Nitrosamine Impurities - Current Status and Expectations

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J. B. Chemicals & Pharmaceuticals Ltd.
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News worldwide

NDMA
India's drug regulator flags antacid Ranitidine use in cancer medicines

More blood pressure medicines recalled

FDA expands blood pressure medicines recall

Zantac Has Low Levels of a Cancer-Causing Chemical, the F.D.A. Says

Causing concerns

Ranitidine is the same drug found in the blood pressure medicines recalled.
Genesis of NDMA Issue

• Medicine Regulatory Authorities first became aware of the presence of the nitrosamine impurity, N-nitrosodimethylamine (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 2019 a 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.

Impacted Molecules

- Valsartan
- Candesartan cilexetil
- Irbesartan
- Olmesartan medoxomil
- Losartan potassium
- Metformin
- Ranitidine
- Nizatidine
- Potassium
- Ranitidine
- Nizatidine
- Metformin
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.

![Image of Nitrosamine Structures]

<table>
<thead>
<tr>
<th>Group</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Carcinogenic to humans</td>
</tr>
<tr>
<td>Group 2A</td>
<td>Probably carcinogenic to humans</td>
</tr>
<tr>
<td>Group 2B</td>
<td>Possibly carcinogenic to humans</td>
</tr>
<tr>
<td>Group 3</td>
<td>Not classifiable as to its carcinogenicity to humans</td>
</tr>
</tbody>
</table>

Figure 1: N’- nitrosodimethylamine (NDMA)  
Figure 2: N’-nitrosodiethylamine (NDEA)

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 NMB are considered by international regulators to exhibit a toxicological profile like NDMA and NDEA.
Toxicity

Interim allowable daily intake limits

<table>
<thead>
<tr>
<th>Impurity name</th>
<th>Chemical name</th>
<th>Allowable Daily Intake (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDMA⁶</td>
<td>N-nitrosodimethylamine</td>
<td>96.0 ng/day</td>
</tr>
<tr>
<td>NDEA⁵</td>
<td>N-Nitrosodiethyamine</td>
<td>26.5 ng/day</td>
</tr>
<tr>
<td>N MBA³</td>
<td>N-Nitroso-N-methyl-4-aminobutyric acid</td>
<td>96.0 ng/day</td>
</tr>
<tr>
<td>DIPNA⁷</td>
<td>N-nitrosodiisopropylamine</td>
<td>26.5 ng/day</td>
</tr>
<tr>
<td>EIPNA⁷</td>
<td>N-nitrosoethylisopropylamine</td>
<td>26.5 ng/day</td>
</tr>
</tbody>
</table>

6 February 2019, EMA/44960/2019: Sartan medicines: companies to review manufacturing processes to avoid presence of nitrosamine impurities.

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:

\[
\text{Less-than-lifetime AI} = 1.5 \text{ µg} \times (365 \text{ days} \times 70 \text{ years lifetime} = 25,550) \\
\text{Total number of treatment days}
\]

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.
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

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

<table>
<thead>
<tr>
<th>Ranitidine Dosage*</th>
<th>Acceptable limits (ppm) of NDMA in relation to years of Ranitidine use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>300 mg</td>
<td>22.4 ppm</td>
</tr>
<tr>
<td>600 mg</td>
<td>11.2 ppm</td>
</tr>
</tbody>
</table>

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

Temporary limits for NDMA and NDEA impurities

<table>
<thead>
<tr>
<th>Active substance (max daily dose)</th>
<th>NDMA</th>
<th>NDEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum daily intake (ng)</td>
<td>Limit (ppm)</td>
</tr>
<tr>
<td>Candesartan (32 mg)</td>
<td>96.0</td>
<td>3.000</td>
</tr>
<tr>
<td>Irbesartan (300 mg)</td>
<td>96.0</td>
<td>0.320</td>
</tr>
<tr>
<td>Losartan (150 mg)</td>
<td>96.0</td>
<td>0.640</td>
</tr>
<tr>
<td>Olmesartan (40 mg)</td>
<td>96.0</td>
<td>2.400</td>
</tr>
<tr>
<td>Valsartan (320 mg)</td>
<td>96.0</td>
<td>0.300</td>
</tr>
</tbody>
</table>

# Nizatidine and Metformin

<table>
<thead>
<tr>
<th>Active substance (max daily dose)</th>
<th>Maximum daily intake (ng)</th>
<th>Limit (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nizatidine (300 mg)</td>
<td>96</td>
<td>0.319</td>
</tr>
<tr>
<td>Metformin Immediate-release tablets or oral solution (2550 mg)</td>
<td>96</td>
<td>0.0376</td>
</tr>
<tr>
<td>Metformin Extended –Release Tablets (2000 mg)</td>
<td>96</td>
<td>0.0479</td>
</tr>
</tbody>
</table>
NDMA & Water

• The EPA’s Integrated Risk Information System (IRIS) estimates that a NDMA concentration of $7 \times 10^{-4}$ 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 $6 \times 10^{-4}$μg/L to $2.4 \times 10^{-2}$μg/L.25
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.\(^{26}\)

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.

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 antagonists). 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.

EDQM listed following APIs with possible NDMA

<table>
<thead>
<tr>
<th>Abacavir</th>
<th>Doxylamine</th>
<th>Cefotetan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Ergometrine</td>
<td>Cefotiam</td>
</tr>
<tr>
<td>Aminopyrimidine</td>
<td>Erythromycin</td>
<td>Cefoxitin</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Etomidine</td>
<td>Cefpiramide</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>Imipramine</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Methapyrilene</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td>Cefmenoxime</td>
<td>Metronidazole</td>
<td>Cliostazol</td>
</tr>
<tr>
<td>Cefonicid</td>
<td>Noscapine</td>
<td>Dalteparin</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>Oxytetracycline</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Zanamivir</td>
<td>Sulbactum</td>
</tr>
<tr>
<td>Promazine</td>
<td>Sodium Lauryl Sarcosinate</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Trimipramine</td>
<td>Metformin#</td>
</tr>
</tbody>
</table>

EDQM Update on Valsartan incident and lesson learned, Ms H Brugeura-4th Indian Pharmaceutical forum Feb 2019 accessed On 02-12-2019  #Dec 2019 by US FDA
Steps Taken By EDQM

Actions on CEPs

Ph. Eur. strategy

Work on sampling strategies and testing methods with OMCLs
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…


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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.


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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

- Advised manufacturers to test products for impurity
- No recall from any agency, unless NDMA found to be above limits
- Manufacturers to verify their products and take appropriate measures to ensure patient safety

## Hyperlinks

### US-FDA

### EDQM

### WHO

### DCG(I)

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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
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.
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.
Analytical Challenges

- Method Development & Standardisation
- Time consuming and costly
- Outsource
- 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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