USP <1469> Nitrosamines Impurities
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Naiffer has more than 20+ years of pharmaceutical industry experience. In his 11 years tenure with USP, he has served several roles: Lead scientist in performance testing compendial reference standards development for dissolution, Manager in charge of compendial support and training for LATAM region, as well as commercial operations. He is also USP Education certified instructor. Most recently, Naiffer joined USP’s Scientific Affair performance cell where he leads scientific technical outreach and engagement for LATAM & US region. His combined pharmaceutical expertise includes Late-stage analytical development, salt and polymorph selection, Development of Dissolution methods, and impurity analytical strategy. Naiffer also serve as member of USP’s Nitrosamine Steering Committee, community host to ‘Nitrosamine Exchange’, a knowledge community in All-things Nitrosamine, and Subject matter expert in Dissolution.
Dr. Amanda Guiraldelli graduated in pharmacy biochemistry and holds a Ph.D. in analytical chemistry from the University of São Paulo, Brazil (plant metabolomics by UHPLC-HRMS, GC-MS and 1H NMR and AQBd principles). Currently, Dr. Amanda Guiraldelli is scientific affairs manager at U.S. Pharmacopeia and visiting professor at the Federal University of Campinas (Unicamp) at the Institute of Chemistry mentoring students in research projects for AQBd. Amanda specializes in chromatography and mass spectrometry.

Dr. Guiraldelli has over 12 years of experience in research and development areas with strong experience in analytical procedure development and validation, AQBd, stability studies of drug products, analysis of pharmaceutical impurities and degradation products, chemometrics, omics science and characterization of compendial standards. Previously, Dr. Guiraldelli worked as senior scientist at the USP reference standard laboratory for 8 years with characterization of compendial standards. She also worked as a research and development scientist in the pharmaceutical industry in Brazil and as a visiting scientist at Technische Universität Berlin in Germany where she worked on proteins characterization by LC-HRMS. Dr. Guiraldelli worked at Leiden University in Netherlands (Center for Proteomics and Metabolomics) on method development for characterization of biological samples by UHPLC-HRMS. She is also a member of the North Jersey Chromatography Group (NJCG) - American Chemical Society (ACS).
This is the QR Code for the questions in Conference IO

Feel free to place in this slide the best way you want!

Replicate this slide in the other modules
What is your main area of responsibility or activities to which you contribute at work?

- Research and Development
- QC Managers
- QC Scientists (DS, DP)
- Excipient Manufacturer
- Research Scientist
- QA staff who authorize drug product release
- Other
Poll: What is your main area of responsibility or activities to which you contribute at work?
Welcome

Participant Expectations

- What do you hope to get out of this course? What are your expectations?
Poll: What do you hope to get out of this course? What are your expectations?
About USP
Our Mission

To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods.
200 years of building trust in medicines, dietary supplements and foods.
Collaborating to Achieve Our Mission

Partnering with stakeholders, including industry, practitioners, and academia

Partnering with our expert volunteers and Vaccine Advisory Group

Partnering with global regulators, including U.S. and international food and drug authorities

Access to quality vaccines and therapeutics

USP Education
Leaders Volunteer Their Expertise to Develop Standards with USP Staff

- **981 Scientific Experts**
- **43%**
- **20%**
- **37%**

**981 Scientific Experts—Volunteers and Government Liaisons**

- 428 EC Members
- 362 EP-Only Members
- 191 Government Liaisons
USP–Public Standards

USP standards used in over 150 countries

Go to https://online.usppf.com/usppf to access the PF
Course Outline

Modules

- Module 1: Nitrosamines Overview
- Module 2: Nitrosamines Risk Assessment
- Module 3: Nitrosamines Test Methods
- Module 4: USP <1469>: Analytical Procedures
Course Objectives

Upon completion of this course, you will be able to:

- Describe the background, scope and approach of *USP <1469>* Nitrosamine Impurities and applicable regulatory guidelines
- Explain pathways and sources of nitrosamine formation along with risk assessment tools and a high-level process flow to develop control strategies
- Describe how to select the appropriate analytical procedures based on test method performance characteristics for nitrosamine methods
Upon completion of this course, you will be able to:

- Discuss the proper use and handling of the *USP* reference standard in the respective analytical procedures.
- Identify factors which impact sensitivity and selectivity of methods.
- Summarize key considerations, challenges and method conditions along with sample and standard preparation of the four test methods described in *USP* <1469>. 
Module 1:
Nitrosamines Overview
Module 1: Introduction

Nitrosamines Overview
“The USP launched an initiative to address the nitrosamine crisis by proposing a new general chapter that outlines a set of analytical methods that manufacturers can use to demonstrate their products are free from unsafe levels of these potential carcinogens. The chapter is aligned with the FDA’s guidance on nitrosamine impurities”.

Pink Sheet Informa Pharma Intelligence
The USP has proposed guidance on how to test active pharmaceutical ingredients and drug products.

The USP general chapter was proposed the day the US Food and Drug Administration issued guidance on controlling nitrosamines in all drug products.
The USP guidance was issued in response to the 2018 discovery of carcinogenic nitrosamines in active pharmaceutical ingredients for certain blood pressure medicines known as angiotensin II receptor blockers or sartans.
Module Outline

Topics

- History of how nitrosamines evolved
- Applicable regulatory guidelines related to nitrosamines
- Background and objective of the chapter
- Overview of approach described in the *USP* chapter
Module Outline

Topics

- Section 1. Regulatory Landscape
- Section 2. Introduction to USP <1469> Nitrosamine Impurities
Section 1—Current Regulatory Guidelines

Topics

- Emergence of nitrosamines as public health concern and drug products recall
- Introduction to ICH M7
- Applicable regulatory guidelines: FDA, EMA, EDQM, WHO
History of Nitrosamine Impurities

Emerged as a public health concern in the summer 2018 due to:

- Harmful levels of nitrosamine impurity, N-nitrosodimethylamine (NDMA) observed in valsartan-containing products.
- Nitrosamine compounds are potent genotoxic agents in several animal species
- Some are classified as probable or possible human carcinogens by the International Agency for Research on Cancer (IARC).
History of Nitrosamines
**History of Nitrosamine Impurities**

**ARBs Regulatory Action (USFDA and EDQM)**

### July-2018
- **FDA**
  - NDMA identified in one valsartan API producer (ZHP-China) by voluntary reporting
  - Valsartan recall initiated due to the presence of NDMA
  - Proposed 96 ng NDMA is considered reasonably safe
- **EDQM**
  - EMA alerted the EDQM and suspended the valsartan CEP for Zhejiang Huahai Pharmaceuticals (ZHP)
  - EDQM initiated the review for manufacturing process of other manufacturers

### August-2018
- **EDQM**
  - EDQM continued the investigation for NDMA impurity in valsartan APIs
  - Based on the EDQM test results and the response received from the manufacturers, EDQM extended the suspension to a few more CEPs.
  - EDQM in coordination with OMCLs is working on developing test procedures to control these impurities.

### September-2018
- **FDA**
  - Tested and expanded the recall to other manufacturers’ valsartan products.
  - NDEA impurity found in one valsartan containing product
- **EDQM**
  - Released test results for the sartan products.
  - New GC-MS single quad method is issued
  - GC-MS/MS triple quad method is issued

### October-2018
- **FDA**
  - Released test results for the sartan products.
  - New GC-MS single quad method is issued
  - GC-MS/MS triple quad method is issued
- **EDQM**
  - EDQM released test method for NDMA and NDEA in sartans by using UHPLC-APCI-MS/MS
  - EDQM continuing the CEPs review for sartans

**USP Education**

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History of Nitrosamine Impurities

**ARBs Regulatory Action (USFDA and EDQM)**

### November to December-2018
- **FDA**
  - FDA has updated lists of valsartan products under recall and valsartan products not under recall.
  - FDA posted Q&A for healthcare professionals and patients.
  - FDA recalled Torrent and Sandoz’s losartan product and Mylan and Teva’s valsartan products.
  - FDA published combined head space and combined direct injection GC-MS methods with LOD and LOQ values.
  - FDA proposed interim limits of nitrosamines for ARBs.

### January to May-2019
- **FDA**
  - FDA continued the testing and recall of nitrosamine impurities containing sartan products and updating the test results.
- **EDQM**
  - EDQM suspended CEPs of ZHP for Irbesartan and Losartan.
  - EDQM proposed temporary limits for NDMA and NDEA impurities in 5 sartan products.
  - OCML proposed test method for NMBA by using LC-MS.

### June to December-2019
- **FDA**
  - FDA continued the testing and recall of nitrosamine impurities containing sartan products and updating the test results.
- **EDQM**
  - EDQM created a new web page for nitrosamine contamination.
  - The general chapter proposes three procedures and are validated as limit tests with a target concentration of 30 ppb, for given active substances.
  - From 1 October 2020, applicants and CEP holders should systematically include a risk assessment regarding the potential formation of nitrosamines in any new CEP application.

### January-2020 to-date
- **FDA**
  - FDA continues the testing and recall of nitrosamine impurities containing sartan products and updating the test results.
- **EDQM**
  - European Commission has issued its final legally binding decision for medicines containing valsartan, candesartan, irbesartan, losartan and olmesartan. It defines a transition period of 2 years.
  - After the transition period (from April 2021) sartans with a tetrazole ring must not contain quantifiable levels of NDMA and NDEA (corresponding to less than 0.03 ppm).
History of Nitrosamine Impurities

Ranitidine and Nizatidine Regulatory Action (USFDA and EDQM)

**September to October-2019**
- **FDA**
  - FDA found NDMA impurity in ranitidine.
  - FDA has set the acceptable daily intake limit for NDMA at 0.096 micrograms or 0.32 ppm for ranitidine.
  - FDA initiated recall and advised companies to recall their ranitidine if testing shows levels of NDMA above the acceptable daily intake.
- **EDQM**
  - In September 2019, EDQM was informed about the presence of low levels of NDMA in ranitidineHCI and the CEPs for ranitidine HCI were suspended until more information on the mechanisms triggering the formation of NDMA in this substance becomes available.

**November to December-2019**
- **FDA**
  - FDA updated laboratory test results for ranitidine and nizatidine.
  - FDA has set the acceptable daily intake limit for NDMA at 0.096 micrograms or 0.32 ppm for ranitidine.
  - FDA identified heating the sample produced more NDMA—hence LC-MS procedure was recommended.
  - FDA released another LC-MS method with widely used triple quad technology.
- **EDQM**
  - Amneal Pharmaceuticals voluntarily recalled nizatidine oral solution (15 mg/mL) from the market.
  - FDA advised companies to recall their nizatidine if testing shows levels of NDMA above the acceptable daily intake limit (96 nanograms per day).

**January-2020**
- **FDA**
  - The agency has determined that the impurity in some ranitidine products increases over time and when stored at higher than room temperatures and may result in consumer exposure to unacceptable levels of this impurity.
- **EDQM**
  - EMA’s human medicines committee (CHMP) recommended the suspension of all ranitidine medicines in the EU due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA).

**April-2020 to-date**
- **FDA**
  - FDA requests removal of all ranitidine products (Zantac) from the market.
History of Nitrosamine Impurities

Metformin Regulatory Action (USFDA and EDQM)

**FDA**
- FDA updated laboratory test results for metformin.
- FDA published LC-HRMS method for the detection of NDMA in metformin drug substance and drug products.

**FDA**
- LC-ESI-HRMS method for the determination of MNP in rifampin and CPNP in rifapentine drug substance and drug product.

**DEC-2019**
- The FDA is aware that some metformin diabetes medicines in other countries were reported to have low levels of NDMA.
- The acceptable daily intake limit for NDMA in the U.S. is 96 nanograms.
- FDA initiated testing for NDMA in metformin.

**JAN-2020**
- In December 2019, EDQM was informed about the presence of traces of NDMA in metformin HCl and contacted all holders of metformin CEPs and requested them to address this issue. At this stage there is no indication that metformin HCl drug substance is affected.

**Jul-2020**
- FDA recalled several extended release (ER) metformin tablets and published the list including details about metformin products. Bayshore Pharmaceuticals voluntarily recalled two lots of extended release (ER) metformin (one lot of 750 mg tablets and one lot of 500 mg tablets).

**Sep-2020**
- FDA published LC-ESI-HRMS method for the determination of MNP in rifampin and CPNP in rifapentine drug substance and drug product.

**Cont’d.**
The FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities

- Mitigate or avoid shortages and to help ensure patients have access to these necessary medicines, FDA will not object to certain manufacturers temporarily distributing rifampin containing 1-methyl-4-nitrosopiperazine (MNP) or rifapentine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP) above the acceptable intake limits until they can reduce or eliminate the impurities.

Recent FDA post on Nitrosamines in Rifapentine and Rifampin

Example

- The FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities
  - The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine. The agency will not object to certain manufacturers temporarily distributing rifampin containing MNP below 5 parts per million (ppm). The agency also will not object to certain manufacturers temporarily distributing rifapentine containing CPNP below 14 ppm. FDA will not object to these higher exposures to maintain patient access to these life-saving medications.

Introduction to ICH M7
Mutagens and Carcinogens

- Mutagens are any compounds that have potential to generate mutations, but not necessarily can cause cancer.
- Carcinogens are any compounds that have potential to generate cancer.
- Most mutagens can be carcinogens and most carcinogens can be mutagens but, it is not necessary all mutagens are carcinogens or vice versa.

Cancer

- Uncontrolled growth of abnormal cells in the body.
Compounds that cause a mutation (change) in the DNA of a cell. DNA changes caused by mutagens may harm cells and cause certain diseases, such as cancer.

## Introduction to ICH M7 Guidelines

<table>
<thead>
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Why develop a control strategy?
Introduction to ICH M7 Guidelines

Guidelines

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✓ Provides recommendations for the assessment and control of mutagenic impurities reasonably expected to reside in final drug substances or products.

Why develop a control strategy?

“Where a potential risk has been identified for an impurity, an appropriate control strategy leveraging process understanding and/or analytical controls should be developed to ensure that the mutagenic impurity is at or below the acceptable cancer risk level.”
Introduction to ICH M7 Guidelines

Hazard Assessment

- Actual and potential impurities are assessed for mutagenic hazards
- Known mutagen – Conduct literature and database searches
- A computational toxicology assessment should be performed using Quantitative Structure-Activity Relationship [(Q)SAR] methodologies that predict the outcome of a bacterial mutagenicity assay (applies to the structure of unknown mutagenicity)
- Apply expert knowledge to review outcomes, if warranted
- Absence of structural alert is sufficient to conclude that impurity is of no concern, and no further testing is recommended
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How should a computational toxicology assessment be conducted?
Introduction to ICH M7 Guidelines

Hazard Assessment

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How should a computational toxicology assessment be conducted?

1. Methodology I: Expert-rule based
2. Methodology II: Statistical based
# Introduction to ICH M7 Guidelines: Classification of Mutagens

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Known mutagenic carcinogens</td>
<td>Identify and control at compound-specific limits (carcinogenic data–derived doses)</td>
</tr>
<tr>
<td>2.</td>
<td>Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*)</td>
<td>Control at appropriate TTC** level (consider human use conditions and LTL where appropriate)</td>
</tr>
<tr>
<td>3.</td>
<td>Structural alert unrelated to drug substance</td>
<td>Conduct follow-up study or control at TTC levels</td>
</tr>
<tr>
<td>4.</td>
<td>Structural alert related to tested drug substance (e.g., process impurities)</td>
<td>Treat as nonmutagenic</td>
</tr>
<tr>
<td>5.</td>
<td>No structural alerts or sufficient data to demonstrate lack of carcinogenicity or mutagenicity</td>
<td>Treat as nonmutagenic</td>
</tr>
</tbody>
</table>

* Or other relevant positive mutagenicity data indicative of DNA-reactivity-related induction of gene mutations (e.g., positive findings in in vivo gene mutation studies)

** Threshold of toxicological concern
TTC-based Acceptable Intakes:

- A threshold of toxicological concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects.
- A value of 1.5 μg/day, corresponding to a theoretical $10^{-5}$ excess lifetime risk of cancer, can be justified.
- A TTC-based approach is a conservative approach for most mutagens (except cohort of concern) for lifetime use (>10 years) for all routes of exposure.
• Acceptable Intakes Based on Compound Specific Risk Assessments:

  – Mutagenic Impurities with Positive Carcinogenicity Data
    • Carcinogenicity data should be used when available to derive specific limits:
      • Linear-derived and threshold approaches can be applied with justification.
      • Read-across or class-specific approaches can be applied with justification.

Introduction to ICH M7 Guidelines: Risk Characterization
Acceptable Intakes Based on Compound Specific Risk Assessments: Cont’d

- Mutagenic Impurities with Evidence for a Practical Threshold:
  - The regulatory approach to such compounds can be based on the identification of a no-observed effect level (NOEL) and use of uncertainty factors (ICH Q3C(R5), Ref. 7) to calculate a permissible daily exposure (PDE) when data are available.
Introduction to ICH M7 Guidelines: Risk Characterization

- **Acceptable Intakes in Relation to LTL Exposure**
  - Acceptable Intakes for an Individual Impurity

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>&lt; 1 month</th>
<th>&gt; 1 – 12 months</th>
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<tbody>
<tr>
<td>Acceptable intake (µg/day)</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- **Acceptable Intakes for Multiple Impurities**
Acceptable Intakes in Relation to LTL Exposure

- Acceptable Intakes for an Individual Impurity

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Acceptable Intakes for Multiple Impurities

- When there are two Class 2 or Class 3 impurities, individual limits apply.
- When there are three or more Class 2 or Class 3 impurities specified on the drug substance specification, total mutagenic impurities should be limited as described below for clinical development and marketed products. For combination products each active ingredient should be regulated separately.

<table>
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<tbody>
<tr>
<td>Total Daily intake (µg/day)</td>
<td>120</td>
<td>60</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>
Higher acceptable intakes may be justified when human exposure to the impurity will be much greater from other sources e.g., food.

Case-by-case exceptions to the use of the appropriate acceptable intake can be justified in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives.

Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkyl-azoxy structures. Intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk.
Summary

- History of Nitrosamines
- ICH M7 Guidelines
- Risk Characterization
Regulatory Guidelines
The FDA published ‘Control of Nitrosamine Impurities in Human Drugs’, guidance for industry on September 1, 2020.

- Guidance briefly covers:
  - Recommendations to API and DP manufacturers
  - Managing the drug supply
  - Reporting changes to FDA within recommended timelines for Risk Assessment, Confirmatory Testing and Submission of Required Changes

The FDA published Revision 1 of “Control of Nitrosamine Impurities in Human Drugs”, guidance for industry on February 1, 2021.

- Guidance was revised to extend recommended implementation timelines of Risk Assessment, Confirmatory Testing and Submission of Required Changes to FDA

Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs
FDA recommends the following acceptable intake (AI) limits for the nitrosamine impurities for NDMA, NDEA, NMBA, NMPA, NIPEA and NDIPA in drug products

Table 1. AI Limits

<table>
<thead>
<tr>
<th>Nitrosamine</th>
<th>AI Limit (ng/day)</th>
</tr>
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<tbody>
<tr>
<td>NDMA</td>
<td>96</td>
</tr>
<tr>
<td>NDEA</td>
<td>26.5</td>
</tr>
<tr>
<td>NMBA</td>
<td>96</td>
</tr>
<tr>
<td>NMPA</td>
<td>26.5</td>
</tr>
<tr>
<td>NIPEA</td>
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Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs
The AI limit is a daily exposure to a compound such as NDMA, NDEA, NMBA, NMPA, NIPEA, or NDIPA that approximates a 1:100,000 cancer risk after 70 years of exposure.

The extrapolation to the excess risk level for cancer is performed by linear back extrapolation to the dose theoretically causing a 1:100,000 risk by dividing the TD50 by 50,000 (50% or 0.5 x 100,000). For a person with a bodyweight of 50 kg the AI level is then calculated as AI = 50 x (TD50/50,000).

NDMA: Example of how the FDA applied ICH M7(R1) to set a limit.

- TD50 values for NDMA are 0.0959 mg/kg/day (rat, based on Peto et al.²)
- TD50 values for NDMA are 0.189 mg/kg/day (mouse) according to the CPDB³.
- For the AI calculation, the lower (more conservative) value of the rat is used.
- The resulting AI associated with a 1 in 100,000 cancer risk over 70 years of exposure is calculated as follows:
  - AI value: \( (0.0959 \text{ mg/kg/day} / 50,000) \times 50 \text{ kg} = 0.0000959 \text{ mg/day NDMA or approx. 96 ng/day NDMA} \)
Asses the risk of nitrosamine impurities in APIs, marketed products and products under approved and pending applications.

Risk assessments should be conducted in a timely manner based on the prioritization of drug product:
- Maximum daily dose
- Treatment duration
- Therapeutic indication
- Number of patients treated

FDA may recommend certain products as high priority.

Manufacturers do not need to submit risk assessment documents to the FDA, but they should retain these documents so that they are available if requested.

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
Conduct confirmatory testing when there is any risk for the presence of nitrosamine impurities.

Due to the physiochemical properties of nitrosamines (low molecular weights, some volatility and high toxicity), the analytical methods for nitrosamines need to have specificity, excellent chromatographic separation, and highly sensitive detection capability.
FDA Recommendations for API and DP Manufacturers

Step 3: Reporting Changes and Updates

- Report changes implemented to prevent or reduce nitrosamine impurities in APIs and drug products to FDA. This includes submission of any drug master file (DMF), drug master file amendments and changes to approved or pending applications.
  - Amendments in accordance with 21 CFR 314.420(c) and changes to approved applications
  - Applications as required under 21 CFR 314.70 and 314.97 and for pending applications
  - Under 21 CFR 314.60 and 314.96

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
Manufacturers should prioritize the 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.

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
The above 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, the total quantity of nitrosamine impurities should not exceed 26.5 ng/day (the AI for the most potent nitrosamines) based on the maximum daily dose (MDD).

Otherwise, the manufacturer should contact the Agency for evaluation.

- Example: Drug products with an MDD of less than 880 mg/day, a recommended limit for total nitrosamines of 0.03 ppm; which is not more than 26.5 ng/day, is considered acceptable. For drug products with an MDD above 880 mg/day, the limit for total nitrosamines should be adjusted so as not to exceed the recommended limit of 26.5 ng/day).

API manufacturers should control nitrosamine level to ensure Drug Product meets these criteria.

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.

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
Generally, sensitive methods with limits of quantitation (LOQ) in the parts-per-billion (ppb) range are needed to meet the low AIs recommended for nitrosamines.

Manufacturers of APIs and drug products should use methods with LOQs at or below 0.03 ppm.

Manufacturers should establish methods for which the LOQ and limit of detection (LOD) are as low as reasonably practical for products for which the maximum daily dose is high (e.g., greater than 1 g).

If more than one nitrosamine listed in Table 1 is detected, then the analytical method should be validated for LOQs below 0.03 ppm to accurately quantify a total nitrosamine level of not more than 26.5 ng/day. For example, if the MDD is 1200 mg, the LOQ should be below 0.02 ppm.

The FDA public webpage includes validated analytical test methods recommended for detecting nitrosamine impurities in several different APIs and products.
Avoid reaction conditions that may produce nitrosamines whenever possible.

- Using bases other than secondary, tertiary, or quaternary amines (when possible).
- Using caution when the ROS involves the use of amide solvents (e.g., DMF, DMA, NMP).
- Replacing nitrites with other quenching agents for azide decomposition processes.
- Optimizing and consistently controlling the sequences of reactions, processes, and reaction conditions (such as pH, temperature, and reaction time).

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
Avoid reaction conditions that may produce nitrosamines whenever possible.

- API manufacturer should develop an appropriate control strategy (specification limits) if a nitrosamine impurity is detected above the LOQ.
- Testing of each batch on release should be conducted for APIs with an impurity detected above the LOQ (or at-risk APIs).

(Ref: https://www.fda.gov/regulatory-information/search-fdaguidancedocuments/control-nitrosamine-impurities-human-drugs)
Avoid reaction conditions that may produce nitrosamines whenever possible.

- 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.

- Any API batch found to contain levels of nitrosamine impurities above the recommended AI should not be released by the API manufacturer for distribution unless, with prior FDA agreement, the API is needed to prevent or mitigate a shortage of a drug.

(Ref: https://www.fda.gov/regulatory-information/search-fdaguidancdocuments/control-nitrosamine-impurities-human-drugs)
If any manufacturing changes or recalls are likely to lead to a disruption in the drug supply, manufacturers should immediately contact CDER’s Drug Shortage Staff at drugshortages@fda.hhs.gov;

The FDA can work with manufacturers to mitigate the risk of nitrosamine impurities in APIs and drug products while avoiding interruptions in the drug supply.
FDA Recommendations to Drug Product Manufacturers

Maintaining the Drug Supply

- Reporting changes to the FDA:
  - 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).
  - Although each DMF may contain only a single synthetic route, if a change in synthetic process is needed to avoid nitrosamine contamination and it is not possible to immediately stop using the original manufacturing process, the API manufacturer should submit both processes in the DMF and provide an estimate for the earliest feasible timeframe for the removal of the original process.

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
According to the FDA guidance, how many nitrosamines are recommended for AI limits?

A. 5
B. 8
C. 7
D. 6
Poll: According to the FDA guidance, how many nitrosamines are recommended for AI limits?
Knowledge Check 2

How many specific nitrosamines are included in EMA guidance for limits?

A. 5
B. 8
C. 7
D. 6
Poll: How many specific nitrosamines are included in EMA guidance for limits?
Recommended Timelines by The FDA

Recommended Timeline for Risk Assessment, Confirmatory Testing and Submission of Required Changes

Approved or Marketed Drug Products

Step 1: Conclude a risk assessment within 7 months from publication of this guidance (March 31, 2021).

Step 2: Confirmatory testing of drug products if risk is identified; immediately for high-risk products.

Step 3: Submission of required changes in drug applications to FDA
(The last two steps should be concluded within 3 years from the publication of this guidance: Oct. 1, 2023).

(Ref: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)
Pre-Submission Stage:

1. Conduct a risk assessment for nitrosamine impurities in APIs and proposed drug products,

2. Conduct confirmatory testing as needed prior to submission of an original application.

Applications Pending with FDA:

1. Conduct the risk assessment expeditiously

2. Inform FDA if confirmatory testing finds nitrosamine levels above the AI limit.

3. If nitrosamine levels above LOQ and below AI, then amendment with control strategy (including specification).
Nitrosamine Impurities in Human Medicinal Products

EMA Assessment Report

- Quality and Safety aspects:
  - Quality:
    - N-nitrosamine formation routes and classification of reaction types
    - Consideration for analytical method development to identify and quantify N-nitrosamines in APIs and finished products
  - Safety:
    - Considerations for calculating risk for exposed patients in case of detection of N-nitrosamines in medicinal product(s)
    - Methodology for defining limits for N-nitrosamines
    - Consideration on epidemiological studies.
Nitrosamine Impurities in Human Medicinal Products

EMA Assessment Report

Limits established for some specific N-nitrosamines

<table>
<thead>
<tr>
<th>N-Nitrosamine (CAS number)</th>
<th>ng/day***</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDMA* (62-75-9)</td>
<td>96.0</td>
</tr>
<tr>
<td>NDEA* (55-18-5)</td>
<td>26.5</td>
</tr>
<tr>
<td>EIPNA** (16339-04-1)</td>
<td>26.5</td>
</tr>
<tr>
<td>DIPNA** (601-77-4)</td>
<td>26.5</td>
</tr>
<tr>
<td>NMBA** (61445-55-4)</td>
<td>96.0</td>
</tr>
<tr>
<td>MeNP** (16339-07-4)</td>
<td>26.5</td>
</tr>
<tr>
<td>NDBA** (924-16-3)</td>
<td>26.5</td>
</tr>
<tr>
<td>NMPA* (614-00-6)</td>
<td>34.3</td>
</tr>
</tbody>
</table>

These limits are acceptable only if a FP contains a single N-nitrosamine

- * Limit calculated on the basis of harmonic mean TD50 derived from carcinogenic potency database (CPDB)
- ** Limit derived using structure-activity-relationship (SAR)/read-across approach
- *** The conversion to a specification limit in ppm for a particular medical product is calculated by dividing the respective above limit (ng) by the maximum daily dose (mg) of a given product as reflected in the SmPC
Limits for individual nitrosamines, for multiple N-nitrosamines and less than lifetime (LTL) approach

- 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, NPIP.

- Limits for individual N-nitrosamines should be set using the compound-specific ICH M7(R1) approach considering a lifetime daily exposure.
- For individual nitrosamines with sufficient animal carcinogenicity data, limits can be calculated using the risk-based approach

- In case more than one N-nitrosamine occurs in manufacture it may be acceptable to limit the sum of N-nitrosamines to the limit of the most potent one found and methodology described in ICH M7(R1) with TD50 as the point of departure (POD).
- In toxicology, POD is defined as the point on a toxicological dose-response curve established from experimental data or observational data generally corresponding to an estimated low effect level or no effect level.
Nitrosamine Impurities in Human Medicinal Products

EMA Assessment Report

Limits for multiple N-nitrosamines:

If more than one N-nitrosamine is identified in a given finished product (or its API), it must be ensured that the total risk level of the sum of all detected N-nitrosamines does not exceed 1 in 100,000 life-time risk. An alternative approach where the sum of all detected N-nitrosamines does not exceed the limit of the most potent N-nitrosamine identified may also be used.

Acceptability of limits higher than AI (LTL approach):

When a single N-nitrosamine cannot be kept below the established limit or the 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 “less-than lifetime” (LTL) concept in ICH M7(R1) may be considered by the competent authorities for the range of a temporarily acceptable exposure until further measures can be implemented to reduce the contaminant at or below the limits.
In-sufficient substance specific toxicity data:

- When N-nitrosamines are identified with insufficient substance specific data to derive a substance specific limit for lifetime exposure as recommended in ICH M7(R1), **a class specific TTC for nitrosamines of 18 ng/d** can be used as default option.
  - This TTC has been derived from the Lhasa carcinogenic potency database and is considered a conservative and acceptable approach.

- If a MAH intends using a higher limit than 18 ng/day, an approach based on **structure-activity-relationship (SAR)** considerations is acceptable. The approach taken needs to be duly justified by the applicant/MAH.
Products intended for advanced cancer:

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).
### Recommendations for sensitivity of analytical methods:

- The analytical methods need to be sufficiently sensitive in order to adequately detect and quantify trace levels of nitrosamine impurities. The following principles apply:
  - For routine control, the LoQ should be ≤ of the acceptable limit
  - To justify skip testing, the LoQ should be ≤ 30% of the acceptable limit
  - To justify omission of specification, the LoQ should be ≤ 10% of the acceptable limit
- Different analytical methods may be used for determination of multiple nitrosamines.
- If the same analytical method is used for multiple nitrosamines, the selectivity of the method should be demonstrated for each nitrosamine.

Recommended Timeline for Risk Evaluation, Confirmatory Testing and Application of Necessary Changes

## Approved or Marketed Drug Products

### Step 1: Conduct a risk evaluation to identify active substances and finished products at risk of N-nitrosamine formation or cross-contamination and report the outcome by:

- 31 March 2021 for products containing chemically synthesized APIs
- 1 July 2021 for products containing biological APIs

### 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: **Update marketing authorizations**: Apply for any necessary **changes to the manufacturing process** resulting from this review by requesting a **variation to the marketing authorization** via standard regulatory procedures.

The last two steps should be completed by:

- **26 September 2022** for products containing chemically synthesized APIs
- **1 July 2023** for products containing biological APIs


# WHO 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>NDMA&lt;sup&gt;6&lt;/sup&gt;</td>
<td>N-nitrosodimethylamine</td>
<td>96.0 ng/day</td>
</tr>
<tr>
<td>NDEA&lt;sup&gt;6&lt;/sup&gt;</td>
<td>N-Nitrosodiethylamine</td>
<td>26.5 ng/day</td>
</tr>
<tr>
<td>NMB&lt;sup&gt;7&lt;/sup&gt;A</td>
<td>N-Nitroso-N-methyl-4-aminobutyric acid</td>
<td>96.0 ng/day</td>
</tr>
<tr>
<td>DIPNA&lt;sup&gt;7&lt;/sup&gt;</td>
<td>N-nitrosodiisopropylamine</td>
<td>26.5 ng/day</td>
</tr>
<tr>
<td>EIPNA&lt;sup&gt;7&lt;/sup&gt;</td>
<td>N-nitrosoethlisopropylamine</td>
<td>26.5 ng/day</td>
</tr>
</tbody>
</table>

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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 NMB, DIPNA and EIPNA impurities in sartan blood pressure medicines
https://www.who.int/medicines/publications/drugalerts/InformationNote Nitrosamine-impurities_Nov2019.pdf?ua=1
Real-World Scenario

How should AI limit from the established TD50 values be calculated?

Example

- TD50 of N-nitrosamine is 0.053 mg/kg/day
- Calculate AI limits in ng/day and convert AI limit into ppm.
- AI in ng/day: \((0.053 \text{ mg/kg/day} / 50000) \times 50 \text{ kg}\)
  \[
  = 0.000053 \text{ mg/day} \\
  = 53 \text{ ng/day}
  \]
- Conversion of AI limit into ppm
- AI limit in ng/mg or ppm = \(53 \text{ (ng/day)} / 100 \text{ (mg/day)}\) (for 100 mg maximum daily dose)
  \[
  = 0.53 \text{ ng/mg (0.53 ppm)}
  \]

(Ref: https://www.edqm.eu/en/edqms-response-nitrosamine-contamination)
Select the timeline(s) to complete risk assessment as per FDA (choose all that apply):

A. March 1, 2021
B. March 31, 2021
C. Seven months from the date of publication of original guidance
D. B and C
E. None of the above
- Live Content Slide
  - When playing as a slideshow, this slide will display live content

- Poll: Select the timeline(s) to complete risk assessment as per FDA (choose all that apply):
Which guidance includes timelines for biological medicines?

A. EMA  
B. EDQM  
C. FDA  
D. None of the above
Poll: Which guidance includes timelines for biological medicines?
The World Health Organization (WHO), US Food and Drug Administration (FDA), European Directorate for the Quality of Medicines (EDQM) and other agencies issued public health alerts and guidance documents, which have interim limits regarding the presence of nitrosamine impurities in several drug products.

- WHO - Information Note Nitrosamine impurities
- FDA - FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls
- EMA - Update on nitrosamine impurities: EMA continues to work to prevent impurities in medicines
Summary

- Background of ARB Drug Recall and Nitrosamine Impurities in other drug products
- ICH M7: Hazard assessment, Classification of Mutagen and Risk characterization
- FDA Guidance: Recommended AI and Timelines
- EMA and EDQM Recommendations to MAH/ CEP holders
- WHO limits
- References
Section 2—Introduction to USP <1469> Nitrosamines Impurities

Topics

- USP General Chapter <1469> – Introduction
- USP General Chapter <1469> – Scope
- USP General Chapter <1469> – Nitrosamine Impurities
The nitrosamine presence in pharmaceutical products emerged as a public health concern in 2018 after reports that harmful levels of nitrosamine impurity, N-nitrosodimethylamine (NDMA), had been observed in Valsartan containing products.
The observation triggered extensive synthetic route assessments and development of analytical procedures to quantify these two nitrosamine impurities.

Subsequently, additional nitrosamine impurities were found in valsartan and other medicines from sartan family of products.

As additional pharmaceuticals were evaluated and, in some cases tested, other nitrosamines beyond NDMA and NDEA were added as impurities of concern.

Other products containing unacceptable levels of nitrosamine impurities which have also been recalled from the market include Ranitidine, Nizatidine, and Metformin HCl.
Given the potentially broad implications of the presence of carcinogenic members of this class of chemicals, this chapter has been developed to provide a science- and risk-based approach for the control of nitrosamine impurities to ensure that the potential presence of nitrosamines in drug substances and drug products is identified, assessed, and controlled.

Recommendations are provided regarding:

- a) the establishment of controls of nitrosamine levels in order to ensure their elimination or reduction.
- b) analytical procedure performance characteristics for procedures used to monitor nitrosamine levels.
The section gives a list of nitrosamines of concern in the pharmaceutical industry, which was compiled from the information shared by multiple global health authorities. It includes relevant additional chemical information for each of the entries (Table in the next slide).

The list of nitrosamines in the table is not intended to be exhaustive but represents those that have been observed and communicated by regulators and manufacturers as being potentially present or observed.

- As additional nitrosamines are identified as potential concerns, the principles described herein should be applied for the assessment of these nitrosamines.

- If a manufacturer finds a nitrosamine not listed in Table 1, the appropriate regulatory authority should be contacted for determining appropriate AI limits.
<table>
<thead>
<tr>
<th>Common Name and Chemical Name</th>
<th>Acronym</th>
<th>CAS #</th>
<th>Structure</th>
<th>Chemical Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrosodimethylamine/N-Methyl-N-nitrosomethanamine</td>
<td>NDMA</td>
<td>62-75-9</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>C₂H₆N₂O</td>
<td>74.08</td>
</tr>
<tr>
<td>N-Nitrosodiethylamine/N-Ethyl-N-nitrosoethanamine</td>
<td>NDEA</td>
<td>55-18-5</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>C₄H₁₀N₂O</td>
<td>102.13</td>
</tr>
<tr>
<td>N-Nitrosodiisopropylamine/N-Isopropyl-N-nitrosoisopropylamine</td>
<td>NDIPA</td>
<td>601-77-4</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>C₆H₁₄N₂O</td>
<td>130.19</td>
</tr>
<tr>
<td>N-nitrosoethyisopropylamine/N-Ethyl-N-nitroso-2-propanamine</td>
<td>NEIPA</td>
<td>16339-04-1</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>C₅H₁₃N₂O</td>
<td>116.16</td>
</tr>
<tr>
<td>N-nitrosodibutylamine/N-Butyl-N-nitroso-1-butanamine</td>
<td>NDBA</td>
<td>924-16-3</td>
<td><img src="structure5.png" alt="Structure" /></td>
<td>C₈H₁₈N₂O</td>
<td>158.24</td>
</tr>
<tr>
<td>N-Nitrosomethylphenylamine/N-Methyl-N-nitrosophenylamine</td>
<td>NMPA</td>
<td>614-00-6</td>
<td><img src="structure6.png" alt="Structure" /></td>
<td>C₇H₈N₂O</td>
<td>136.15</td>
</tr>
<tr>
<td>N-Nitrosomethylaminobutyric acid / 4-[Methyl(nitroso)amino] butanoic acid</td>
<td>NMBA</td>
<td>61445-55-4</td>
<td><img src="structure7.png" alt="Structure" /></td>
<td>C₅H₁₀N₂O₃</td>
<td>146.14</td>
</tr>
</tbody>
</table>
The section also positions nitrosamines from the ICH M7 perspective.

- “N-nitroso compounds are among the structural groups of high potency mutagenic carcinogens in several animal species, and some are classified as probable or possible human carcinogens referred to as the “cohort of concern” in ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, a designation that carries with it a recommendation to control the impurities at or below the acceptable cancer risk.”

The section states the reason of the need to control nitrosamine impurities in the pharmaceutical products.

- As a result of the potential toxicity associated with these impurities, it is recommended to take steps to control and limit their presence in pharmaceutical materials.
Nitrosamine impurities are a concern for:

A. Sartan product family  
B. Ranitidine  
C. Metformin hydrochloride  
D. All drug products on the market
Poll: Nitrosamine impurities are a concern for:
Check Your Knowledge

The scope of USP <1469> includes:

A. Science and risk-based approach
B. Establishment of controls for nitrosamine levels
C. Analytical procedures and performance characteristics for procedures used in monitoring nitrosamine impurities
D. All of the above
Poll: The scope of USP <1469> includes:
Nitrosamines listed in the chapter represent:

A. Nitrosamines observed or communicated by regulators and manufacturers at the time the chapter was written
B. A final list of nitrosamines of concern in pharmaceuticals
C. Nitrosamine impurities recently identified
D. None of the above
Poll: Nitrosamines listed in the chapter represent:
Questions