Welcome

Empowering a healthy tomorrow
SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

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Of Indian Pharmaceutical Alliance
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OUTLINE

BACKGROUND

- Introduction
- Emergence of Nitrosamines as Public Health Concern in Pharmaceutical Products
- USP (Pharmacopeial) Perspective for Addressing Nitrosamine Presence in Pharmaceuticals

USP NITROSAMINE IMPURITIES JOINT SUBCOMMITTEE (JSC)

- JSC Charge
- JSC Membership
- JSC Immediate and Long-Term Deliverables
OUTLINE

- TIMELINE OF GENERAL CHAPTER (GC) 〈1469〉
  - Publication in Pharmacopeial Forum Volume 46 Issue 5
  - Publication in Compendia and Official Date

- GC 〈1469〉 CONTENT AND RATIONALE
  - Introduction (1), Scope (2), Sources of Nitrosamine (3)
  - Risk Assessment and Control Strategy (4), Limits of Nitrosamines (5)
  - Testing for Nitrosamines (6) and Test Methods Performance Characteristics (7)
  - Analytical Procedures (8)
  - Additional Sources of Information (9)
Introduction

- Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.

- However, their presence in medicines, even at trace level poses high safety risks to patients because Nitrosamine impurities are probable human carcinogens.

- There are part of a group of high potency mutagenic carcinogens referred to as the “cohort of concern” in ICH M7. This “cohort of concern comprises aflatoxin-like, N-nitroso- (functional group of nitrosamines), and alkyl-azoxy compounds.
Emergence of Nitrosamines as Public Health Concern in Pharmaceutical Products

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. Nitrosamines are toxic compounds, and some are known carcinogens.
Subsequently, additional nitrosamine impurities were found in valsartan and other medicines from sartan family of products which are in the daily medication regimen of hundred of millions of people.

Other products containing unacceptable levels of Nitrosamine impurities which have also been recalled from the market include Ranitidine, Nizatidine, and Metformin HCl.

Presence of nitrosamines in multiple drug products having drug substances of diverse chemical structure indicates that, in addition to the drug substance itself, other components of the drug products could be the source for them.

Following these reports, and after further investigation, 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
General Notices 3-Conformance to Standards

- Standards for an article recognized in the compendia (USP–NF) are expressed in the article's monograph, applicable general chapters, and General Notices.
- “Applicable general chapters” means general chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in General Notices, a monograph, or another applicable general chapter numbered below 1000.
- General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these General Notices.

Monographs

- Set forth the article's name, definition, specification, and other requirements related to packaging, storage, and labeling.
- The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article.
BACKGROUND

USP (Pharmacopeial) Perspective for Addressing Nitrosamine Presence in Pharmaceuticals – Development of Public Standards

- **General Chapters**
  - Descriptions of tests and procedures for application through individual monographs.
  - Descriptions and specifications of conditions and practices for pharmaceutical compounding.
  - General information for the interpretation of the compendial requirements,
  - Descriptions of general pharmaceutical storage, dispensing, and packaging practices, or
  - General guidance to manufacturers of official substances or official products

- A general chapter is better positioned as an overarching standard to address the nitrosamines impurity in several drug products and/or their components.

- Developing the Informational General Chapter <1469> Nitrosamine Impurities as the initial step of the larger USP involvement to immediately assist stakeholders.

- Developing sub-1000 General Chapter(s) as needed, when the regulatory requirements have been finalized.
The JSC charge is the development of a roadmap and guide for USP for developing public standards and assist USP efforts in other activities related to Nitrosamines topics.

Chair: Mark Schweitzer, GC-CA EC member, Industry

Members

- **General Chapters-Chemical Analysis EC**
  - Oscar Quattrocchi, Industry
  - Helmut Rockstroh, Industry
  - Kevin Swiss, Industry

- **Chemical Medicines Monographs 3 Expert Committee**
  - Bernard Olsen, Industry
  - Yuri Goldberg, Industry

- **Chemical Medicines Monographs 2 Expert Committee**
  - Ernest Parente, Industry
  - Luciano Virgili, Industry

- **Government Liaison to the JSC**
  - Susan Daniela Selaya, FDA Representative to the JSC
  - Michael Wierer, EP Representative to JSC

**USP Staff**
- Edmond Biba, Liaison for JSC
- Donald Min, Liaison for JSC
- Ken Freebern, EC Manager for JSC
The first deliverable of the JSC was the development of informational General Chapter (<1469>) and publication in PF for public comments as the first step toward creation of robust public standards regarding Nitrosamines in official articles.

Addressing the public comments, incorporate inputs as necessary, and proposing to the lead Expert Committee that chapter <1469> be balloted for approval as public standard for incorporation in the USP-NF, or

If significant changes to the proposal are necessary, based on public comments, the proposed chapter be revised and published again in PF for public comments.
General Chapter <1469> Nitrosamine Impurities was published in Pharmacopeial Forum Volume 46 Issue 5, available on-line from **September 1st, 2020**, for public comments.

The comment period ends on **November 30, 2020**.

The JSC is responsible for addressing public comment and revising the standard as needed.

The JSC proposes to send the standard for balloting or to publish a revised proposal in PF.

The Standard is balloted for approval by General Chapter Chemical Analysis Expert Committee.

Planning to publish the chapter in Compendia-USP 2021 Issue 3, available on-line on **May 1st, 2021** with official date **December 1st, 2021**.
Content and rationale

1. INTRODUCTION outlines the concern of presence of nitrosamine impurities in pharmaceuticals and current regulatory and industry thinking. It also presents the scope of the chapter to the reader: “to provide guidance in the assessment of materials to ensure that the potential presence of nitrosamines is identified, provide recommendations regarding establishing controls and to provide initial guidance on analytical procedure performance criteria for procedures used to monitor nitrosamine levels”.

2. NITROSAMINE IMPURITIES gives a list of nitrosamines of concern in pharmaceutical industry, which was compiled from the information shared by multiple global health authorities. It includes additional chemical information for each entry. It also positions nitrosamines from the ICH M7 perspective “N-nitroso compounds are listed as Class 1 mutagens in ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk “
3. SOURCES OF NITROSAMINES

- The section includes a summary on how nitrosamine impurities are formed and could end up in pharmaceuticals. The summary is followed by a bulleted list of examples of sources/pathways compiled from literature or identified empirically.
- The section includes also a fish-bone (Ishikawa) diagram for the potential sources of nitrosamines.

Diagram:
- Packaging
- Solvents/Water
- Drug Substance
- Formation During Storage
- Manufacturing Process
- Excipients
- Nitrosamines in Drug Product

- Primary source
- Secondary source
- From a mechanism other than DS degradation
3. SOURCES OF NITROSAMINES

- The section has a table for each potential source of nitrosamines and associated observed or assessed risk.
- The section shows also the general chemical reaction of nitrosamine formation and recommended action if the potential for the presence of nitrosamines is identified.
Content and rationale

4. NITROSAMINE RISK ASSESSMENTS—DEVELOPMENT OF A CONTROL STRATEGY

- The section states the goal of a control strategy
  “-ensuring that levels of nitrosamines, if their presence could not be totally avoided, are at or below the provisional acceptable intake (AI)

- The section also recommend how to achieve the goal
  “--the components of DP should be assessed for the potential to form nitrosamines or be contaminated with nitrosamines.”

- The section include a high-level process flow for development of nitrosamine impurity control strategy
4. High-level Control Strategy Process Flow Chart

- **Start**
- Conduct risk assessment of Manufacturing Process. Address potential modes of contamination as applicable
- **Decision D1**: Potential Nitrosamine presence identified?
  - **Yes**: Take necessary measures to control risk as appropriate. E.g. reevaluate/modify process, supply materials
  - **No**: Risk acceptance?
    - **Yes**: Establish control strategy to maintain acceptable levels of nitrosamine contaminants
    - **No**: End of process
Content and rationale

5. LIMITS OF NITROSAMINES

- The section presents the approach used for establishing material specific daily acceptable intake (AI)

“-Since nitrosamines are classified as Class 1 mutagenic impurities, rather than applying a Threshold of Toxicological Concern (TTC), the available safety data should be used to establish a material-specific AI”

- The section shows how the concentration limits are calculated based on the AI and the maximum daily dose of the drug substance (MDD) from the drug product label.

- The section direct the reader to FDA webpage for the current official AI

FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls
6. TESTING FOR THE PRESENCE OF NITROSAMINES
   - The section discusses the general approach on decision, when testing is needed, based on risk assessment and control strategy.
   - The section addresses also the presence of two or more nitrosamines in a drug product.

7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS
   - The section provides general considerations and requirements (sensitivity, selectivity, etc.) needed for test procedures for nitrosamines in pharmaceuticals.
   - It includes a subsection on considerations for sample preparation.
7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS

Lastly, the section provides recommended performance criteria for quantitative and qualitative procedures used for testing for nitrosamines.

**Recommended Quantitative Analytical Procedure Performance Criteria**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommended Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>50%–150% of the limit corresponding to Al</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Recovery 70%–130%</td>
</tr>
<tr>
<td>Repeatability (n =6)</td>
<td>Relative Standard Deviation (%)RSD ≤ 25%</td>
</tr>
<tr>
<td>Intermediate precision</td>
<td>RSD ≤ 30% (n=12)</td>
</tr>
<tr>
<td>Limit of Quantitation</td>
<td>Dependent on material MDD and Al</td>
</tr>
</tbody>
</table>

(see 〈1225〉)
7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS

- **Recommended Test Results Acceptance Criteria and Performance Acceptance Criteria for Limit Test Analytical Procedures**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results*</td>
<td>$R_U(i)/R_{SI}(i) = \text{NMT } 0.5$</td>
</tr>
<tr>
<td>Specificity</td>
<td>The procedure must be able to unequivocally assess (see Validation of Compendial Procedures &lt;1225&gt;) each Target Compound in the presence of components that may be expected to be present, including other Target Compounds and matrix components.</td>
</tr>
<tr>
<td>Recovery</td>
<td>70%–130%</td>
</tr>
<tr>
<td>Detectability</td>
<td>The minimum concentration at which the analyte can reliably be detected is established (signal-to-noise ratio 10:1).</td>
</tr>
<tr>
<td>Solution Stability</td>
<td>The Detectability should meet the requirements throughout the testing period.</td>
</tr>
</tbody>
</table>

$R_U(i)$ is Peak response ratio of the respective Target NNO(i) to the internal standard from the Sample solution.  
$R_{SI}(i)$ is Peak response ratio of the respective Target NNO(i) to the internal standard from the Spiked sample solution.
Content and rationale

8. ANALYTICAL PROCEDURES—Quantitative Analytical Procedures

- There are four quantitative Analytical Procedures in the chapter. The user should verify the suitability of these procedures for their specific samples under consideration.

- The verification process requires, as a minimum, meeting the “Recommended Quantitative Analytical Procedure Performance Criteria” discussed previously.

- Other suitability criteria may be added by the user, on a case by case bases, based on the nature of their sample and the goal of the test.
### Summary of Four Quantitative Analytical Procedures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Procedure 1</th>
<th>Procedure 2</th>
<th>Procedure 3</th>
<th>Procedure 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatography Technique</td>
<td>LC</td>
<td>GC</td>
<td>LC</td>
<td>GC</td>
</tr>
<tr>
<td>Injection</td>
<td>N/A</td>
<td>Headspace</td>
<td>N/A</td>
<td>Split/Spitless (Split with purge)</td>
</tr>
<tr>
<td>Column packing/phase</td>
<td>L 43</td>
<td>G-16</td>
<td>L 1</td>
<td>G 16</td>
</tr>
<tr>
<td>Detection</td>
<td>HRMS</td>
<td>MS-MS (triple quadrupole)</td>
<td>MS-MS (triple quadrupole)</td>
<td>MS-MS (triple quadrupole)</td>
</tr>
<tr>
<td>Ionization</td>
<td>Electrospray</td>
<td>Electron Impact</td>
<td>Atmospheric Pressure Chemical Ionization</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>Acquisition Mode</td>
<td>Multiple Reaction Monitoring and Single Ion Monitoring</td>
<td>Multiple Reaction Monitoring</td>
<td>Multiple Reaction Monitoring</td>
<td>Multiple Reaction Monitoring</td>
</tr>
<tr>
<td>Use of internal Standard (isotopically labeled)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quantitation</td>
<td>Single point calibration</td>
<td>Single point calibration</td>
<td>Calibration curve</td>
<td>Calibration curve</td>
</tr>
</tbody>
</table>
### Summary for 4- Analytical Procedures

**Procedure, Sample Concentration and Limit of Quantification**

- **Procedure-1**
  - **LC–HRMS**
  - **Impurities**: NDMA, NDEA, NEIPA, NDIPA, NMBA, NDBA
  - **Sample Concentration**: 20 mg/mL
  - **LOQ (solution Concentration)**: 0.001 µg/mL
  - **LOQ (w.r.t sample Concentration)**: 0.05 µg/g

- **Procedure-2**
  - **GC–HS-MS/MS (Triple-Quad)**
  - **Impurities**: NDMA, NDEA, NEIPA, NDIPA
  - **Sample Concentration**: 100 mg/mL
  - **LOQ (solution Concentration)**: 0.002 µg/mL
  - **LOQ (w.r.t sample Concentration)**: 0.02 µg/g

- **Procedure-3**
  - **LC–MS/MS (Triple-Quad)**
  - **Impurities**: NDMA, NDEA, NEIPA, NDIPA, NMBA, NDBA
  - **Sample Concentration**: 66.67 mg/mL (NDEA), 0.0013 (other impurities) µg/mL
  - **LOQ (solution Concentration)**: 0.00066 (NDEA), 0.0013 (other impurities) µg/mL
  - **LOQ (w.r.t sample Concentration)**: 0.01 (NDEA), 0.02 (other impurities) µg/g

- **Procedure-4**
  - **GC–MS/MS (Triple-Quad)**
  - **Impurities**: NDMA, NDEA, NEIPA, NDIPA, NDBA
  - **Sample Concentration**: 100 mg/mL
  - **LOQ (solution Concentration)**: 0.0005 µg/mL
  - **LOQ (w.r.t sample Concentration)**: 0.005 µg/g
9. ADDITIONAL SOURCES OF INFORMATION

- Recognizing that several procedures have been developed and made publicly available for the specific testing of nitrosamines in sartans and/or other official articles based on different scientific principles, the section include hyperlinks to the web pages of FDA, EDQM and Pharm Europa where many of the procedures can be accessed.

- These procedures can be used as alternative procedures and must be validated under actual use to meet the respective performance characteristics acceptance criteria set forth in 7. Test Method Performance Characteristics of Nitrosamine Methods.

- Links to other procedures
  1. FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities
  2. Ph. Eur. 2.4.36 N-Nitrosamines in active substances
  3. EDQM—Work on sampling strategies and testing methods with OMCLs
USP Nitrosamine Reference Standards

USP developed six Nitrosamine Reference Standards for use with General Chapter <1469> Nitrosamine Impurities

<table>
<thead>
<tr>
<th>Catalog # / Lot</th>
<th>Name / Label Value</th>
<th>Structure</th>
<th>Catalog # / Lot</th>
<th>Name / Label Value</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1466674 F145F0</td>
<td>N-Nitroso dimethylamine (NMDA) 1.00 mg/mL in Methanol</td>
<td><img src="image1" alt="N-Nitroso dimethylamine Structure" /></td>
<td>1466663 F145E0</td>
<td>N-Nitroso diisopropylamine (NDIPA) 1.00 mg/mL in Methanol</td>
<td><img src="image2" alt="N-Nitroso diisopropylamine Structure" /></td>
</tr>
<tr>
<td>1466652 F145D0</td>
<td>N-Nitroso diethylamine (NDEA) 1.00 mg/mL in Methanol</td>
<td><img src="image3" alt="N-Nitroso diethylamine Structure" /></td>
<td>1466641 F145C0</td>
<td>N-Nitroso dibutylamine (NDBA) 1.00 mg/mL in Methanol</td>
<td><img src="image4" alt="N-Nitroso dibutylamine Structure" /></td>
</tr>
<tr>
<td>1466685 F145G0</td>
<td>N-Nitroso ethylisopropylamine (NEIPA) 0.98 mg/mL in Methanol</td>
<td><img src="image5" alt="N-Nitroso ethylisopropylamine Structure" /></td>
<td>1466696 F145H0</td>
<td>N-Nitroso methylamino butyric acid (NMBA) 0.99 mg/mL in Acetonitrile</td>
<td><img src="image6" alt="N-Nitroso methylamino butyric acid Structure" /></td>
</tr>
</tbody>
</table>
BRIEFING

\(1469\) Nitrosoamine impurities. Starting in July 2018 the World Health Organization (WHO), the FDA, the European Directorate for the Quality of Medicines (EDQM), and other regulatory and global health agencies issued guidance documents and public health alerts regarding the presence of nitrosamine impurities in several drug products. To protect patients from the adverse effects of nitrosamines as impurities in drug products, USP’s General Chapters—Chemical Analysis Expert Committee, Chemical Medicines Monographs 2 Expert Committee, and Chemical Medicines Monographs 3 Expert Committee are proposing this new general chapter. This chapter is aligned with current scientific and regulatory approaches developed to ensure the appropriate control of nitrosoamine impurities in drug substances and drug products. The objective of this standard is to provide a science-based approach for the control of nitrosoamine impurities, eliminating or reducing their presence in drug products. The approach described thereby ensures the quality of the product as it relates to safety.

1. The \(7\), introduction presents the concern of nitrosoamine presence and summarizes the current
Request for public comments on <1469>

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Send Comments to:
301-230-3270 | exb@usp.org,
or/and pfcomments@USP.org

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Questions

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Thank You