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# 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)
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  - 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)

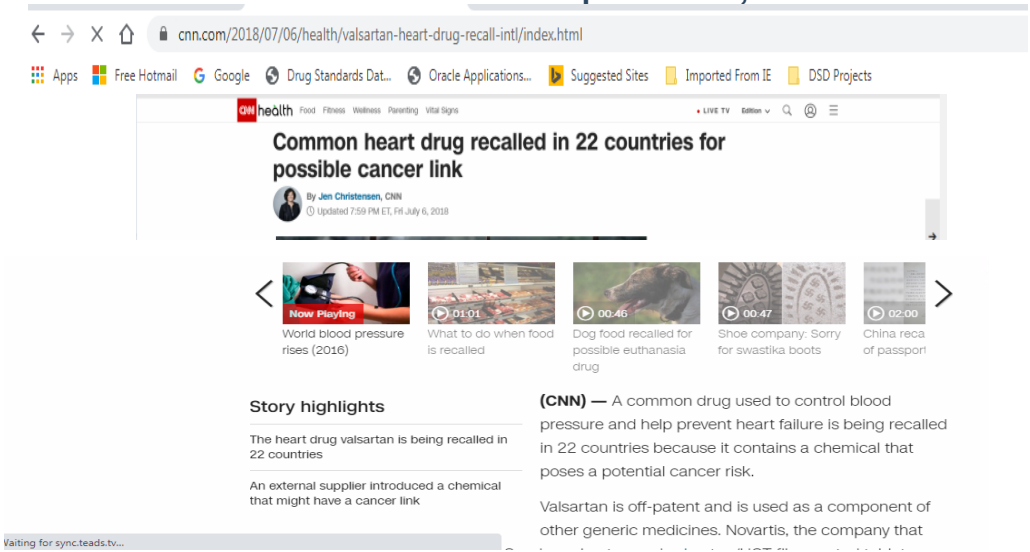
# Background

## 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.



## Emergence of Nitrosamines as Public Health Concern in Pharmaceutical Products (contd…)

- 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

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

- 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.

# USP NITROSAMINE IMPURITIES JOINT SUBCOMMITTEE (JSC)

## JSC CHARGE, MEMBERSHIP, AND MEMBERS

- 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** | **Chemical Medicines Monographs 3 Expert Committee** |
| Oscar Quattrocchi, Industry | Bernard Olsen, Industry |
| Helmut Rockstroh, Industry | Yuri Goldberg, Industry |
| Kevin Swiss, Industry | |
| **Chemical Medicines Monographs 2 Expert Committee** | **Government Liaison to the JSC** |
| Ernest Parente, Industry | Susan Daniela Selaya, FDA Representative to the JSC |
| Luciano Virgili, Industry | Michael Wierer, EP Representative to JSC |
| **USP Staff** | |
| Edmond Biba, Liaison for JSC | |
| Donald Min, Liaison for JSC | |
| Ken Freebern , EC Manager for JSC | |

# USP NITROSAMINE IMPURITIES JOINT SUBCOMMITTEE (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.

# TIMELINE OF GENERAL CHAPTER (GC) ‹1469›

- 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**.

# GC ‹1469› NITROSAMINE IMPURITIES

## 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".

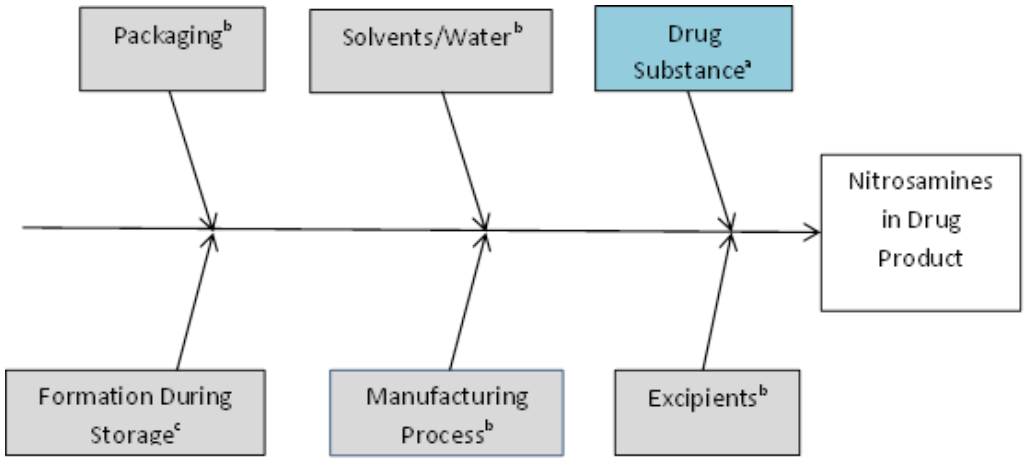
- 2. NITROSAMINE IMPURITIES gives a list of nitrosamines of concern in pharmaceutical industry, which was compiled from the information shared by multiple global health authorities. It includes additional chemical information for each entry. It also positions nitrosamines from the ICH M7 perspective

"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 "

# GC ‹1469› NITROSAMINE IMPURITIES

## Content and rationale

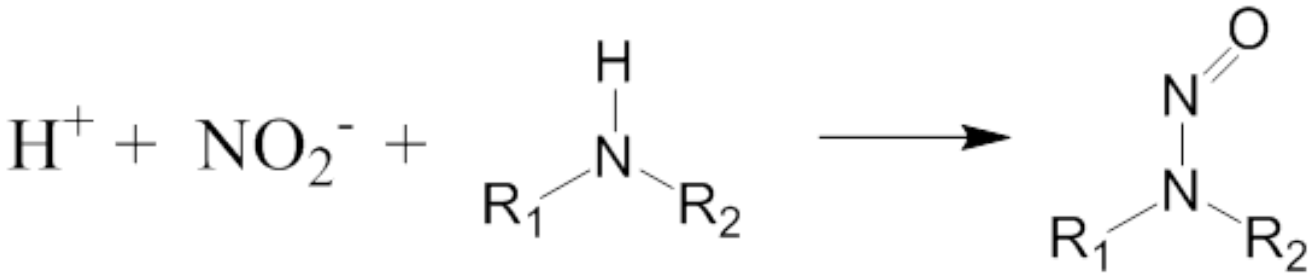
- 3. SOURCES OF NITROSAMINES
  - The section include a summary on how nitrosamine impurities are formed and could end up in pharmaceuticals. The summary is followed by a bulleted list of examples of sources/pathways compiled from literature or identified empirically
  - The section include also a fish-bone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




[a] Primary source
[b] Secondary source
[c] From a mechanism other than DS degradation

## Content and rationale

- 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.



# GC ‹1469› NITROSAMINE IMPURITIES

## 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)

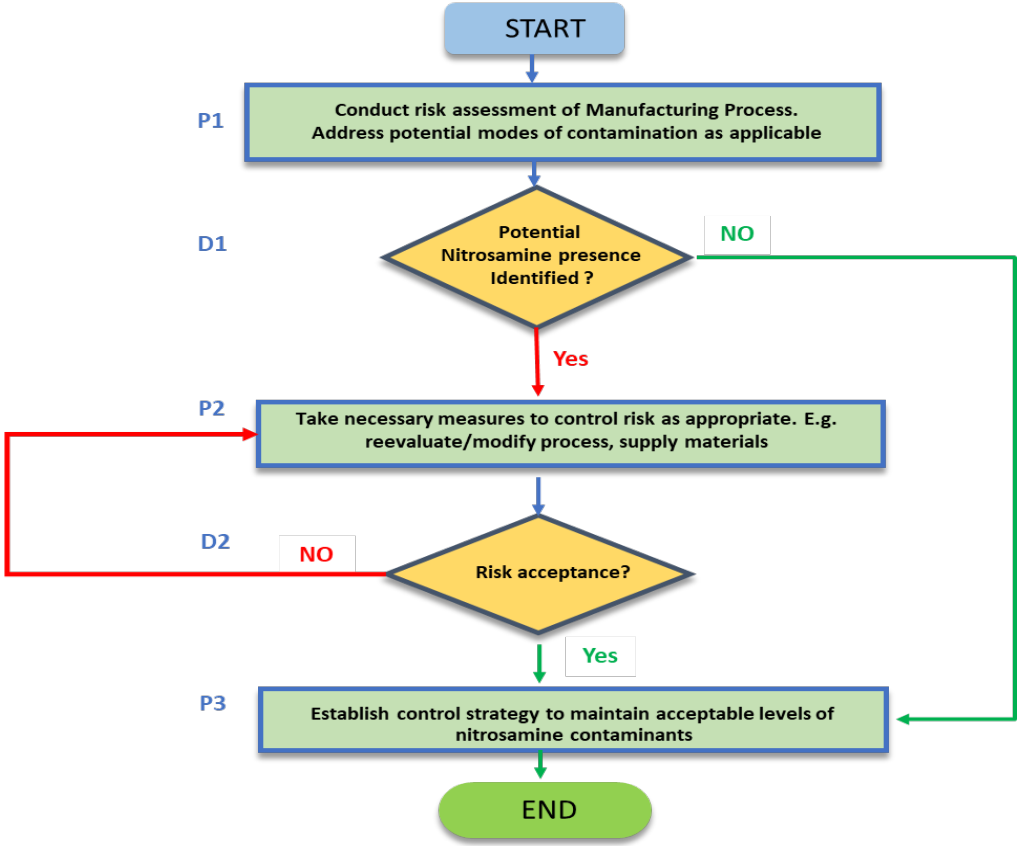
  - The section also recommend how to achieve the goal

  “--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

# GC ‹1469› NITROSAMINE IMPURITIES

## 4. High-level Control Strategy Process Flow Chart



# GC ‹1469› NITROSAMINE IMPURITIES

## 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

# GC ‹1469› NITROSAMINE IMPURITIES

## Content and rationale

- 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

# GC ‹1469› NITROSAMINE IMPURITIES

## Content and rationale

- 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**

| Parameter | Recommended Acceptance Criteria |
|---|---|
| **Range** | 50%–150% of the limit corresponding to AI |
| **Accuracy** | Recovery 70%–130% |
| **Repeatability (n =6)** | Relative Standard Deviation (%)RSD ≤ 25% |
| **Intermediate precision** | RSD ≤ 30% (n=12) |
| **Limit of Quantitation (see ⟨1225⟩)** | Dependent on material MDD and AI |

# GC ‹1469› NITROSAMINE IMPURITIES

## Content and rationale

- 7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS
  - **Recommended Test Results Acceptance Criteria and Performance Acceptance Criteria for Limit Test Analytical Procedures**

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

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

# GC ‹1469› NITROSAMINE IMPURITIES

## 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

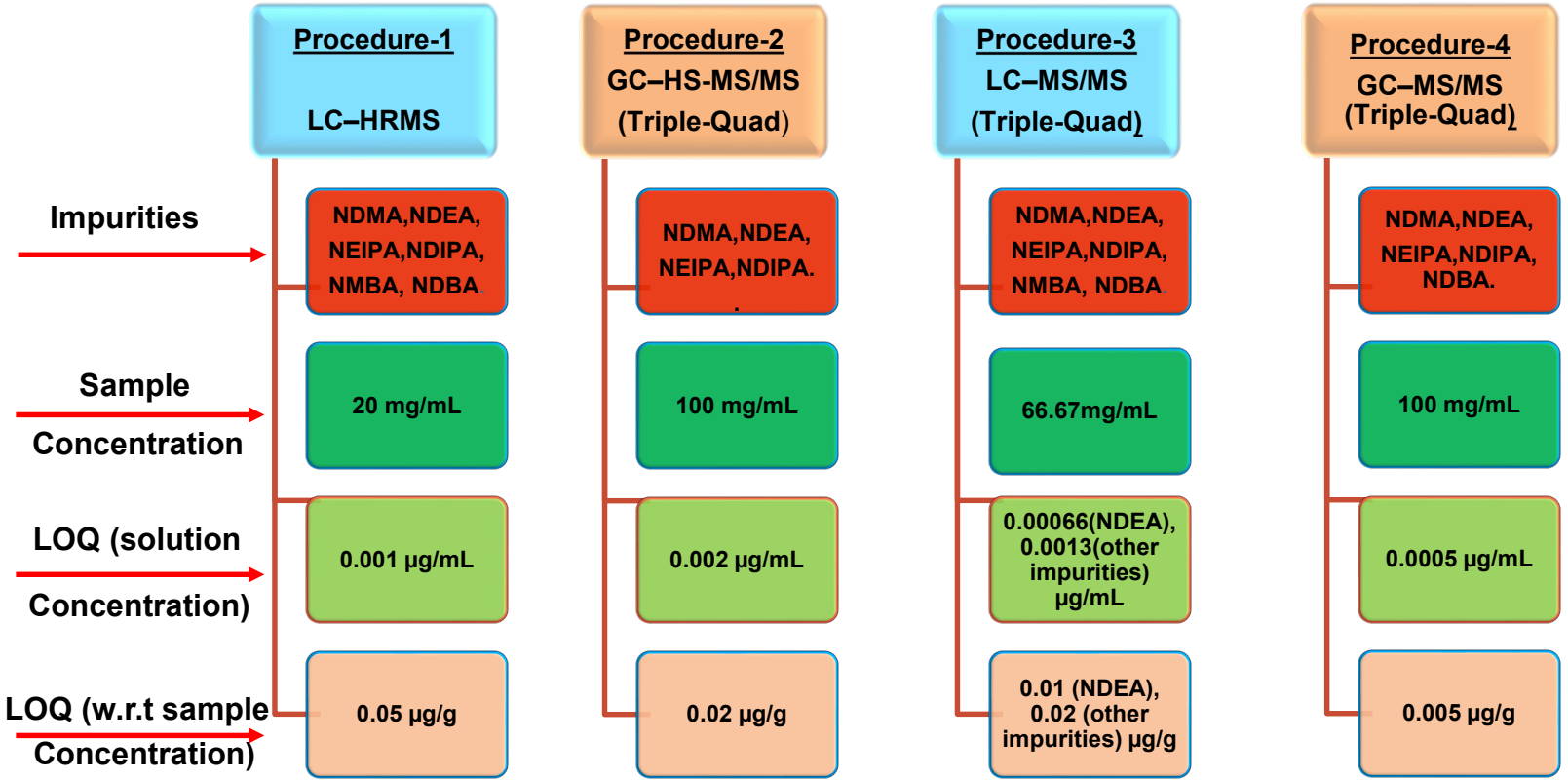
# GC ‹1469› NITROSAMINE IMPURITIES

- Summary of Four Quantitative Analytical Procedures

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

# Summary for 4- Analytical Procedures

## Procedure, Sample Concentration and Limit of Quantification



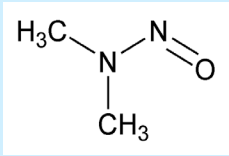
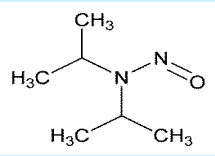
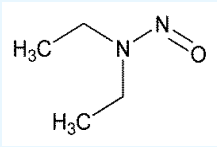
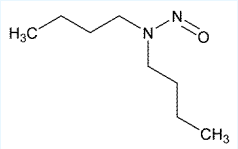
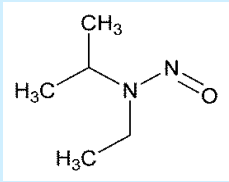
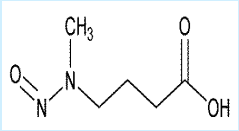
## Content and rationale

- 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

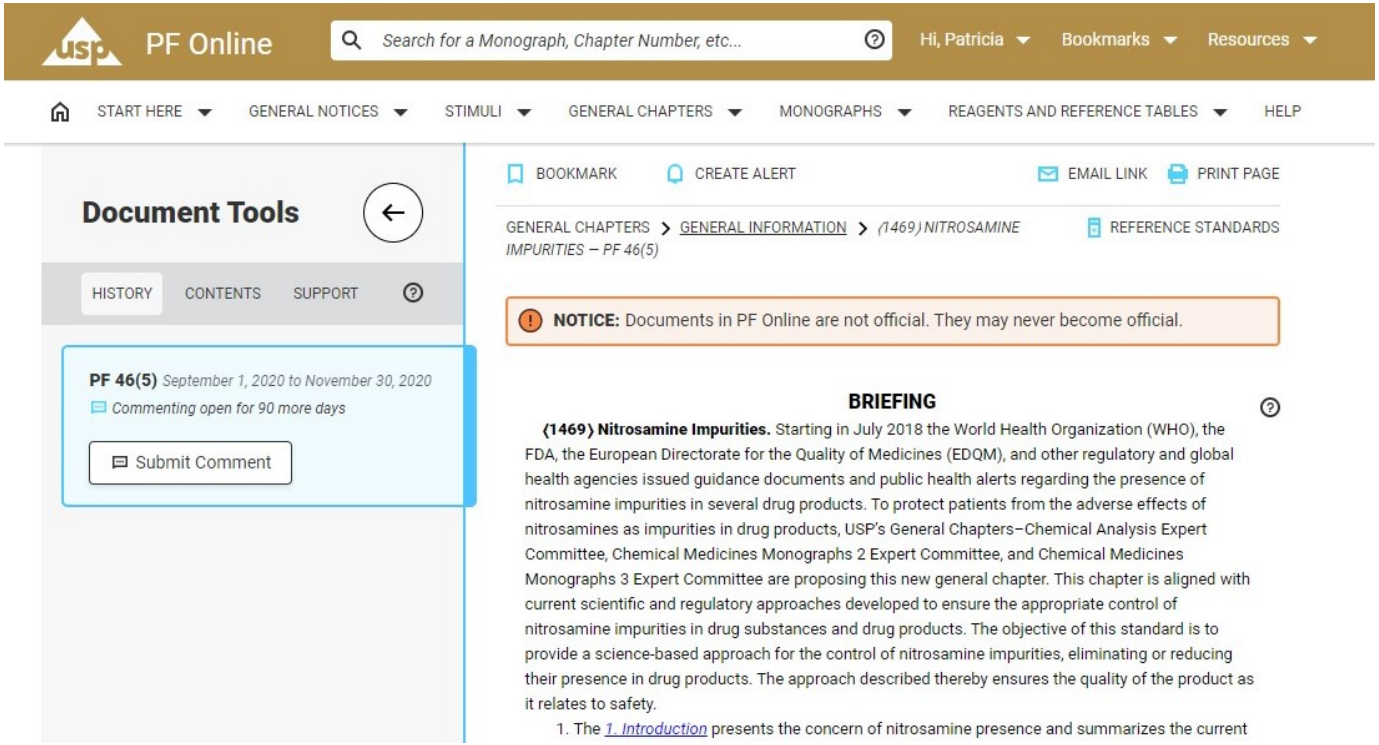
- USP developed six Nitrosamine Reference Standards for use with General Chapter <1469> Nitrosamine Impurities

| Catalog # Lot | Name / Label Value | Structure | | Catalog # / Lot | Name / Label Value | Structure |
|---|---|---|---|---|---|---|
| 1466674 F145F0 | N-Nitroso dimethylamine (NMDA) 1.00 mg/mL in Methanol |  | | 1466663 F145E0 | N-Nitroso diisopropylamine (NDIPA) 1.00 mg/mL in Methanol |  |
| 1466652 F145D0 | N-Nitroso diethylamine (NDEA) 1.00 mg/mL in Methanol |  | | 1466641 F145C0 | N-Nitroso dibutylamine (NDBA) 1.00 mg/mL in Methanol |  |
| 1466685 F145G0 | N-Nitroso ethylisopropylamine (NEIPA) 0.98 mg/mL in Methanol |  | | 1466696 F145H0 | N-Nitroso methtylamino butyric acid (NMBA) 0.99 mg/mL in Acetonitrile |  |

# GC ‹1469› NITROSAMINE IMPURITIES – Content and rationale

## Published in Pharmacopeia Forum Volume 46 Issue 5

**Comment period:** *September 1, 2020 to November 30, 2020*



# Request for public comments on <1469>

## Stay Connected

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