

Welcome



Empowering a healthy tomorrow

SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

By: Edmond Biba
Senior Scientific Liaison,
Science – General Chapters

Webinar
July 28, 2020



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, Scope, Sources of Nitrosamine
 - 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

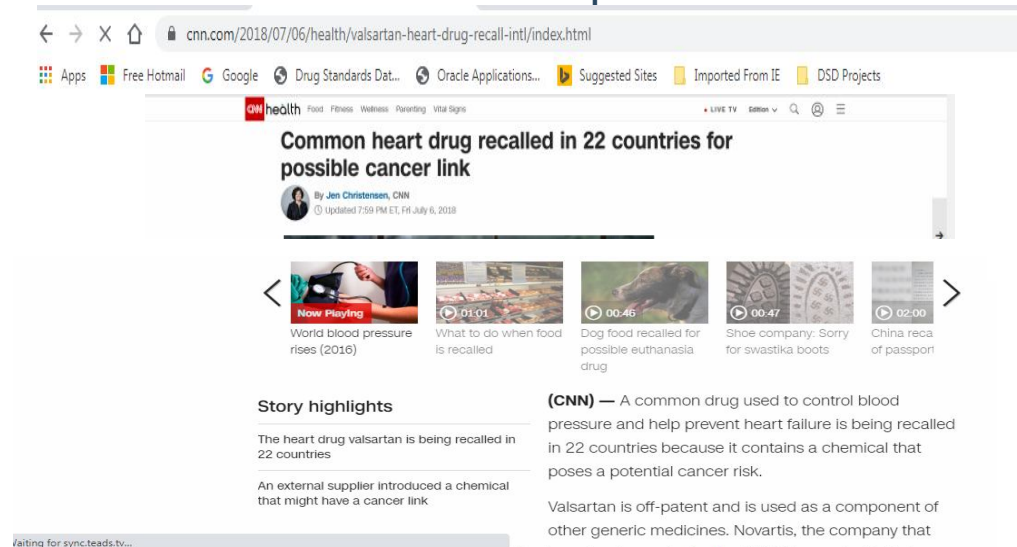
- ▶ Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- ▶ However, their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens.
- ▶ They 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

BACKGROUND



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.



BACKGROUND

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



- ▶ Subsequently, additional nitrosamine impurities (e.g. N-nitrosodiethylamine (NDEA), N -nitrosodiisopropylamine (NDIPA), N -nitrosoethylisopropylamine (NEIPA) and N -nitroso-N-methyl-4-aminobutyric acid (NMBA)) were found in valsartan and other medicines from sartan family of products which are in the daily medication regimen of hundreds of millions of people. More recently, 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.

BACKGROUND

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



- ▶ 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](#)

BACKGROUND

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.
- ▶ 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 General Information Chapter <1469> Nitrosamine Impurities as the initial step of the larger USP involvement to immediately assist the stakeholders.
- ▶ Developing sub-1000 General Chapter(s) as needed, when the regulatory requirements have been finalized.

BACKGROUND

USP (Pharmacopeial) Perspective for Addressing Nitrosamine Presence in Pharmaceuticals – USP Standard Development Process

- ▶ Proposal for a new Public Standard or revision to existing Standards comes from expert committee member, staff or other stakeholders
 - General chapters numbered 1000 to 1999 are for informational purposes only.
- ▶ Expert Committee, or sub-committee evaluates the proposal and decides to proceed with internal resources or establish an expert panel.
- ▶ Several mechanisms are utilized to solicit preliminary public inputs
 - Stimuli Article (common for new General Chapter) or draft chapter published in PF.
 - Prospectus of the planned standard, workshop or other public meeting scheduled for “high-impact” chapters.
- ▶ The Committee, sub-committee, or panel develops and prepares a proposal and publish it in Pharmacopeia Forum (PF).
- ▶ Public comments on the proposal are received during the public comments period from direct commenting, public forums etc., and addressed by committee/panel.
- ▶ The committee/panel update the proposal as necessary and the updated proposal is balloted by the responsible Expert Committee for inclusion in USP-NF

USP NITROSAMINE IMPURITIES JOINT SUBCOMMITTEE (JSC)

JSC CHARGE, MEMBERSHIP, AND MEMBERS



- ▶ The JSC charge is the development of a roadmap for USP and guide USP for creating public standards and assist USP efforts in other activities regarding 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 is the development of an informational General Chapter (Chapter <1469>) as the first step toward creation of robust public standards regarding Nitrosamines in official articles and publishing the proposed chapter in Pharmacopeial Forum (PF) for public comments.
- ▶ **Addressing** the public comments, incorporate inputs on merits and proposing approval of the proposed chapter as a public standard for incorporation in pharmacopeia.

TIMELINE OF GENERAL CHAPTER (GC) <1469>



- ▶ General Chapter <1469> Nitrosamine Impurities will be published in Pharmacopeial Forum Volume 46 Issue 5, available on-line on **September 1st, 2020**, for public comments.
- ▶ The comment period would end on **November 30, 2020**.
- ▶ The JSC is responsible for addressing public comment and revising the standard as needed.
- ▶ 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 AND 2. NITROSAMINE IMPURITIES.

- 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 “

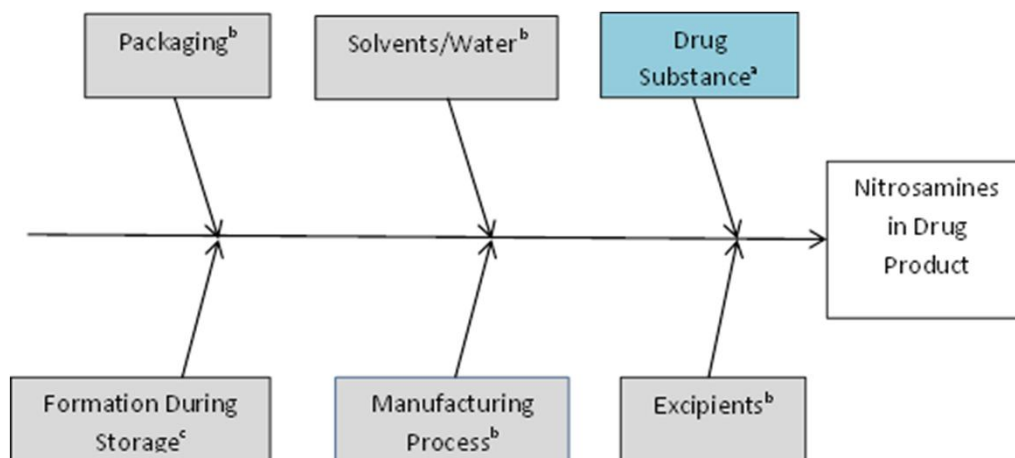
GC ‹1469› NITROSAMINE IMPURITIES



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

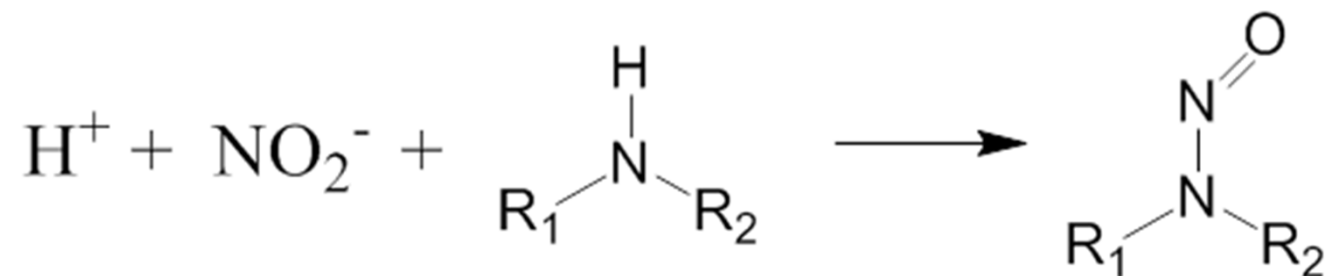
GC ‹1469› NITROSAMINE IMPURITIES



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

[High-level process for development of a nitrosamine impurity control strategy](#)

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 (%) $RSD \leq 25\%$
Intermediate precision	$RSD \leq 30\%$ (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*	$R_U(i)/R_{St}(i) = \text{NMT } 0.5$
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 a number of 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



Content and rationale

▶ 8. ANALYTICAL PROCEDURES—Quantitative Analytical Procedures

- ▶ **Procedure 1**— Quantitation of six nitrosamines (NDMA, NDEA, NDIPA, NEIPA, NMBA, and NDBA) using LC-HRMS
- ▶ Key parameters of the procedure.

Solutions:

Diluent: Methanol

Mobile phase A: 0.1% formic acid in water

Mobile phase B: 0.1% formic acid in methanol

Standard solution: 6.0 ng/mL of each USP N-Nitrosamine Reference Standard (RS) in Diluent.

Sensitivity solution: 1.0 ng/mL each of USP N-Nitrosamine RS in Diluent.

Sample solution: 20 mg/mL of DS in diluent.

GC ‹1469› NITROSAMINE IMPURITIES



Content and rationale

▶ 8. ANALYTICAL PROCEDURES – Procedure 1

- ▶ Key parameters of the procedure.

Chromatographic system:

Mode: LC **Column:** 4.6 mm x 10-cm, 2.6 µm packing L43

Detector: High Resolution Mass Spectrometer (HRMS)

MS conditions:

Ionization: Electrospray Ionization (ESI)

Scan Settings:

Impurity	NDMA	NMBA	NDEA	NEIPA	NDIPA	NDBA
Scan Type	SIM	SIM	PRM	SIM	SIM	PRM
Polarity	Positive	Negative	Positive	Positive	Positive	Positive
m/z Isolated for PRM	N/A	N/A	103.0866	N/A	N/A	159.1492

GC ‹1469› NITROSAMINE IMPURITIES



Content and rationale

▶ 8. ANALYTICAL PROCEDURES – Procedure 1

- Key parameters of the procedure.

System suitability:

Samples: Standard solution and Sensitivity solution

Suitability requirements

Relative standard deviation: NMT 20.0% from six replicate injections, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration (ppm) of each specified nitrosamine impurity in the portion of DS taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 10^6$$

GC ‹1469› NITROSAMINE IMPURITIES



Content and rationale

▶ 8. ANALYTICAL PROCEDURES—Quantitative Analytical Procedures

- **Procedure 2**— Quantitation of four nitrosamines (NDMA, NDEA, NDIPA, NEIPA) using Headspace GC-MS
- Key parameters of the procedure.

Solutions:

Diluent: Methanol

Internal standard stock solution: 0.4 µg/mL of NDMA-d₆ in Diluent.

Internal standard solution: 0.016 µg/mL of NDMA-d₆ in Diluent.

Standard stock solution: 0.016 µg/mL of each USP N-Nitrosamine RS in Diluent that contain Internal standard solution.

Standard solution: Transfer 1.0 mL of *Standard stock* solution to an appropriate headspace vial containing about 100 mg of imidazole and 1.0 mL of acetonitrile. Apply the stopper, cap and crimp tightly.

Sensitivity solution: 0.004 µg/mL of each USP N-Nitrosamine RS in Diluent that contain Internal standard solution. Transfer 1.0 mL of this solution to an appropriate headspace vial containing about 100 mg of imidazole and 1.0 mL of acetonitrile. Apply the stopper, cap and crimp tightly.

Sample solution: 200 ± 10 mg of DS and 100 mg of imidazole in a headspace vial. Add 1.0 mL of Internal standard solution and 1.0 mL of acetonitrile. Apply the stopper, cap and crimp tightly.

GC ‹1469› NITROSAMINE IMPURITIES



Content and rationale

▶ 8. ANALYTICAL PROCEDURES – Procedure 2

- ▶ Key parameters of the procedure.

Chromatographic Conditions:

Mode: GC

Injector: Headspace

Detector: Mass Spectrometer (Triple Quadrupole)

Column: 0.32-mm × 30-m fused-silica coated with a 1.0-μm layer of phase G16

Column Temperature

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
45	0	45	3
45	10	130	3
130	15	190	-
190	40	240	10

GC ‹1469› NITROSAMINE IMPURITIES – Content and rationale



Content and rationale

► 8. ANALYTICAL PROCEDURES – Procedure 2

- Key parameters of the procedure.

MS conditions:

Ionization: Electron Impact

Scan Settings:

Impurity	NDMA	NDMA-d ₆	NDEA	NEIPA	NDIPA
Acquisition Mode	MRM	MRM	MRM	MRM	MRM
Polarity	Positive	Positive	Positive	Positive	Positive
MRM 1	74 amu→44 amu	80 amu→50 amu	102 amu→85.1 amu	116.0 amu→99.1 amu	130.0 amu→42 amu
MRM 2	74 amu→42 amu		102 amu→56.1 amu	99.0 amu→44.1 amu	130.0 amu→43.1 amu

GC ‹1469› NITROSAMINE IMPURITIES – Content and rationale



Content and rationale

▶ 8. ANALYTICAL PROCEDURES – Procedure 2

- ▶ Key parameters of the procedure.

System suitability:

Samples: Standard solution, blank and Sensitivity solution

Suitability requirements

Relative standard deviation: NMT 20.0% for the ratios of the impurity standard peak response to the internal standard peak response from six replicate injections, *Standard solution*

Signal-to-noise ratio: NLT 10 for each nitrosamine, *Sensitivity solution*

Blank: No interfering peaks from the blank

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (ppm) of each specified nitrosamine impurity in the portion of Drug Substance taken:

Result = $(1/W) \times (R_U / R_{ST}) \times C_{ST}$

GC ‹1469› NITROSAMINE IMPURITIES – Content and rationale



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](#)

Thank You



Request for public comments on <1469>

Stay Connected

Send Comments to:

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



Empowering a healthy tomorrow

USP Nitrosamines Impurities Reference Standards for use with General Chapter <1469>

Ravi Reddy
Senior Director
Reference Standards Development



Empowering a healthy tomorrow



USP Reference Standards Introduction



- ▶ USP Reference Standards are highly characterized specimens (physical materials) of Drug substances, Excipients, Impurities, Biologics, Food Ingredients, Dietary Supplements, Dissolution Performance Test Tablets etc.
- ▶ Over 4000 Reference Standards are available from USP
- ▶ Development is triggered by monographs, General Chapter or Industry interest
- ▶ Developed using Quality Systems, e.g. Operational Manuals, SOPs, policies
- ▶ Rigorously tested within USP Labs and/or Government and industry labs
 - Testing is customized based on the type of material and intended use

USP Reference Standards Introduction (contd..)

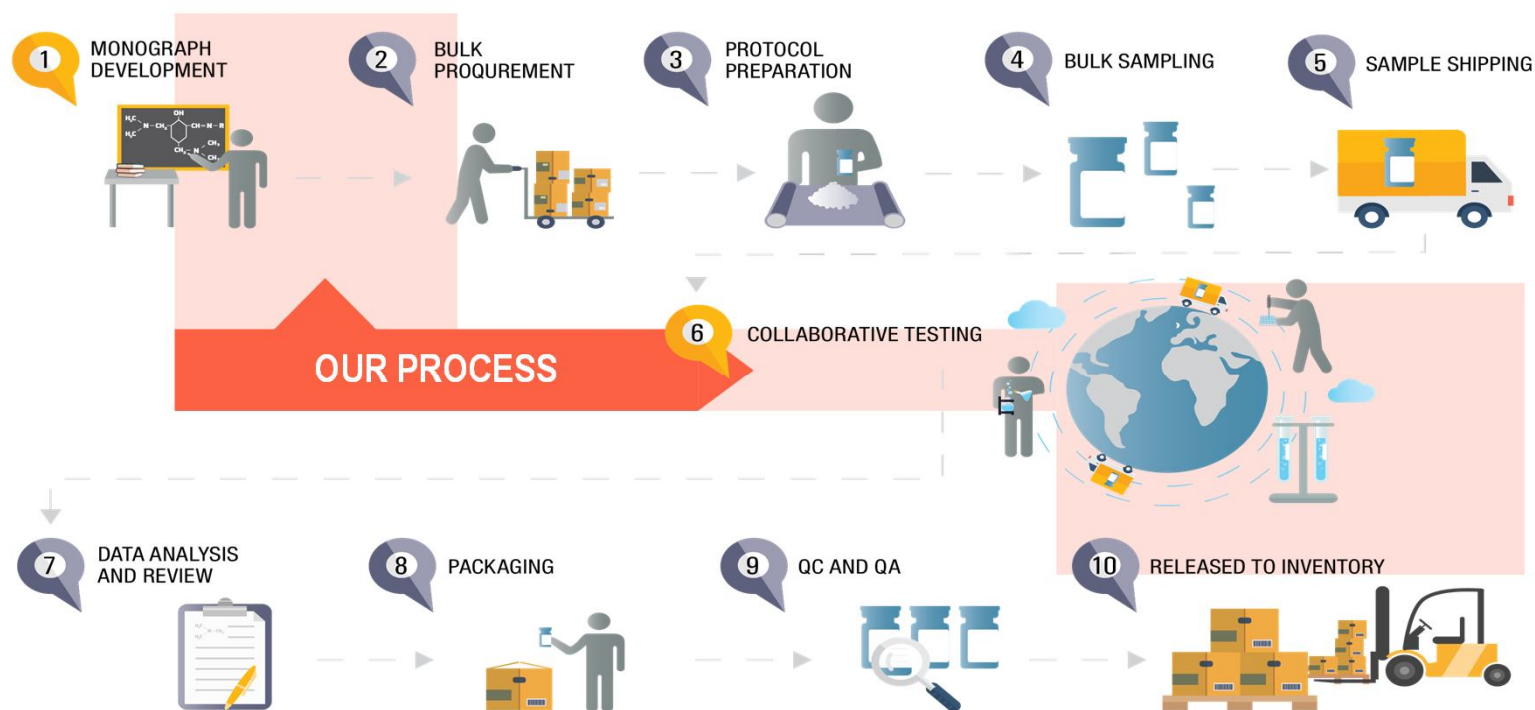


- ▶ Several Types of Reference Standards
 - Quantitative: Assay and Impurities
 - Qualitative: Impurities or APIs for Identification only, Resolution, Peak Identification
 - Special category: Melting Point, Particle Count, Dissolution Tablets
 - Non-USP Compendial: Developed based on industry interest
- ▶ USP RS are intended for use as defined in the compendial methods including General Chapters
 - May also be used for other purposes as determined by the users

Development of a USP Reference Standard



High level general process



USP Nitrosamine Reference Standards

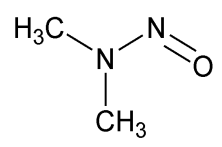
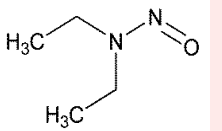
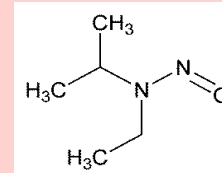


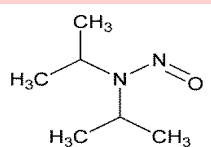
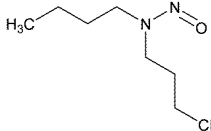
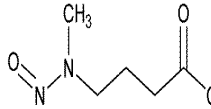
- ▶ USP developed six nitrosamine impurities Reference Standards for use with General Chapter <1469> Nitrosamine Impurities
- ▶ Supplied as a solution at 1 mg/mL in methanol or acetonitrile (NMBA) in an ampule
 - Dilute to concentrations as per the method e.g. LOQ, Standard
- ▶ USP Nitrosamine RSs are Characterized by GC-MS and/or LC-MS
- ▶ Value on the label was assigned by testing against Certified Reference Material
- ▶ Storage: Freezer
- ▶ Certificates are available on USP website (Store)
- ▶ Ampules (Primary packaging) in a secondary package (Plastic tube)

USP Nitrosamine Reference Standards



- ▶ USP developed six Nitrosamine Reference Standards for use with General Chapter <1469> Nitrosamine Impurities
- ▶ All six USP RS available in the catalog

Catalog # Lot	Name / Label Value	Structure
1466674 F145F0	N-Nitroso dimethylamine (NMDA) 1.00 mg/mL in Methanol	
1466652 F145D0	N-Nitroso diethylamine (NDEA) 1.00 mg/mL in Methanol	
1466685 F145G0	N-Nitroso ethylisopropylamine (NEIPA) 0.98 mg/mL in Methanol	

Catalog # / Lot	Name / Label Value	Structure
1466663 F145E0	N-Nitroso diisopropylamine (NDIPA) 1.00 mg/mL in Methanol	
1466641 F145C0	N-Nitroso dibutylamine (NDBA) 1.00 mg/mL in Methanol	
1466696 F145H0	N-Nitroso methylamino butyric acid (NMBA) 0.99 mg/mL in Acetonitrile	

USP Nitrosamine Reference Standards



► NDMA Labels

For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSODIMETHYLAMINE (NDMA) 1 mL (1 mg/mL) (*N*-Methyl-*N*-nitrosomethanamine)

This is a solution of N-nitrosodimethylamine (NDMA) in methanol. For quantitative applications, use a value of 1.00 mg of N-nitrosodimethylamine per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.



Danger! Highly flammable liquid and vapor. Toxic if swallowed. Toxic in contact with skin. Toxic if inhaled. May cause cancer. Causes damage to organs.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. -No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe mist or vapor. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. If exposed: Call a poison center/doctor. If swallowed: Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Wash with plenty of water. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. In case of fire: Use appropriate media to extinguish. Keep cool. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

LOT: F145F0

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466674 Material mfd. in United States



REFERENCE STANDARD

N-NITROSODIMETHYLAMINE (NDMA) 1 mL (1 mg/mL)

(*N*-Methyl-*N*-nitrosomethanamine)

Danger! See outer package label for full hazard information.



This is a solution of N-nitrosodimethylamine (NDMA) in methanol. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666

Cat. No. 1466674

Lot: F145F0

Material mfd. in United States

For use with specified USP compendial tests.
Not for use as a drug. See SDS prior to use
at www.usp.org/sds.

USP Nitrosamine Reference Standards



► NDEA Labels



REFERENCE STANDARD

N-NITROSODIETHYLAMINE (NDEA) 1 mL (1 mg/mL)

(*N*-Ethyl-*N*-nitrosoethanamine)

This is a solution of *N*-nitrosodiethylamine (NDEA) in methanol. For quantitative applications, use a value of 1.00 mg of *N*-nitrosodiethylamine per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.



Danger! Highly flammable liquid and vapor. Toxic if swallowed. Toxic in contact with skin. Toxic if inhaled. May cause cancer. Causes damage to organs.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe mist or vapor. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. If exposed: Call a poison center/doctor. If swallowed: Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Wash with plenty of water. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. In case of fire: Use appropriate media to extinguish. Keep cool. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466652 Material mfd. in United States

LOT: F145D0



For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSODIETHYLAMINE (NDEA) 1 mL (1 mg/mL)

(*N*-Ethyl-*N*-nitrosoethanamine)

Danger! See outer package label for full hazard information.

This is a solution of *N*-nitrosodiethylamine (NDEA) in methanol. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466652 Lot: F145D0
Material mfd. in United States



For use with specified USP compendial tests.
Not for use as a drug. See SDS prior to use at www.usp.org/sds.

USP Nitrosamine Reference Standards



► NEIPA Labels



REFERENCE STANDARD

N-NITROSOETHYLISOPROPYLAMINE (NEIPA)

1 mL (1 mg/mL)

(N-Ethyl-N-nitroso-2-propanamine)

This is a solution of N-nitrosoethylisopropylamine (NEIPA) in methanol. For quantitative applications, use a value of 0.98 mg of N-nitrosoethylisopropylamine per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.

Danger! Highly flammable liquid and vapor. Toxic if swallowed. Toxic in contact with skin. Toxic if inhaled. Suspected of causing cancer. Causes damage to organs.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe mist or vapor. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. If exposed: Call a poison center/doctor. If swallowed: Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Wash with plenty of water. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. In case of fire: Use appropriate media to extinguish. Keep cool. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466685 Material mfd. in United States

LOT: F145G0



For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSOETHYLISOPROPYLAMINE (NEIPA) 1 mL (1 mg/mL)

(N-Ethyl-N-nitroso-2-propanamine)

Danger! See outer package label for full hazard information.

This is a solution of N-nitrosoethylisopropylamine (NEIPA) in methanol. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466685 Lot: F145G0
Material mfd. in United States

For use with specified USP compendial tests.
Not for use as a drug. See SDS prior to use
at www.usp.org/sds.



USP Nitrosamine Reference Standards



▶ NDIPA Labels



REFERENCE STANDARD

N-NITROSODIISOPROPYLAMINE (NDIPA) 1 mL (1 mg/mL)

(*N*-Isopropyl-*N*-nitrosoisopropylamine)

This is a solution of N-nitrosodiisopropylamine (NDIPA) in methanol. For quantitative applications, use a value of 1.00 mg of N-nitrosodiisopropylamine per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.



Danger! Highly flammable liquid and vapor. Toxic if swallowed. Toxic in contact with skin. Toxic if inhaled. Suspected of causing cancer. Causes damage to organs.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe mist or vapor. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. If exposed: Call a poison center/doctor. If swallowed: Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Wash with plenty of water. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. In case of fire: Use appropriate media to extinguish. Keep cool. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466663 Material mfd. in United States

LOT: F145E0



For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.

For use with specified USP compendial tests.
Not for use as a drug. See SDS prior to use
at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSODIISOPROPYLAMINE (NDIPA) 1 mL (1 mg/mL)

(*N*-Isopropyl-*N*-nitrosoisopropylamine)

Danger! See outer package label for full hazard information.

This is a solution of N-nitrosodiisopropylamine (NDIPA) in methanol. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666

Cat. No. 1466663 Lot: F145E0

Material mfd. in United States

USP Nitrosamine Reference Standards



► NDBA Labels



REFERENCE STANDARD

N-NITROSODIBUTYLAMINE (NDBA) 1 mL (1 mg/mL)
(*N*-Butyl-*N*-nitroso-1-butanamine)



This is a solution of N-nitrosodibutylamine (NDBA) in methanol. For quantitative applications, use a value of 1.00 mg of N-nitrosodibutylamine per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.

Danger! Highly flammable liquid and vapor. Toxic if swallowed. Toxic in contact with skin. Toxic if inhaled. Suspected of causing cancer. Causes damage to organs.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Do not breathe mist or vapor. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/protective clothing/eye protection/face protection. If exposed: Call a poison center/doctor. If swallowed: Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Wash with plenty of water. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. In case of fire: Use appropriate media to extinguish. Keep cool. Store in a well-ventilated place. Keep container tightly closed. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466641 Material mfd. in United States

LOT: F145C0



For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSODIBUTYLAMINE (NDBA) 1 mL (1 mg/mL)
(*N*-Butyl-*N*-nitroso-1-butanamine)



Danger! See outer package label for full hazard information.

This is a solution of N-nitrosodibutylamine (NDBA) in methanol. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466641 Lot: F145C0
Material mfd. in United States

For use with specified USP compendial tests. Not for use as a drug. See SDS prior to use at www.usp.org/sds.

USP Nitrosamine Reference Standards



► NMBA Labels



REFERENCE STANDARD

N-NITROSOMETHYLAMINO BUTYRIC ACID (NMBA)

1 mL (1 mg/mL)

(4-[Methyl(nitroso)amino]butanoic acid)



This is a solution of N-nitrosomethylaminobutyric acid (NMBA) in acetonitrile. For quantitative applications, use a value of 0.99 mg of N-nitrosomethylaminobutyric acid per mL of solution on the as is basis. Discard unused portion after opening. Store in a freezer. Protect from light.

Danger! Highly flammable liquid and vapor. Harmful if swallowed. Harmful in contact with skin. Causes serious eye irritation. Harmful if inhaled. Suspected of causing cancer.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Keep away from heat/sparks/open flames/hot surfaces. - No smoking. Keep container tightly closed. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools. Take precautionary measures against static discharge. Avoid breathing vapors. Wash thoroughly after handling. Use only outdoors or in a well-ventilated area. Wear protective gloves/ protective clothing/eye protection/face protection. If swallowed: Call a poison center/doctor if you feel unwell. Rinse mouth. If on skin (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower. Call a poison center/doctor if you feel unwell. Wash contaminated clothing before reuse. If inhaled: Remove person to fresh air and keep comfortable for breathing. Call a poison center/doctor if you feel unwell. If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical advice/attention. If exposed or concerned: Get medical advice/attention. In case of fire: Use appropriate media to extinguish. Store in a well-ventilated place. Keep cool. Store locked up. Dispose of contents/container in accordance with local/regional/national/international regulations.

See certificate for any additional information.

KEEP AMPULE IN SECONDARY CONTAINER!

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666
Cat. No. 1466696 Material mfd. in United States

LOT: F145H0



For use with specified USP compendial tests. Not for use as a drug.
See SDS prior to use at www.usp.org/sds.



REFERENCE STANDARD

N-NITROSOMETHYLAMINO BUTYRIC ACID (NMBA) 1 mL (1 mg/mL)

(4-[Methyl(nitroso)amino]butanoic acid)



Danger! See outer package label for full hazard information.

This is a solution of N-nitrosomethylaminobutyric acid (NMBA) in acetonitrile. See USP Certificate and outer package for content information. Discard unused portion after opening. Store in a freezer. Protect from light.

See certificate for any additional information.

USP, 12601 Twinbrook Pkwy, Rockville, MD, +1-301-881-0666

Cat. No. 1466696

Lot: F145H0

Material mfd. in United States

For use with specified USP compendial tests.
Not for use as a drug. See SDS prior to use
at www.usp.org/sds.

USP Nitrosamine Reference Standards



► Development of other Nitrosamine standards

- Planning to develop NDMA-d6 for use as an internal standard
- Other labelled nitrosamine reference standards can be developed as required by the General Chapter and/or industry interest
 - ✓ C13NDMA-D6, NDEA-D10, NMBA-D3, NDBA-D18

Thank You



Summary



- ▶ **USP general chapter <1469> Nitrosamine Impurities to be published in PF46(5).**

Please send in your comments to below email id:

EXB@usp.org.

- ▶ **Nitrosamine impurities testing procedures to support the proposed general chapter <1469>.**
 - ▶ **6 USP Nitrosamine Impurities reference standards are available to support the test method for nitrosamine impurities.**
 - ▶ **This chapter will provide tools and solutions to manufacturers and regulators to analyze and monitor Nitrosamine impurities in medicines and protect patients.**
-

On-going activities and future plan:



- The development of test procedure(s) for drug products.
- The development of test procedure(s) for nitrosamine impurities in solvent(s).
- The test method validation for Ranitidine DS and DP.
- The development of simple test procedure(s) using technique other than triple-quad mass spectroscopy with adequate sensitivity for nitrosamines
- Metformin test procedure evaluation
- Harmonization with EDQM for nitrosamine impurities

Questions



Empowering a healthy tomorrow

Thank You



Empowering a healthy tomorrow