Updated: Oct 14, 2019, 07:58 AM IST
1 Comments
Save
A+
HEALTH
More blood pressure medicines recalled over possible cancer-
causing impu
N. Miller USA TODAY
ed 11:57 a.m. ET Sep. 23, 2019 | Upd
RECALL
RECALL
RECALL

History – 'Nitrosamine Impurities'

- In 1956, two British scientists, John Barnes and Peter Magee, reported that dimethyl nitrosamine produced liver tumors in rats.
- Subsequent studies showed that ***~300 nitrosamines tested and found ~ 90% were carcinogenic***.
- Nitrite and nitrosamine intake are associated with risk of gastric cancer and esophageal cancer.
- In the 1970s, an elevated frequency of liver cancer was found in Norwegian farm animals.
- These compounds can be commonly found in water, in animals, in smoked and grilled foods, dairy products, as well as alcoholic beverages and vegetables.
- Nitrosamine impurities exposure within safe limits represents a low risk of health problems.
- However, exposure above acceptable levels and for long period may increase the risk of cancer.



‘Nitrosamine Impurities’

- ***N*-Nitrosamines** are a class of compounds characterized by the binding of ***a nitroso group (-N=O) to an amine functional group (-NR_2).***

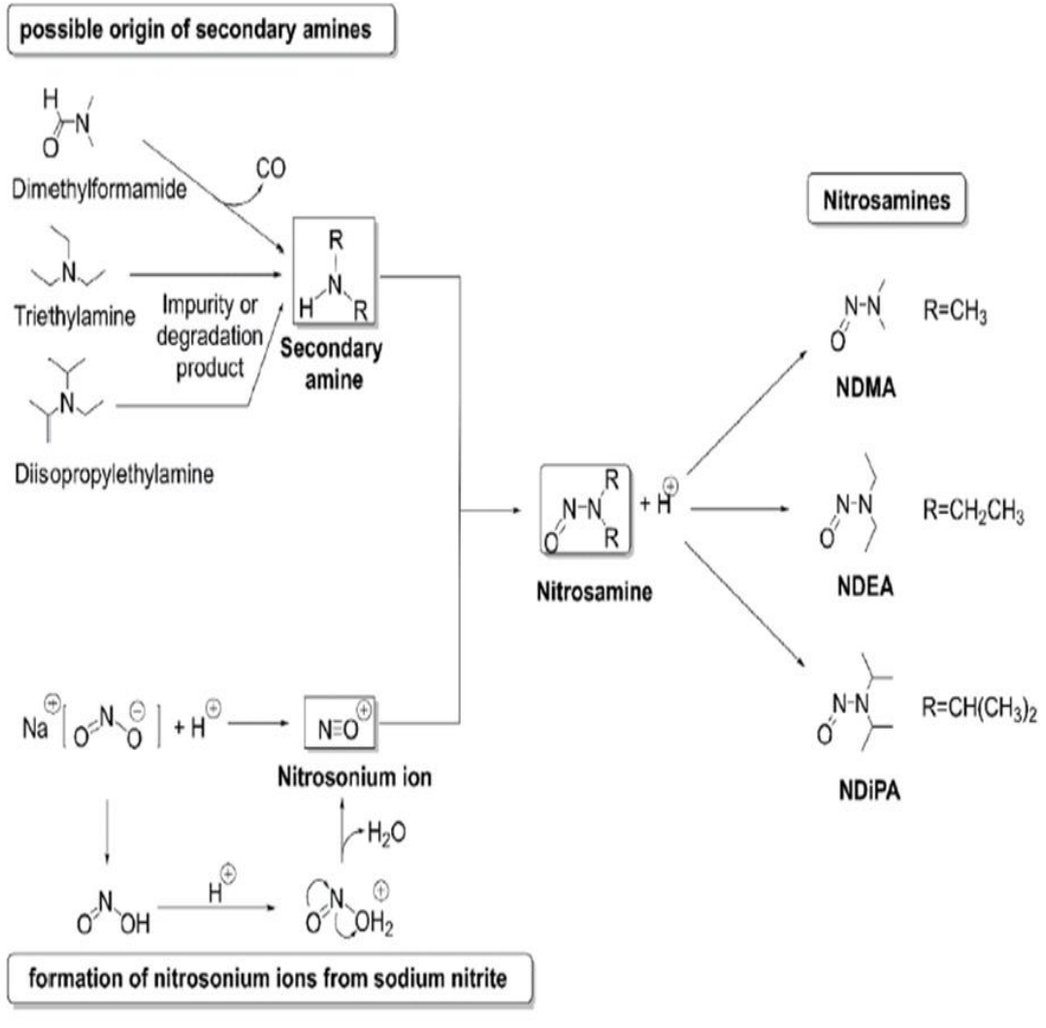
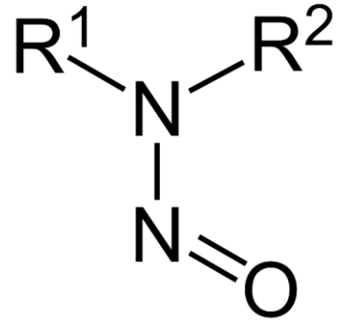


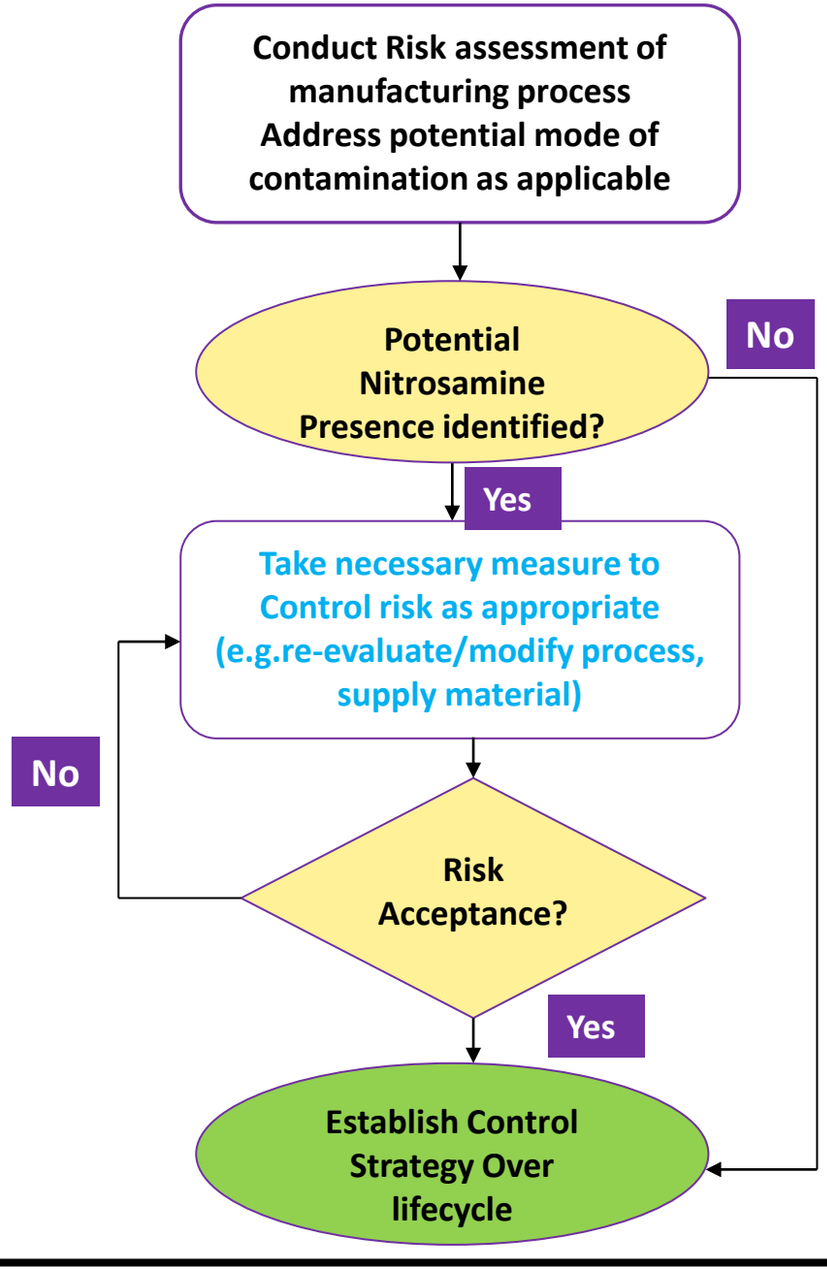
Fig. 1. Origin and chemical structure of nitrosamines found in sartans.



- N-Nitrosamines are mutagenic and carcinogenic chemicals resulting from the reaction of Nitrosonium ion (NO+) from nitrosating agents with secondary amines, tertiary amines or quaternary ammonium salts.
- The World Health Organization has classified nitrosamines as carcinogenic to humans.

Amines	Corresponding Nitrosamine Impurities
Dimethylamine	N-Nitrosodimethylamine (NDMA)
Diethylamine	N-Nitrosodiethylamine (NDEA)
Dipropylamine	N-Nitrosodipropylamne (NDPA)
Diisopropylamine	N-Nitrosodiisopropylamine (NDIPA)
Dibutylamine	N-Nitrosodibutylamine (NDBA)
Ethylmethylamine	N-Nitrosomethylethylamine (NMEA)
4-(Methylamino)butanoic acid	N-Nitroso-N-Methyl-4-aminobutyric acid (NMBA)

Compliance Strategy - Nitrosamine Impurities



- ✓ Risk Assessment.
- ✓ Confirmatory testing
- ✓ Update to regulatory agencies & market actions
- ✓ Meeting the timelines specified by the Agency

Evaluation, Management of Risk and Regulatory Timeline

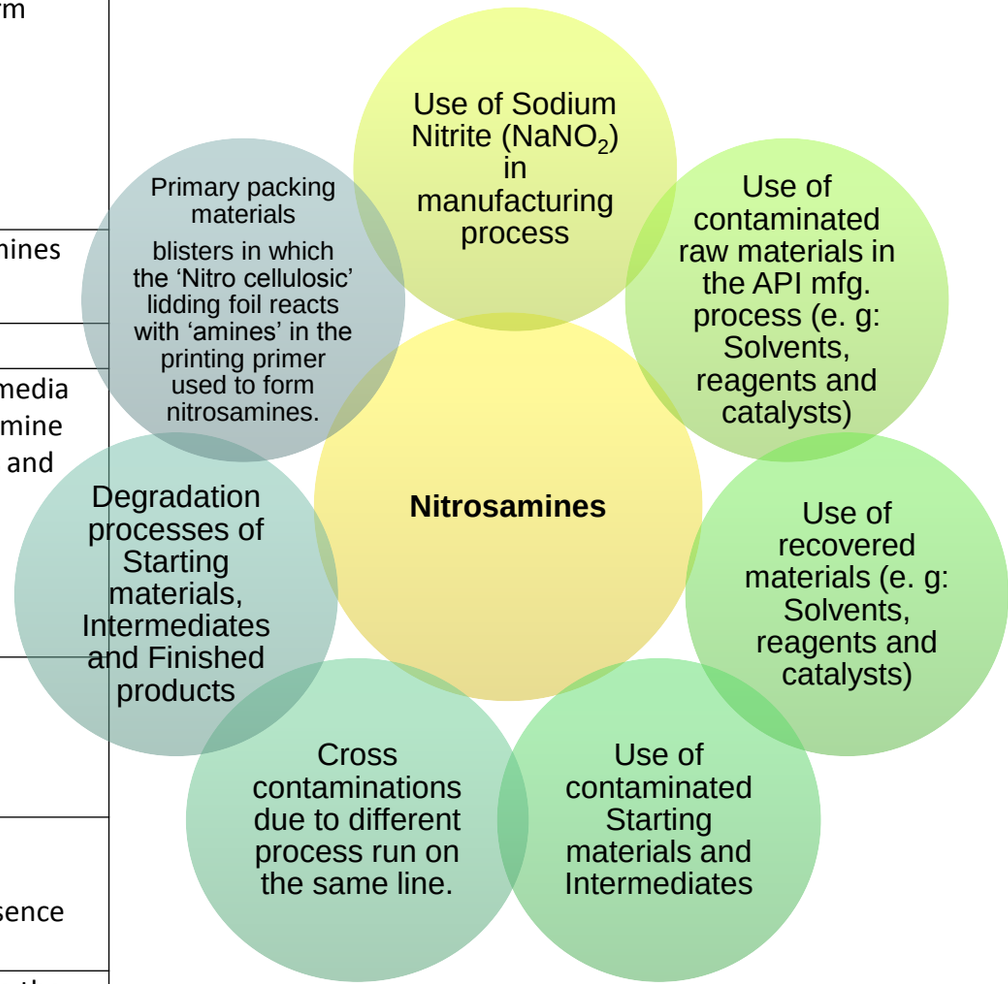
RISK EVALUATION PROCESS:

- **Step 1:** MAHs to perform a risk evaluation to identify if APIs and/or FPs could be at risk of presence of nitrosamine;
- **Step 2:** if a risk is identified, MAHs to proceed with confirmatory testing in order to confirm or refute the presence of nitrosamines. MAHs should report outcomes as soon as possible;
- **Step 3:** if the presence of nitrosamine(s) is confirmed, MAHs should implement effective risk mitigating measures through submission of variation.

Steps	Type	EMA/409815/2020/ Rev. 11 29 July, 2022	FDA / Feb 2021	ANVISA April 28, 2022	SwissMedic Sep 14, 2022	Health Canada April, 2022
		Human Medicinal products	**Human Drugs**	**Medicines for Human use**	**Human Medicinal Products**	**Human Pharmaceutical, Biological and Radiopharmaceutical Products**
Call for review Scope	Chemical Synthesis, Biological API	Drug Product, Drug Substance	Drug Product, Drug Substance	Drug Product, Drug Substance	Drug Product, Drug Substance	Drug Product, Drug Substance
Step 1: Risk Evaluation	Chemical Synthesis	31st March 2021	March 31, 2021	**March 1, 2023-Very high risk products** June 1, 2023-High risk products June 2, 2025-for other products Up to 36 months from risk assessment conclusion	31st March 2021	March 31, 2021
	Biological API	1st July 2021			1st July 2021	November 30, 2021
Step 2: Confirmatory testing	Chemical Synthesis	**26th September 2022**	**October 1, 2023**		**26th Sep 2022**	**October 1, 2022**
	Biological API	1st July 2023			1st July 2023	November 30, 2023
Step 3: Changes to the market authorization	Chemical Synthesis	**October 1, 2023**	**October 1, 2023**		**October 1, 2023**	**October 1, 2023**
	Biological API	1st July 2023			1st July 2023	November 30, 2023

Risk Assessment: Potential Source

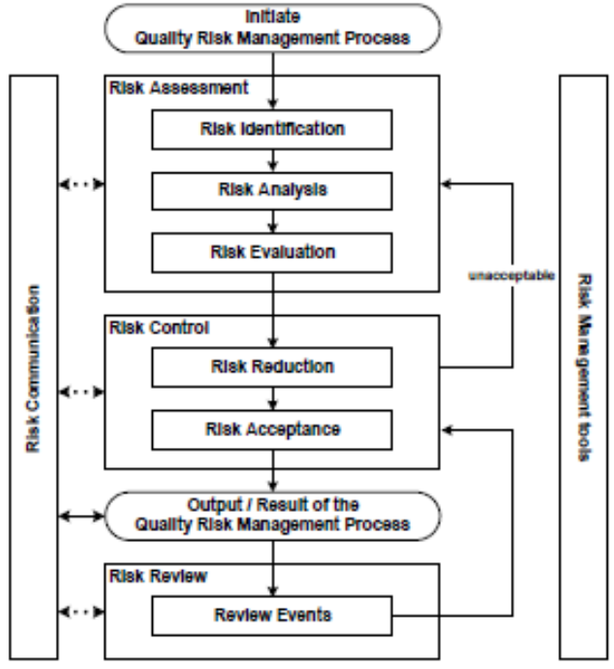
Potential sources	Observed Risk
Solvents	❖ Presence of residual dialkyl amines or tri-substituted amines that can degrade to form dialkyl amines (e.g., triethylamine). ❖ Presence of nitrites or other nitrosating agents ❖ Presence of acid ❖ Limited controls/specification limits for recycled solvents. ❖ Poor Quality water or solvents
Water	❖ Presence of residual dialkyl amines or impurities that can degrade to form dialkyl amines ❖ Presence of nitrites or other nitrosating agents in presence of acid.
Excipients	❖ Presence of nitrites or other nitrosating agents
Drug substance	❖ Use of sodium azide and sodium nitrite for azide quenching in the synthesis in acid media ❖ Use of di- or tri-alkylamines and amides (e.g., dimethylformamide [DMF], dimethylamine [DMA], triethylamine [TEA], N-methyl pyrrolidone [NMP]) in the presence of nitrites and acid media ❖ Use of recycled solvents that may contain nitrosamines or their precursors ❖ Use of sanitized water (e.g., chloramines) ❖ Need of additional purification steps (Crystallization)
Manufacturing process	❖ Contamination ❖ Use of recycled solvents that may contain nitrosamines or their precursors ❖ Poor quality solvents ❖ Presence of nitrous oxides in air used to dry the API or drug product
Drug product (including stability)	❖ Secondary or tertiary amine group in molecule in presence of nitrite counter ions (potentially as an impurity) ❖ Potential reactions within the formulation matrix during stability/shelf life (e.g., presence or generation of acidic conditions, moisture, and heat).
Container–Closures	❖ Thermal decomposition of nitrocellulose to produce nitrites followed by migration to the drug product. Eg: Nitrocellulose coated blister foils. ❖ Biodegradation of nitrocellulose to produce nitrites followed by migration to the drug product.



Reference: Nitrosamine Impurities <USP 1469>

Control Strategy, if Risk Identified

LIKELY SOURCES	CONTROL STRATEGY
▪ Impurities of Raw materials	✓ Quality of material (Raw material, solvent, intermediate)
▪ Manufacturing process	✓ Process Control (Controlling reaction, in-process controls & purification)
▪ Recovered solvents / recovered material	✓ Recovered solvent / material quality.
▪ Inadequate equipment cleaning	✓ Effective equipment cleaning to control residual carryover of impurities



Setting Limits:

- Nitrosamine impurities identified have potential and established toxicity with no therapeutic value.
- Because nitrosamines are among the structural groups of high potency mutagenic carcinogens of the **"cohort of concern"** in ICH M7, the **threshold of toxicological concern (TTC) does not apply.**
- Instead, the available safety data should be used to establish a material specific AI on case by case basis.
- The AI is defined as an intake level that poses a negligible health risk.

Derivation of Acceptable Intake Limits:

- There are several methodologies that toxicologists have applied in establishing.
- The limits have been published in the FDA Guidance for Industry to Control of Nitrosamine Impurities in Human Drugs.
- A description of the AI derivation for NDMA, which is an example of how FDA applied ICH M7(R1) to set a limit.
- 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/day)/MDD (mg/day).

List of Known Nitrosamine Impurities with Acceptable Intake

Acceptable Intake (AI) limits of Specific Nitrosamine Impurities							
Impurity	**Code**	**CAS No.**	**EMA (AI - ng/day)**	**FDA (AI - ng/day)**	**ANVISA (AI - ng/day)**	**SwissMedic (AI - ng/day)**	**Health Canada (AI - ng/day)**
N-Nitrosodimethylamine	NDMA	62-75-9	**96.0**	**96.0**	**96.0**	**96.0**	**96.0**
N-Nitroso-4-(methylamino)butyric acid	NMBA	61445-55-4	**96.0**	**96.0**	**96.0**	**96.0**	**96.0**
1-Methyl-4-nitrosopiperazine	MNP/MeNP	16339-07-4	**26.5**	**-**	**26.5**	**26.5**	**96.0**
N-Nitrosodiethylamine	NDEA	55-18-5	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosodiisopropylamine	NDIPA/ DIPNA	601-77-4	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosoethylisopropylamine	NEIPA/NIPEA/EI PNA	16339-04-1	**26.5**	**26.5**	**26.5**	**26.5**	**26.5**
N-Nitrosodibutylamine	NDBA	924-16-3	**26.5**	**USP**	**26.5**	**26.5**	**26.5**
N-Nitrosomethylphenylamine	NMPA	614-00-6	**34.3**	**26.5**	**34.3**	**34.3**	**-**
N-Nitrosomorpholine	NMOR	59-89-2	**127.0**	-	-	**127.0**	**127.0**
N-Nitrosovarenicline	NNV	-	**37.0**	-	-	**37.0**	**37.0**
N-Nitrosodipropylamine	NDPA	621-64-7	**26.5**	-	-	**26.5**	**26.5**

USFDA: 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

Limit (ppm) = Acceptable Intake (ng/day) / Maximum Daily Dose (mg/day)

List of Known Nitrosamine Impurities with Acceptable Intake

Acceptable Intake (AI) limits of Specific Nitrosamine Impurities					
Impurity	**Code**	**CAS No.**	**(AI - ng/day)**	**Newly listed May/July-22 (AI - ng/day)**	**Newly listed Sep-22 (AI - ng/day)**
N-Nitrosodimethylamine	NDMA	62-75-9	96.0	-	-
N-Nitroso-4-(methylamino)butyric acid	NMBA	61445-55-4	96.0	-	-
1-Methyl-4-nitrosopiperazine	MNP/MeNP	16339-07-4	26.5	-	-
N-Nitrosodiethylamine	NDEA	55-18-5	26.5	-	-
N-Nitrosodiisopropylamine	NDIPA/DIPNA	601-77-4	26.5	-	-
N-Nitrosoethylisopropylamine	NEIPA/NIPEA/EIPNA	16339-04-1	26.5	-	-
N-Nitrosodibutylamine	NDBA	924-16-3	26.5	-	-
N-Nitrosomethylphenylamine	NMPA	614-00-6	34.3	-	-
N-Nitrosovarenicline	NNV	-	37.0	-	-
N-Nitrosodipropylamine	NDPA	621-64-7	26.5	-	-
N-nitrosomethylphenidate	-	-	-	1300	1300
N-nitrosopiperidine	-	100-75-4	-	1300	1300
N-nitrosorasagilene	-	-	-	18	-
7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3- a]pyrazine	-	-	-	37	37
N-nitroso-1,2,3,6-tetrahydropyridine	-	55556-92-8	-	37	37
N-nitrosonortriptyline	-	-	-	8	8
N-methyl-N-nitrosophenethylamine,	NMPEA	13256-11-6	-	8	8
N-Nitrosodabigatran	-	-	-	18	18
N-nitroso-duloxetine	NDLX	-	-	-	100
4-(methylnitrosamino)-1-(3-pyridyl)-1-(butanone)	NNK	-	-	-	100
N-nitroso-rasagiline	-	-	-	-	18
N-nitroso-tamsulosin	-	-	-	-	18

Analytical Testing Strategy

Regulatory	Omission	Skip testing	Routine control
EMA	the LoQ of the analytical method employed should be ≤ 10% of the acceptable limit based on the AI	the LoQ of the analytical procedure employed should be ≤ 30% of the acceptable limit based on the AI	the LoQ should be ≤ of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity
FDA	Alternate approaches (e.g., upstream test of an intermediate) should be supported by sufficient process understanding and evidence of adequate statistical control and should be submitted to FDA in a supplement prior to implementation		If a nitrosamine impurities in Table 1 (NDMA, NDEA, NMBA, NMPA, NIPEA, NDIPA) listed is detected above the LOQ
ANVISA	Admitted the absence of nitrosamines when <10% of the AI limit	▪ If results are >10% of AI limit, control must be included. ▪ Other approaches can be justified, not exceeding the 30% limit. ▪ If the >1 nitrosamine to be controlled, the limits must be adjusted in order to ensure the maintenance of negligible risk	
SWISSMEDIC	The detection of every nitrosamine impurity must lead to an investigation of the causes, and appropriate CAPAs should be taken in accordance with GMP. As with any case of an identified problematic risk, companies must follow the standard procedure and inform Swiss medic immediately if nitrosamines are detected in APIs or medicinal products – regardless of the quantities – and submit a risk evaluation.		
Health Canada	Analytical procedures may need to be validated with LOQs well below the most conservative AI limit of the nitrosamines present, if proposals for a reduced testing program or absence of testing of the drug product are anticipated.		The API specification should include a test and acceptance criterion for each nitrosamine impurity when the risk for nitrosamine presence is considered to be high and/or when the concentration of any nitrosamine is found to be at significant levels (e.g. greater than 30% of the acceptable intake) during confirmatory testing.

Analytical Method Sensitivity

Testing	EMA	FDA	ANVISA	SwissMedic	Health Canada
Method	Validated sensitive method	Validated sensitive method	Validated sensitive method	Validated sensitive method	Validated sensitive method
Testing type	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Sensitivity of the method	LoQ should be ≤ of the acceptable limit based on the relevant acceptable intake (AI) for the respective nitrosamine impurity	LoD/LoQ are reasonably practical for products MDD is high (>1 g) If >1 nitrosamine listed, the method LOQ should be <0.03 ppm. If MDD >1 g (e.g. 1200 mg), LOQ should be below 0.02 ppm	LoD or LoQ <10% of limit of AI	Analytical method with sufficient sensitivity must be used for confirmatory testing. The general requirement previously used by Swissmedic calling for a method with a LOQ of 30 ppb no longer applies	LoQ should be ≤ to the acceptable limit for most **conservative** nitrosamine detected in an API or drug product

Analytical Challenges

Analytical challenges	Suggested approach
▪ **Need of high sensitive methods** ▪ **Matrix interference**	**Instrument needs** ➢ Selection of adequate mass platform E.g. LC-MS / GC-MS ➢ Focus on GC-HS/MS, GC-HS-Triple quadrupole (QqQ) techniques to minimize matrix interference. ➢ LC-HRMS, GC-Triple quadrupole (QqQ) can be used to minimize interference of close molecular weight compounds E.g. Ranitidine, metformin published method using HRMS. **Chromatographic control** ➢ Short length / ID columns shall be used to improve method sensitivity. ➢ Evaluation of various column chemistries like biphenyl column, hybrid charged surface column chemistries, modified silica column, end-caped caped columns shall be evaluated for chromatographic separation better peak shape.
▪ **Solubility variation between analyte and impurities** ▪ **Chromatographic Separation active and impurities from diluent and sample matrix**	**Sample preparation techniques** ➢ Use of solid and liquid phase extraction techniques. E.g. : Dissolving samples in minimum quantity of organic and dilution with aqueous solutions. ➢ Use of SPE cartridges/ syringe filters to avoid matrix interference ➢ Liquid phase extraction technique: EU general chapter 2.5.42 N-Nitrosamines in active substances.
Laboratory set up	Needs dedicated facility
Peak shape of the Nitrosamine	Optimization of organic modifier Evaluation of column chemistries; biphenyl, End-caped caped columns, charged surface hybrid technologies and new generation modified silica columns
Method Transfer & Reproducibility at LOQ	Anticipating future needs method sensitive should be set high (S/N-should be high) during development stage.
Regular monitoring at QC ▪ **Vast product range** ▪ **Single product multiple methods** ▪ **Analysis time & cost**	Instrument maintenance, regular source cleaning and use of diverter valve to avoid detector contamination is paramount importance.

✓ Establishing the Harmonized Test Method for Multiple Markets

Impurity	CAS No.	Reference	MDD (mg)	Published AI (ng/day)	Considered AI (ng/day)	(AI/MDD) Limit in ppm	MDD Type	# of Impurities	LOQ requirement
NDMA	[62-75-9]	USFDA	20	96	96	4.8	< 1 g	>1	<0.03 ppm
NDEA	[55-18-5]	USFDA	20	26.5	26.5	1.325	< 1 g	>1	<0.03 ppm
1-4, Dinitrosopiperazine	[140-79-4]	USFDA	20	-	26.5	1.325	< 1 g	>1	<0.03 ppm
1-Nitrosopiperazine	[5632-47-3]	USFDA	20	-	26.5	1.325	< 1 g	>1	<0.03 ppm
1-Methyl-4-Nitrosopiperazine	[16339-07-4]	USFDA	20	-	26.5	1.325	< 1 g	>1	<0.03 ppm
NDMA	[62-75-9]	EMA	20	96	96	4.8	< 1 g	>1	<0.48 (<10% of Limit)
NDEA	[55-18-5]	EMA	20	26.5	26.5	1.325	< 1 g	>1	<0.1325 (<10% of Limit)
1-4, Dinitrosopiperazine	[140-79-4]	EMA	20	-	18	0.9	< 1 g	>1	<0.09 (<10% of Limit)
1-Nitrosopiperazine	[5632-47-3]	EMA	20	-	18	0.9	< 1 g	>1	<0.09 (<10% of Limit)
1-Methyl-4-Nitrosopiperazine	[16339-07-4]	EMA	20	26.5	26.5	1.325	< 1 g	>1	<0.1325 (<10% of Limit)
NDMA	[62-75-9]	HC	20	96	96	4.8	< 1 g	>1	<0.27 ppm (At least <30% of most conservative limit)
NDEA	[55-18-5]	HC	20	26.5	26.5	1.325	< 1 g	>1	<0.27 ppm (At least <30% of most conservative limit)
1-4, Dinitrosopiperazine	[140-79-4]	HC	20	-	18	0.9	< 1 g	>1	<0.27 ppm (At least <30% of most conservative limit)
1-Nitrosopiperazine	[5632-47-3]	HC	20	-	18	0.9	< 1 g	>1	<0.27 ppm (At least <30% of most conservative limit)
1-Methyl-4-Nitrosopiperazine	[16339-07-4]	HC	20	96	96	4.8	< 1 g	>1	<0.27 ppm (At least <30% of most conservative limit)

Actions against Risk assessment

UPDATE TO THE AGENCY & MARKET ACTIONS:

Outcome of risk assessment and confirmatory testing, manufacturers should update to regulatory agency about the outcome of this evaluation.

- ✓ Nitrosamine impurity is likely to be present : Yes / No.
- ✓ Control Strategy.
- ✓ Field Alert Report / Filing Non-standard Quality Alert.
- ✓ Recall.
- ✓ Improvement plans – control on quality of raw material / process.

REPORTING CHANGES TO THE AGENCY:

- ✓ Drug Product manufacturer must report changes implemented to prevent / reduce nitrosamine impurities.
- ✓ API DMF holder makes process changes in the ROS as a result of the risk assessment and confirmatory testing, the DMF holder must submit amendments and inform each drug product manufacturer that references the DMF.
- ✓ Change in synthetic process / alternate process needed to avoid nitrosamine contamination should be reported.

Life Cycle of Risk Assessment

- ✓ Risk assessment is a live document, which will be updated whenever additional knowledge is obtained on the API or process change is conducted (when risk assessment may need repeated).
- ✓ Mitigation actions should be defined if a risk is identified.
- ✓ If new information is obtained, such as late supplier information, and such information increases the risk level versus the previous version of the risk assessment, such new information will have to be communicated to the customers accordingly.
- ✓ The results of analytical testing change control and investigation systems should also feed the risk assessment.
- ✓ Impact on existing risk assessment shall be evaluated in the case of followings;
  - ❖ Change in process.
  - ❖ Change in Source water.
  - ❖ Change in ROS of vendor.
  - ❖ Change in vendor.
  - ❖ Change in specification.
  - ❖ Any updates from regulatory/Supplier.
  - ❖ Pharmacopeial updates if any.

Industry Next Level Challenges

- Control of ‘Nitrite’ in Water/Excipients
- ‘Nitrosamine impurities’ content in API cleaning samples from non dedicated equipment's used for manufacturing
- Unavailability (either unstable and/or unable to synthesis) of few possible Nitrosamine impurities
- Lack of ‘Sufficient Testing infrastructure (in-house and / or CRO labs)’
- ‘High’ testing costs
- ‘Lack of skilled manpower’ for testing.
- Nitrosamine impurities assessment (from Packing materials) and control strategy
- Inappropriate support from Raw material, KSM, API, excipients and Packing materials vendors

IPA Members Team – 'Nitrosamine Impurities'

Name	Mail ID	From
Dr. BM Rao	Drbmrao@qdotassociates.com drbmrao@gmail.com	Ex. Dr. Reddy's Current : Qdot Associates, Hyderabad
Dr. Gunvantsinh Desai	Gunvantsinh.Desai@zyduslife.com	Zydus Lifesciences
Dr. Rajiv Desai	rajivdesai@lupin.com	Lupin
Mr. BNV Ganapati Rao	venkataganapati@drreddys.com	Dr. Reddy's
Mr. Nalin Karkra	Nalin.Karkra@sunpharma.com	Sun Pharma
Mr. Vijay Shanbhag	Vijvijay.shanbhag@cipla.com	Cipla
Dr. Priti Shah	PritiShah@TorrentPharma.com	Torrent Pharmaceutical
Mr. Ramreddy Chandireddy	Ramreddy.Chandireddy@zyduslife.com	Zydus Lifesciences

Thank you