5th INDIA PHARMACEUTICAL FORUM 2020

Indian Pharmaceutical Alliance
IPA
Innovation, Quality and Global Reach

Nitrosamine Impurities - Current Status and Expectations

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J. B. Chemicals & Pharmaceuticals Ltd.

28th February 2020

News worldwide

NDMA

FDA expands blood pre
fifth time this ye
Not all versions of the
shortages, an FD

HEALTH

More blood pressure medicines recalled over possible cancer-causing imp

Ryan W. Miller USA TODAY

Published 11:57 a.m. ET Sep. 23, 2019 | U

The New York Times

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

India's drug regulator flags antacid Ran

Ranitidine is an over-the-counter prescription drug for easing h

Moneycontrol News
@moneycontrolcom

the impurity.

By Teena Thacker, ET Bureau | Last Updated: Oct 14, 2019, 07.58 AM IST

1 Comments

Statemen
profession

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

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d health care found in samples of e

Ranitidine under lens after carcinogen alert

In India, a host of companies including GalxoSmithKline & Sun Pharma sell over 180 versions of the drug.

By Teena Thacker, ET Bureau | Last Updated: Oct 14, 2019, 07.40 PM IST

5 Comments

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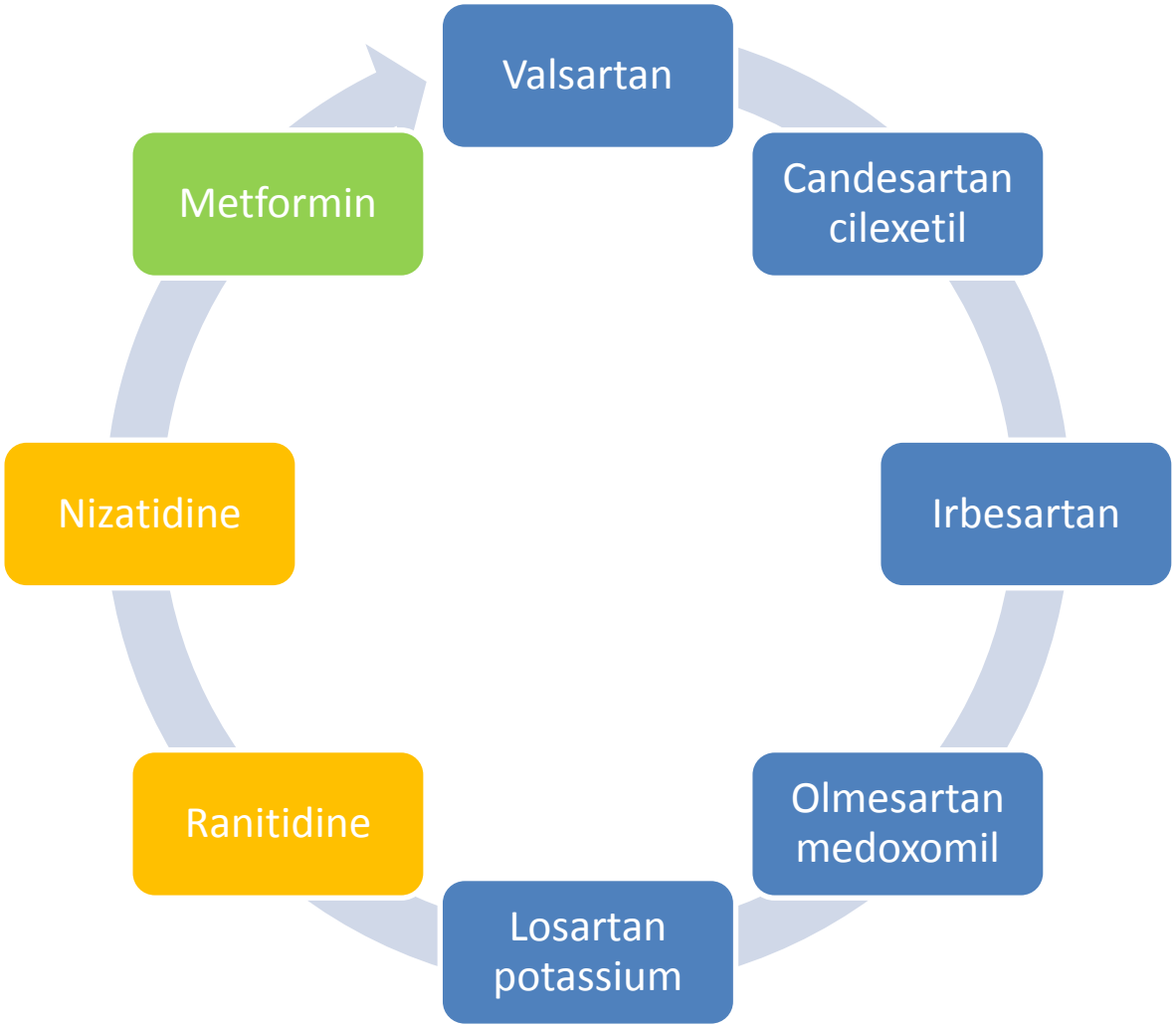
Genesis of NDMA Issue

- Medicine Regulatory Authorities first became aware of the presence of the nitrosamine impurity, Nnitrosodimethylamine (NDMA), in products containing valsartan in July 2018. Valsartan is an Angiotensin II Receptor Blocker (ARB) and belongs to a family of analogue compounds commonly referred to as the sartans.
- Further nitrosamine impurities were subsequently detected in other medicines belonging to the sartan family, including: N-nitrosodiethylamine (NDEA), N -nitrosodiisopropylamine (NDIPA), N -nitrosoethylisopropylamine (NEIPA) and N -nitroso-N-methyl-4-aminobutyric acid (NMBA).
- Subsequently, in Sept 2019a nitrosamine impurity has been detected in batches of ranitidine, a medicine used to treat heartburn and stomach ulcers
- On 6 December 2019, EMA confirmed that trace amounts of NDMA had been found in a small number of metformin-containing medicines outside the EU. There were no data indicating that EU medicines were affected.

- https://www.who.int/medicines/publications/drugalerts/InformationNote_Nitrosamine-impurities/en/
- https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

Impacted Molecules



What are Nitrosamines?

- Any molecule containing the nitroso functional group.
- These molecules are of concern because nitrosamine, are classified as probable carcinogens by International Agency for Research on Cancer [IARC].
- Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- Although they are also present in some foods and drinking water supplies, their presence in medicines is nonetheless considered unacceptable.

Group 1	Carcinogenic to humans
Group 2A	Probably carcinogenic to humans
Group 2B	Possibly carcinogenic to humans
Group 3	Not classifiable as to its carcinogenicity to humans

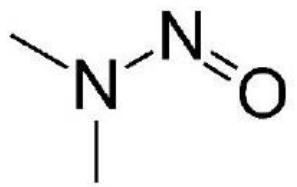


Figure 1: *N*- nitrosodimethylamine (NDMA)

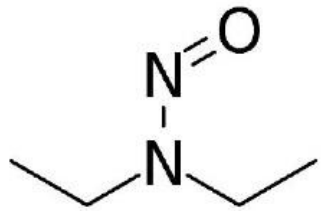


Figure 2: *N*-nitrosodiethylamine (NDEA)

Park J et al. Distribution of Seven N-Nitrosamines in Food. Toxicol Res. 2015; 31(3): 279–288.

Toxicity

- NDMA and NDEA belong to group of highly potent mutagenic carcinogens.
- Despite the potency of these impurities, there is still a very low risk that nitrosamine impurities at the levels found could cause cancer in humans.
- Only limited impurity-specific toxicity data is available for NDMA and NDEA.
- Due to their structural similarity, NDIPA, NEIPA, and NMBA are considered by international regulators to exhibit a toxicological profile like NDMA and NDEA.

Toxicity

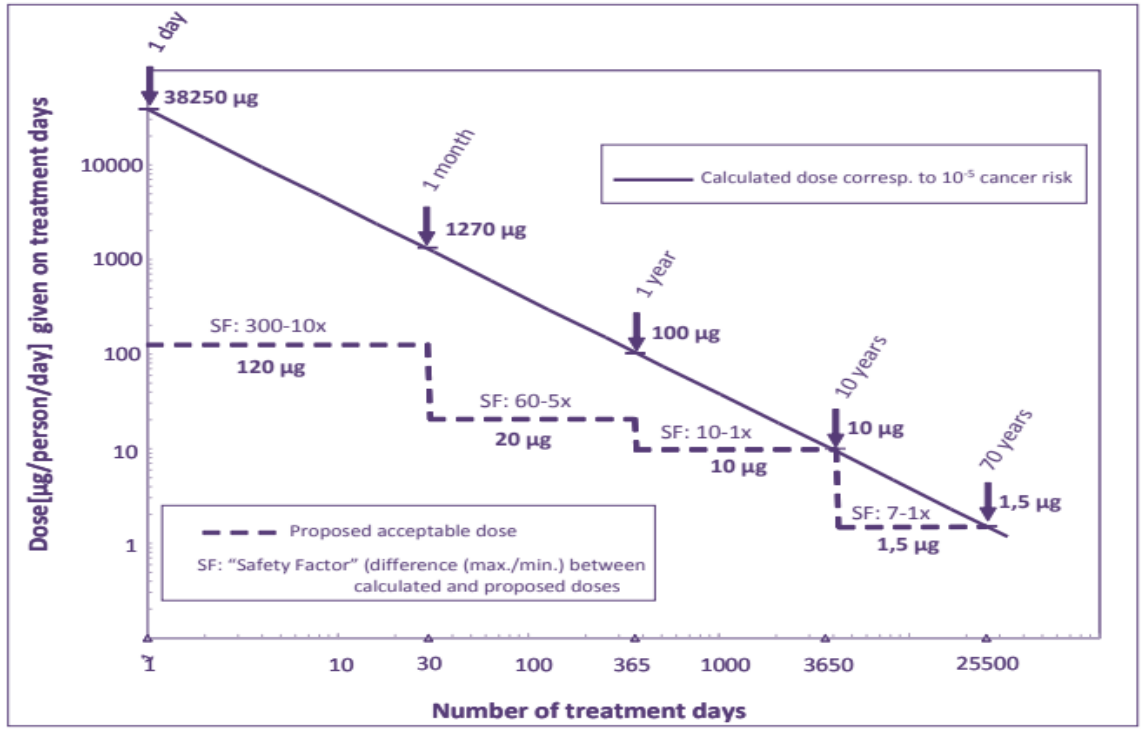
Interim allowable daily intake limits

Impurity name Abbreviation	Chemical name	Allowable Daily Intake (AI)
NDMA[6]	N-nitrosodimethylamine	96.0 ng/day
NDEA[6]	N-Nitrosodiethylamine	26.5 ng/day
NMBA[7]	N-Nitroso-N-methyl-4-aminobutyric acid	96.0 ng/day
DIPNA[7]	N-nitrosodiisopropylamine	26.5 ng/day
EIPNA[7]	N-nitrosoethylisopropylamine	26.5 ng/day

https://www.who.int/medicines/publications/drugalerts/InformationNoteNitrosamine-impurities_Nov2019.pdf?ua=1
6 February 2019, EMA/44960/2019: Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities.
7 20 August 2019 EMA/351053/2019 rev 1: Temporary interim limits for NMBA, DIPNA and EIPNA impurities in sartan blood pressure medicines.

ICH (M7)

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7 (R1) - (Current Step 4 version dated 31 March 2017)



The solid line in Figure represents the linear relationship between the amount of daily intake of a mutagenic impurity corresponding to a 10^{-5} cancer risk and the number of treatment days. The calculation is based on the TTC level as applied in this guidance for life-long treatment, i.e., 1.5 µg per person per day using the formula:

$$\text{Less-than-lifetime AI} = \frac{1.5\ \mu g \times (365\ \text{days} \times 70\ \text{years lifetime} = 25{,}550)}{\text{Total number of treatment days}}$$

Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels.

https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf Last accessed on 12th October,

Ranitidine – Since 40 years

- Ranitidine is an acidity inhibitor meant for short term use
- Commercially introduced in 1981
- Available >120 countries worldwide
- Features on WHO's List of Essential Medicines

Mills et al. Aliment Pharmacol Ther 1997; 11: 129-137.
Palop et al. Arzneimittelforschung. 1997; 47(4A): 439-46.

The calculation of less-than-lifetime Acceptable Intakes (AI) is predicated on the principle of Haber's rule, a fundamental concept in toxicology **where concentration (C) x time (T) = a constant (k)**. Therefore, the carcinogenic effect is based on both dose and duration of exposure.

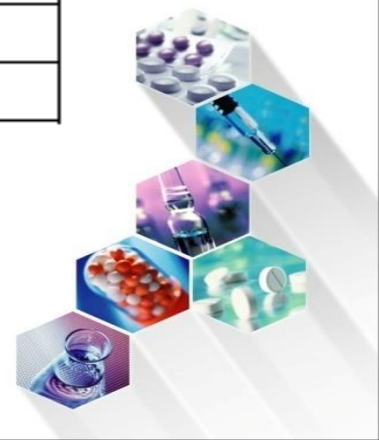
For NDMA: Less-than-lifetime Acceptable Intake (AI) = 96 ng x (365 days x 70 years lifetime = 25,550) ÷ Total number of treatment days

Summarized chart: Dosage (ranitidine) vis-à-vis years of exposure[45]

Ranitidine Dosage*	Acceptable limits (ppm) of NDMA in relation to years of Ranitidine use			
	1 year	5 years	10 years	70 years (Lifelong)
300 mg	22.4 ppm	4.48 ppm	2.24 ppm	0.32 ppm
600 mg	11.2 ppm	2.24 ppm	1.12 ppm	0.16 ppm

*Usual dose should not exceed Ranitidine dose 600 mg /day.

Calculations Data on file (using the ICH M7, Quality Risk Management Guidelines)



Sartans

Temporary limits for NDMA and NDEA impurities

	NDMA		NDEA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**	**Maximum daily intake (ng)**	**Limit (ppm)**
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)	96.0	0.320	26.5	0.088
Losartan (150 mg)	96.0	0.640	26.5	0.177
Olmesartan (40 mg)	96.0	2.400	26.5	0.663
Valsartan (320 mg)	96.0	0.300	26.5	0.082

https://www.ema.europa.eu/en/medicines/human/referrals/angiotensin-ii-receptor-antagonists-sartans-containing-tetrazole-group

Nizatidine and Metformin

	NDMA	
Active substance (max daily dose)	**Maximum daily intake (ng)**	**Limit (ppm)**
Nizatidine (300 mg)	96	0.319
Metformin Immediate-release tablets or oral solution (2550 mg)	96	0.0376
Metformin Extended –Release Tablets (2000 mg)	96	0.0479

NDMA & Water

- The EPA's Integrated Risk Information System (IRIS) estimates that a NDMA concentration of 7×10^{-4} µg/L in drinking water is associated with a 10^{-6} cancer risk.[23]
- The World Health Organization (WHO) (2006) estimates that 0.1 µg/L NDMA in drinking water corresponds to an upper-bound 10^{-5} cancer risk.[24]
- A recent study of 21 U.S. and Canadian drinking water treatment plants reported a range of NDMA levels from below the minimum reporting level (MRL) of 6×10^{-4}µg/L to 2.4×10^{-2}µg/L.[25]

NDMA

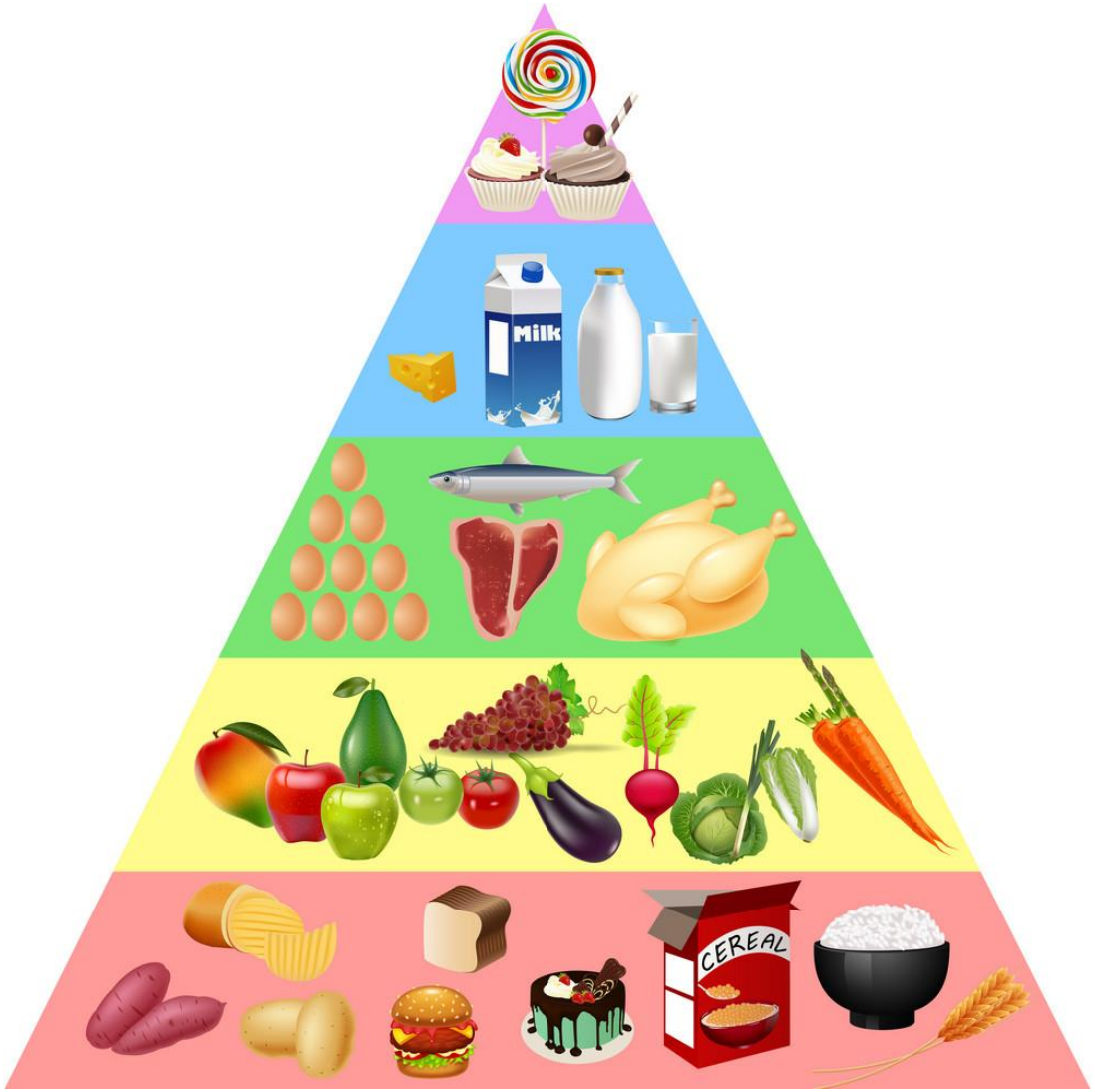
23. EPA 1993 Integrated Risk Information System (IRIS): NNitrosodimethylamine (CASRN 62-75-9). US Environmental Protection Agency, Office of Research and Development, URL: http://www.epa.gov/iris/substance_nmbr=0045. Accessed: 9/26/04.

24. https://www.who.int/water_sanitation_health/dwq/chemicals/ndma_2add_feb2008.pdf. Last accessed on 14th October, 2019.

25. Valentine, R. L., Zho Chen, J. C., Barrett, S. E., Cordelia Hwang, C., Guo, Y., Wehner, M., Fitzsimmons, S., Andrews, S. A., Werker, A. G., Brubacher, C. & Kohut, K. 2006. Factors affecting the formation of NDMA in water and occurrence. American Water Works Research Foundation, Denver, CO, pp. 99–138.

NDMA & Food

- NDMA can form in food when secondary amines are exposed to nitrite during processing or preservation. Dietary sources of NDMA include
  - Beer,
  - Fish and fish products,
  - Dairy products including cheese, dried milk and infant formula,
  - Meat and cured meats,
  - Cereals and vegetables.[26]



26. Chowdhury S. N-Nitrosodimethylamine (NDMA) in Food and Beverages: A Comparison in Context to Drinking Water, Human and Ecological Risk Assessment: An International Journal 2014; 20(5): 1291-1312. DOI: 10.1080/10807039.2013.817144.

EDQM Guidance to avoid nitrosamines in human medicines

STEP 1

- **Conduct a risk evaluation** to identify products at risk of N-nitrosamine formation or (cross-)contamination and report the outcome **by 26 March 2020 at the latest**.

STEP 2

- **Perform further confirmatory testing** on the products identified to be at risk of N-nitrosamine formation or (cross-)contamination and report confirmed presence of nitrosamines **as soon as possible**.

STEP 3

- Apply for any necessary **changes to the manufacturing process** resulting from this review using the established regulatory procedures.

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

EDQM Initiatives

Review of ranitidine medicines

- At the request of the European Commission, EMA is currently reviewing ranitidine medicines after tests showed that some of these products contained NDMA.

Review of sartans

- EMA has completed its review of sartan blood pressure medicines (also known as angiotensin II receptor anatgonists). Manufacturers of sartan medicines must **review their manufacturing processes** to ensure they do not produce nitrosamine impurities.

Metformin-containing medicines

- EMA and national competent authorities are working closely with the official medicines control laboratories (OMCLs) and companies to test EU medicines. EMA will provide further updates as soon as possible.
- EMA advised patients in the EU to **continue to take metformin medication** as the risks from not treating diabetes far outweigh any possible effects of the low levels of NDMA seen in tests.

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

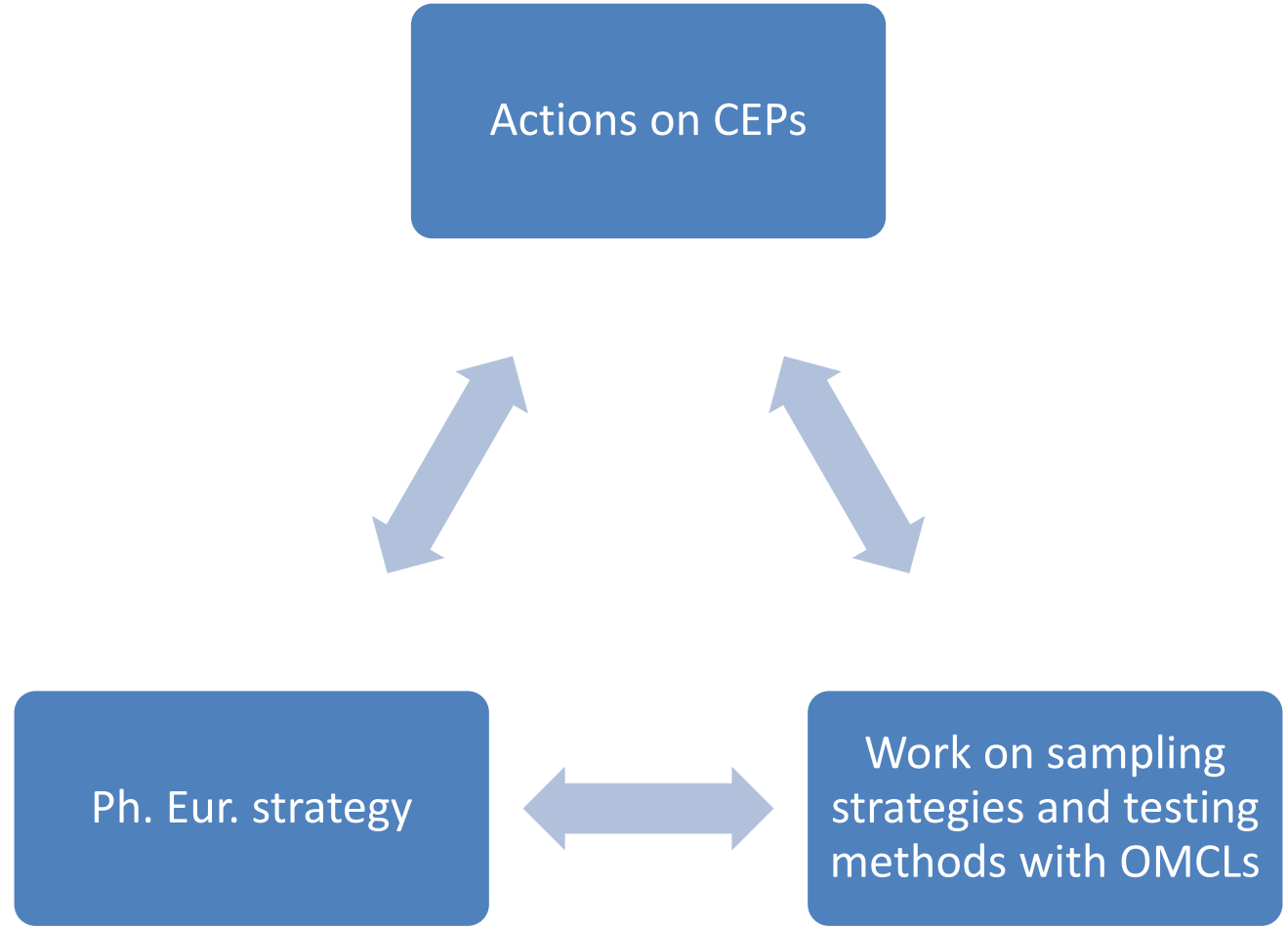
EDQM listed following APIs with possible NDMA

European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

Abacavir	Doxylamine	Cefotetan
Alfentanil	Ergometrine	Cefotiam
Aminopyrimidine	Erythromycin	Cefoxitin
Amitriptyline	Etomidate	Cefpiramide
Cefamandole	Imipramine	Chloramphenicol
Cefazolin	Methapyrilene	Chlorpromazine
Cefmenoxime	Metronidazole	Cliostazol
Cefonicid	Noscapine	Dalteparin
Cefoperazone	Oxytetracycline	Diphenhydramine
Pregabalin	Zanamivir	Sulbactum
Promazine	Sodium Lauryl Sarcosinate	Tetracycline
Propoxyphene	Trimipramine	Metformin[#]

EDQM Update on Valsartan incident and lesson learned, Ms H Brugeura-4th Indian Pharmaceutical forum Feb 2019 accessed 0n 02-12-2019 [#]Dec 2019 by US FDA

Steps Taken By EDQM



Steps Taken By EDQM

- Contacting all CEP holders concerned to obtain the relevant information;
- Undertaking a major re-assessment of relevant CEP dossiers, and taking the necessary action (e.g. revisions of CEPs, suspension of CEPs when the detected nitrosamine content is above the commonly agreed temporary limits in the EU);
- Extending the exercise, which started with sartans with a tetrazole ring, to ranitidine HCl and subsequently to all synthesised APIs;
- Conducting GMP inspections of manufacturing sites for the APIs concerned;

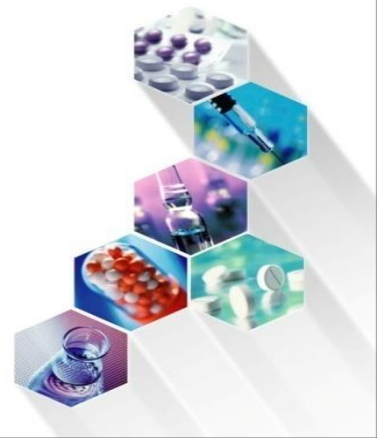
Continued…

https://www.edqm.eu/en/edqms-response-nitrosamine-contamination

Steps Taken By EDQM

- Revising relevant European Pharmacopoeia (Ph. Eur.) monographs to add limits for N-nitrosamine impurities, an important part of ensuring the continuity of the supply of medicines for the benefit of patients in Europe;
- Elaborating a general chapter providing analytical procedures to control the relevant N-nitrosamine impurities;
- Working with its network of Official Medicines Control Laboratories (OMCLs) to co-ordinate sampling and testing and to ensure that analytical test procedures for determination of nitrosamines are developed and made available to stakeholders.;
- Regularly updating all stakeholders concerned, from national authorities to manufacturers, on the state of the works and on initiatives taken.

https://www.edqm.eu/en/edqms-response-nitrosamine-contamination



EMA Directives

Steps companies should take

- Evaluate possibility of nitrosamines being present in every concerned medicine within 6 months
- Prioritise evaluations, starting with medicines more likely to be at risk of containing nitrosamines
- Take into account findings from CHMP’s review of sartans
- Notify authorities of outcome of risk evaluations
- Test products at risk of containing any nitrosamines
- Immediately report detection of nitrosamines to authorities
- Apply for necessary changes to marketing authorisations to address nitrosamine risk
- Complete all steps within 3 years, prioritising high risk products

Response of International Agencies on NDMA, in Ranitidine

FDA U.S. FOOD & DRUG ADMINISTRATION	Advised manufacturers to test products for impurity
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	No recall from any agency, unless NDMA found to be above limits
CENTRAL DRUGS STANDARD CONTROL ORGANISATION CDSCO CDSCO INDIA	Manufacturers to verify their products and take appropriate measures to ensure patient safety

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

Hyperlinks

US-FDA

- https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications
- https://www.fda.gov/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan
- https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
- https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin

EDQM

- https://www.edqm.eu/en/edqms-response-nitrosamine-contamination
- https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities

WHO

- https://www.who.int/medicines/publications/drugalerts/InformationNote_Nitrosamine-impurities/en

DCG(I)

- Letter

DCGI Letter

NDMA formation in medicines' is

Process driven & **not Molecule related**

- If found in medicines, some correctable measures are:
  - ✓ Use of different solvents
  - ✓ Adopting order of steps to avoid formation
  - ✓ Control measures in raw materials

EDQM Update on Valsartan incident and lesson learned, Ms H Brugeura-4th Indian Pharmaceutical forum Feb 2019

What is the risk of taking a drug that contains nitrosamines?

- FDA does not expect nitrosamines to cause harm when ingested at low levels. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines at, or below, the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

Facts

Why are some drugs being recalled due to a potential nitrosamine impurity while others are not?

- FDA, in collaboration with regulatory counterparts around the world, has set internationally-recognized acceptable daily intake limits for nitrosamines. Nitrosamines below this level are acceptable in drugs. If drugs contain levels of nitrosamines above the acceptable daily intake limit, FDA recommends these drugs be recalled by the manufacturer.
- Some manufacturers have recalled certain drugs as a precautionary measure, while others have been recalled after testing positive for nitrosamine levels above the acceptable daily intake limits. Information about drugs that have been recalled due to potential nitrosamine impurities can be found on the FDA recalls webpage.

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

Analytical Challenges

- Method Development & Standardisation
- Time consuming and costly
- Outsourse
- Sensitivity – LOD LOQ
- LCMS / LCHRMS – Not widely available

Industry Expectations

- Adopt risk based approach as per ICH Quality Risk Management Q9.
- Evaluate possibility of NDMA present in API.
- Focus on obtaining APIs with possibility of no NDMA or well within acceptable limit of NDMA
- Time frame of 6 months is given for the risk evaluation.
- Based on the outcomes of the risk evaluations further studies to be taken.
- Time frame of 3 years for completion of all related activities.
- Determine appropriate method analysis and ensure validated analytical methods are used.

Industry Expectations

- Infrastructure development for analysis of nitrosamines in the laboratories of:
  - API manufacturers
  - Formulation manufacturers
  - Government Laboratories
  - Accredited Laboratories.
- Awareness and education campaign to be taken by industrial association in consultation with regulatory authorities, so as to disseminate right information.
- Regulatory action, if any, to be in force from prospective effect and not retrospective.
- Similar approach to be taken for nitrosamines present in food and water supplies.

Thank you !!!

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