

Future of Commenting Forum USP-NF Online Update

Trey White, Ph.D.

March 29, 2022





USP-NF Online updates March, 2022





Latest Features



Digital Object Identifiers (DOIs)



What are Digital Object Identifiers (DOIs)?

A Digital Object Identifier (DOI) is a unique alphanumeric string assigned by a registration agency to identify content and provide a persistent link to its location on the Internet.

▶ How is USP implementing DOI in USP-NF Documentary Standard content?

Beginning with USP-NF 2022 Issue 1, USP will assign a DOI to all new and revised content in the USP-NF when it is made available electronically.

▶ Is the DOI system a Standard?

Yes. The DOI system was created by the International DOI Foundation and was adopted as International Standard ISO 26324 in 2012.

What are the benefits of using DOI?

- ▶ DOIs provide a robust mechanism for sharing and citation of scientific content, including the USP-NF. Additionally, DOI implementation in the USP-NF means that current Documentary Standard content will, for the first time, be indexed by public search engines and data providers, making it easier to find on the Internet.

Example of DOI



ACS ACS Publications C&EN CAS Find my institution Log In

ACS Publications Most Trusted. Most Cited. Most Read.

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Late-Stage β -C(sp³)-H Deuteration of Carboxylic Acids

Alexander Uttry, Sourjya Mal, and Manuel van Gemmeren*

Cite this: *J. Am. Chem. Soc.* 2021, XXXX, XXX, XXX-XXX
Publication Date: July 19, 2021
<https://doi.org/10.1021/jacs.1c06474>
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DOI: Standard form and abbreviated form



How DOI is displayed within a document:

Current DocID: GUID-33AD0880-7404-4169-BDD5-F74D808EE77F_4_en-US

DOI: https://doi.org/10.31003/USPNF_M150_04_01 ⓘ

DOI ref: [dsv5r](#) ⓘ

How DOI is displayed within a PDF:

Printed on: Wed Oct 27 2021, 05:16:05 AM(EST)

Printed by: Rebecca Cambroner

Official Status: Currently Official on 27-Oct-2021

Official Date: Official as of 01-May-2020

DOI Ref: dsv5r

DocId: 1_GUID-33AD0880-7404-4169-BDD5-F74D808EE77F_4_en-US

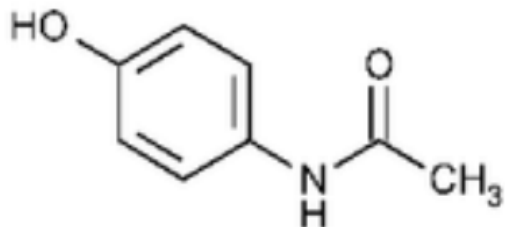
Document Type: USP

DOI: https://doi.org/10.31003/USPNF_M150_04_01

@2021 USPC

1

Acetaminophen



$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

- r_u = peak response from the *Sample solution*
- r_s = peak response from the *Standard solution*
- C_s = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)
- C_u = concentration of Acetaminophen in the *Sample solution* (mg/mL)

10/27/21, 6:16 AM

USP-NF Acetaminophen

Printed on: Wed Oct 27 2021, 06:16:05 am

Printed by: Rebecca Cambrono

Official Status: Currently Official on 27-Oct-2021

Official Date: Official as of 1-May-2020

Document Type: USP

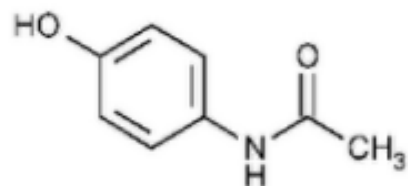
DocId: 1_GUID-33AD0880-7404-4169-BDD5-F74D808EE77F_4_en-US

DOI: https://doi.org/10.31003/USPNF_M150_04_01

DOI Ref: dsv5r

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Acetaminophen



$C_8H_9NO_2$

151.16

Acetamide, *N*-(4-hydroxyphenyl)-;

4'-Hydroxyacetanilide [103-90-2]; UNII: 36209ITL9D.

DOI Landing Page – Google Searchable!



This is a preview of
USP-NF content.

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Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules

» Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of aspirin ($C_9H_8O_4$), caffeine ($C_8H_{10}N_4O_2$), and dihydrocodeine bitartrate ($C_{18}H_{23}NO_3 \cdot C_4H_6O_6$).

USP Reference Standards for Purchase

[USP Dihydrocodeine Bitartrate RS](#)
[USP Aspirin RS](#)
[USP Caffeine RS](#)
[USP Salicylic Acid RS](#)

United States Pharmacopeia (2022). *USP Monographs, Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules*. USP-NF, Rockville, MD: United States Pharmacopeia.

DOI: https://doi.org/10.31003/USPNF_M6312_03_01
Doc ID: GUID-9B6F9EFB-F1E6-4149-AE59-991F2E7CCAFO_3_en-US

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Sneak-peek into the Upcoming USP-NF Online + PF



How We Got Here...



- ▶ **Goal: To improve the user experience, particularly for “less experienced users,” and to update the UI to current industry standards.**
- ▶ Design done by *Atomic Object*, which has extensive UX expertise, and has worked on the USP-NF Online since 2017.
- ▶ Inputs included:
 - Almost 4 years of feedback from users, including emails with comments, suggestions, and complaints from users in many different roles at a wide range of companies inside and outside the US
 - Analysis of navigation and usage patterns from the Nabu platform
 - Multiple surveys, with responses from >2500 individuals
 - Focus groups and one-on-one “live usage” interviews from more than 30 users

DISCLAIMER



- ▶ The following images are design mock-ups – **NOT the actual pages**
- ▶ The final look and feel may be slightly different than shown in these mock-ups
 - There are multiple iterations of some of these views and some are still evolving – please disregard small inconsistencies between screens
- ▶ Please disregard dates and document status – these are examples only, NOT actual USP-NF documents

USP-NF Online Home Page - Current



The screenshot shows the USP-NF Online Home Page. At the top is a dark red navigation bar with the USP-NF logo, a search bar containing the text "Search for General Chapter, Monograph here!", and user information including "Hi," "Bookmarks", "EN", and a "Help" link. Below the navigation bar is a white header with a home icon and menu items: "START HERE", "GENERAL NOTICES", "GENERAL CHAPTERS", "MONOGRAPHS", "REAGENTS AND REFERENCE TABLES", and "RESOURCES". The main content area features a "USP-NF Online Dashboard" section with a heading and a help icon. Below this is a paragraph: "Get the most out of your USP-NF Online! Explore this area for helpful video tutorials and links to USP resources." The dashboard is organized into two rows of four cards each. The first row includes: "Supporting COVID-19 health response" (yellow card), "Improved Search Tutorial" (dark red card), "Navigation Basics Tutorial" (dark red card), and "COVID-19 Vaccine Handling Toolkit" (yellow card). The second row includes: "USP-NF Mobile App" (dark red card), "Please Read: Release Notes" (orange card), "Spanish USP-NF Online" (dark red card), and "Understanding Official Status Tutorial" (dark red card). Each card has a title, a brief description, and a call-to-action link. A circular arrow icon is located at the bottom right of the dashboard area.

USP-NF Online Dashboard






Get the most out of your USP-NF Online! Explore this area for helpful video tutorials and links to USP resources.

USP-NF ONLINE DASHBOARD




Supporting COVID-19 health response	Improved Search Tutorial Get relevant contextual results much faster.	Navigation Basics Tutorial Browse smartly with information arranged relevantly.	COVID-19 Vaccine Handling Toolkit
STAY CONNECTED DURING COVID-19 Click here for latest updates to services	IMPROVED SEARCH TUTORIAL Watch a video tutorial on the improved search tool!	NAVIGATION BASICS TUTORIAL Learn how to navigate the new USP-NF Online	COVID-19 VACCINE HANDLING TOOLKIT Click here to download the toolkit
USP-NF Mobile App Download this app to have access to the USP-NF Online on your device.	Please Read: Release Notes Please read for known issues on this release.	Spanish USP-NF Online The Spanish USP-NF Online will be launched in 2020! Click here for FAQs.	Understanding Official Status Tutorial What you need to know about USP-NF versions and official status
USP-NF MOBILE APP USP-NF Mobile App is here! Click here for the latest info	PLEASE READ: RELEASE NOTES Please read for known issues on this release	SPANISH USP-NF ONLINE Click here for details	OFFICIAL STATUS TUTORIAL Understand official dates for monographs and general chapters

Updated USP-NF + PF: Dashboard



  USP-NF   

My Dashboard

-  **Currently Official** [USPNF 2021 Issue 3](#) *Published June 01, 2021*
-  **PF 47(6)** *Commenting closed*
-  **PF 48(1)** *Commenting open for 55 more days* [January 3, 2022 to March 31, 2022](#)






My Resources

MY VIEWING ACTIVITY BOOKMARKS COMMENTS




DATE ▾	PAGE ▾	SECTION ▾	PUBLICATION ▾
04-Feb-2022	Test Solutions	Reagents	Forum USP41-NF36
03-Feb-2022	Isopropyl Alcohol	Monographs	Forum USPNF 2021 Issue 3
01-Feb-2022	〈17〉 Prescription Container Labeling	General Chapters	Forum USPNF 2021 Issue 3

Updated USP-NF + PF: Dashboard- A Closer Look



Navigation bar:   USP-NF   

My Dashboard

-  **Currently Official** [USPNF 2021 Issue 3](#) [Published June 01, 2021](#)
-  **PF 47(6)** [Commenting closed](#)
-  **PF 48(1)** [Commenting open for 55 more days](#) [January 3, 2022 to March 31, 2022](#)

Updated USP-NF + PF: Bookmarks



MENU USP-NF [Advanced Search](#) [Home](#) [User](#) [EN](#)

My Dashboard

Currently Official [USPNF 2021 Issue 3](#) *Published June 01, 2022*

PF 47(6) *Commenting closed*

PF 48(1) *Commenting open for 55 more days* *January 3, 2022*

YOUR BOOKMARKS

- [Acetaminophen Tablets, Monograph](#)
- [Acetaminophen Capsules, Monograph](#)
- [\(227\) 4-Aminophenol in Acetaminophen-Containing Drugs, General Chapter](#)
- [USP Admissions List, Front Matter](#)

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My Resources

[MY VIEWING ACTIVITY](#) **BOOKMARKS** [COMMENTS](#)

DATE ▾	PAGE ▾	SECTION ▾	PUBLICATION ▾
04-Feb-2022	Test Solutions	Reagents	Forum USP41-NF36
03-Feb-2022	Isopropyl Alcohol	Monographs	Forum USPNF 2021 Issue 3
01-Feb-2022	(17) Prescription Container Labeling	General Chapters	Forum USPNF 2021 Issue 3

Navigation- Current



Alphabet Bar Filters Document Results

USP-NF Hi, Trey Bookmarks EN Help

START HERE GENERAL NOTICES GENERAL CHAPTERS **MONOGRAPHS** REAGENTS AND REFERENCE TABLES RESOURCES

USP

ALL A B C D E F G H I J K L

Filters

Clear All
Expand All Collapse All

► PUBLICATION

► MONTHLY POSTING

▼ OFFICIAL STATUS

- Official (3888)
- To Be Official (218)
- No Longer Official (3568)
- Never Official (140)

USP

Click here for an alphabetical list of USP monographs

NF

Click here for an alphabetical list of NF monographs along with a list of excipients used in these monographs

Dietary Supplements

Click here for an alphabetical list of Dietary Supplement monographs

Global Health

Click here for an alphabetical list of Global Health monographs

Monographs

This section contains a complete list of monographs associated with the USP-NF edition you selected. Monographs contain tests, procedures, and acceptance criteria to ensure the identity, strength, quality, and purity of an article. A monograph also contains the article's name, definition, specification, and other requirements related to packaging, storage, and labeling. Refer to the General Notices under the "Start Here" tab for more information.

- Acetaminophen
- Acebutolol
- Acepromazine

Updated USP-NF + PF: New Look for Navigation



✕
 USP-NF

🏠
📖
👤

- [🏠 Dashboard](#)
- [Start Here ▶](#)
- [General Notices ▶](#)
- [General Chapters ▶](#)
- [Monographs ▶](#)
- [Reagents & Reference Tables ▶](#)
- [Resources ▶](#)

GENERAL CHAPTERS
Guidelines on activities related to tests and procedures in monographs, descriptions of tests and procedures, general information on the interpretation of compendial requirements, and general guidance on official substances or official products.

- [General Tests & Assays \(1 to 999\) ▶](#)
- [General Information \(1000 to 1999\)](#)
- [Dietary Supplements \(2000 to 2999\)](#)
- [Chapter Charts](#)

GENERAL TESTS & ASSAYS

- [General Requirements for Tests and Assays \(1 to 20\)](#)
- [Apparatus for Tests & Assays \(21 to 50\)](#)
- [Microbiological Tests \(51 to 80\)](#)
- [Biological Tests & Assays \(81 to 180\)](#)
- [Chemical Tests & Assays ▶](#)
- [Physical Tests & Determinations \(601 to 999\)](#)

CHEMICAL TESTS & ASSAYS

- [Identification Tests \(181 to 203\)](#)
- [Limit Tests \(204 to 300\)](#)
- [Other Tests & Assays \(301 to 600\)](#)

MY VIEWING ACTIVITY BOOKMARKS COMMENTS

DATE ▾	PAGE ▾	SECTION ▾	PUBLICATION ▾
04-Feb-2022	Test Solutions	Reagents	Forum USP41-NF36

Document View – Current Version



usp USP-NF Hi, [Bookmarks](#) [EN](#) [Help](#)

[START HERE](#) [GENERAL NOTICES](#) [GENERAL CHAPTERS](#) [MONOGRAPHS](#) [REAGENTS AND REFERENCE TABLES](#) [RESOURCES](#)

CURRENTLY OFFICIAL
Official as of 1-May-2020

Document Tools

[HISTORY](#) [CONTENTS](#) [SUPPORT](#)

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Official as of 1-May-2020

OLDER VERSION
Official 1-Jan-2018 to 30-Apr-2020

BOOKMARKED

MONOGRAPHS > [USP](#) > [ACETAMINOPHEN](#) **REFERENCE STANDARDS**

Acetaminophen

$C_8H_9NO_2$ 151.16

Updated USP-NF + PF: Document - Currently Official



MENU USP-NF Search Filters EN

E CURRENTLY OFFICIAL Official as of 01-May-2021

Revisions Off

[Monographs](#) ▶ [USP](#) ▶ [Atenolol](#)

Atenolol

CLICK IMAGE TO ENLARGE

$C_{14}H_{22}N_2O_3$ 266.34
Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]-;
2-[p-[2-Hydroxy-3-(isopropylamino)propoxy]-phenyl] acetamide [29122-68-7]; UNII: 50VV3VW0T1.

DEFINITION
Atenolol contains NLT 98.0% and NMT 102.0% of $C_{14}H_{22}N_2O_3$, calculated on the dried basis.

IDENTIFICATION
Change to read:

- A. [SPECTROSCOPIC IDENTIFICATION TESTS <197>](#), [Infrared Spectroscopy: 197K](#) (CN 1-May-2020)

Change to read:

- B. [SPECTROSCOPIC IDENTIFICATION TESTS <197>](#), [Ultraviolet-Visible Spectroscopy: 197U](#) (CN 1-May-2020)

Sample solution: 20 µg/mL in methanol

ASSAY

Tools

- Print
- Email
- PDF
- Set Alert
- Bookmark
- Search Term

Updated USP-NF + PF: Doc Status Comparisons



MENU USP-NF X Search Filters Home EN ? | Bookmarks User

E **CURRENTLY OFFICIAL** Official as of 01-May-2021 ? Revisions Off ◀ Prev Next ▶ Reference Standards Document Info

MENU USP-NF X Search Filters Home EN ? | Bookmarks User

RB **NOT YET OFFICIAL** To be Official on 1-Dec-2022 ? Revisions Off ◀ Prev Next ▶ Reference Standards Document Info

MENU USP-NF X Search Filters Home EN ? | Bookmarks User

OLDER VERSION Official on 01-May-2021 ? Revisions Off ◀ Prev Next ▶ Reference Standards Document Info

MENU USP-NF X Search Filters Home EN ? | Bookmarks User

FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022 ? Revisions Off ◀ Prev Next ▶ Reference Standards Document Info

Full Document Views with Watermarks



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FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022
CURRENTLY OFFICIAL Official as of 01-May-2021
OLDER VERSION Effective 01-May-2021
OLDER VERSION Effective 01-Nov-2020 to 30-Apr-2021
FORUM PF 46(2) 02-Mar-2020 to 31-May-2020

(1469) Nitrosamine Impurities

1. INTRODUCTION
The presence of nitrosamine impurities has been detected recently in several drug substances and drug products. In 2016, N-ethyl-N-nitrosodimethylamine (NEDA) in some valproate drug substances and the drug products manufactured from drug substances using specific synthetic routes. The development of analytical procedures to quantify these two nitrosamine impurities. As additional pharmaceuticals were evaluated, added as impurities of concern. Given the potentially broad implications of the presence of carcinogenic members of this class of based approach for the control of nitrosamine impurities to ensure that the potential presence of nitrosamines in drug substances. Recommendations are provided regarding: a) the establishment of controls of nitrosamine levels in order to ensure their elimination procedures used to monitor nitrosamine levels.

2. NITROSAMINE IMPURITIES
Nitrosamines addressed in this general chapter are listed in Table 1 by their common names and chemical names. This list is a compilation of the information additional nitrosamines are identified as potential concerns, the principles described herein should be applied for the assessment of the appropriate regulatory authority should be contacted for determining appropriate AI limits. The potential presence of any one or more of these nitrosamines is not intended to be exhaustive but represents those that have been observed and communicated by regulators and the nitroso compounds are among the structural groups of high potency mutagenic carcinogens in several animal species, and some are classified as the "highest of concern" in ICH M7. Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit their Recommendation to control the impurities at or below the acceptable cancer risk. As a result of the potential toxicity associated with presence in pharmaceutical materials.

Common Name and Chemical Name	Acronym	CAS #	Structure
Nitrosodimethylamine N-Methyl-N-nitrosomethanamine	NDMA	62-75-9	
Nitrosodimethylamine N-Ethyl-N-nitrosobutylamine	NDEA	55-18-5	
Nitrosodipropylamine N-Isopropyl-N-nitrosodipropylamine	NDIPA	601-77-4	
Nitrosoethylpropylamine N-Ethyl-N-nitroso-2-propanamine	NEIPA	16329-04-1	
Nitrosobutylamine N-Butyl-N-nitroso-1-butanamine	NDBA	924-18-3	
Nitrosodiphenylamine N-Methyl-N-nitrosophenylamine	NMPA	614-00-6	
Nitrosomethylaminobutyric acid 4-Methyl(nitrosamino)butanoic acid	NMBA	61445-55-5	

IMPURITIES
Inorganic Iodides

Standard solution: 0.01 mg/mL of USP Atanolol BS in Mobile phase
Sample solution: 0.01 mg/mL of Atanolol in Mobile phase. Sonicate for 5 min
Chromatographic system
(See Chromatography <621> System Suitability)

Mode: LC
Detector: UV 226 nm
Column: 3.9 mm x 30 cm; packing L1
Flow rate: 0.6 mL/min
Injection size: 10 µL
System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 5000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of C₁₂H₁₇N₃O₂ in the portion of Atanolol take

f_u = peak response from the Sample solution
 f_s = peak response from the Standard solution
 C_s = concentration of USP Atanolol BS in the Standard solution
 C_u = concentration of Atanolol in the Sample solution (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

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(1469) Nitrosamine Impurities

1. INTRODUCTION
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Common Name and Chemical Name	Acronym	CAS #	Structure	Chemical Name
Nitrosodimethylamine N-Methyl-N-nitrosomethanamine	NDMA	62-75-9		C ₂ H ₇ N ₂ O
Nitrosodimethylamine N-Ethyl-N-nitrosobutylamine	NDEA	55-18-5		C ₆ H ₁₃ N ₂ O
Nitrosodipropylamine N-Isopropyl-N-nitrosodipropylamine	NDIPA	601-77-4		C ₁₂ H ₁₉ N ₂ O
Nitrosoethylpropylamine N-Ethyl-N-nitroso-2-propanamine	NEIPA	16329-04-1		C ₇ H ₁₅ N ₂ O
Nitrosobutylamine N-Butyl-N-nitroso-1-butanamine	NDBA	924-18-3		C ₈ H ₁₇ N ₂ O
Nitrosodiphenylamine N-Methyl-N-nitrosophenylamine	NMPA	614-00-6		C ₇ H ₉ N ₂ O
Nitrosomethylaminobutyric acid 4-Methyl(nitrosamino)butanoic acid	NMBA	61445-55-5		C ₅ H ₉ N ₂ O ₃

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(1469) Nitrosamine Impurities

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The presence of nitrosamine impurities has been detected recently in several drug substances and drug products. In 2016, N-ethyl-N-nitrosodimethylamine (NEDA) in some valproate drug substances and the drug products manufactured from drug substances using specific synthetic routes. The development of analytical procedures to quantify these two nitrosamine impurities. As additional pharmaceuticals were evaluated and, in some cases, tests added as impurities of concern. Given the potentially broad implications of the presence of carcinogenic members of this class of chemical, this chapter is based approach for the control of nitrosamine impurities to ensure that the potential presence of nitrosamines in drug substances and drug products is identified. Recommendations are provided regarding: a) the establishment of controls of nitrosamine levels in order to ensure their elimination or reduction; and b) procedures used to monitor nitrosamine levels.

2. NITROSAMINE IMPURITIES
Nitrosamines addressed in this general chapter are listed in Table 1 by their common names and chemical names. This list is a compilation of the information additional nitrosamines are identified as potential concerns, the principles described herein should be applied for the assessment of these nitrosamines. If appropriate regulatory authority should be contacted for determining appropriate AI limits. The potential presence of any one or more of these nitrosamines is not intended to be exhaustive but represents those that have been observed and communicated by regulators and the nitroso compounds are among the structural groups of high potency mutagenic carcinogens in several animal species, and some are classified as the "highest of concern" in ICH M7. Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (I) recommendation to control the impurities at or below the acceptable cancer risk. As a result of the potential toxicity associated with these impurities, it is present in pharmaceutical materials.

Common Name and Chemical Name	Acronym	CAS #	Structure	Chemical Name
Nitrosodimethylamine N-Methyl-N-nitrosomethanamine	NDMA	62-75-9		C ₂ H ₇ N ₂ O
Nitrosodimethylamine N-Ethyl-N-nitrosobutylamine	NDEA	55-18-5		C ₆ H ₁₃ N ₂ O
Nitrosodipropylamine N-Isopropyl-N-nitrosodipropylamine	NDIPA	601-77-4		C ₁₂ H ₁₉ N ₂ O
Nitrosoethylpropylamine N-Ethyl-N-nitroso-2-propanamine	NEIPA	16329-04-1		C ₇ H ₁₅ N ₂ O
Nitrosobutylamine N-Butyl-N-nitroso-1-butanamine	NDBA	924-18-3		C ₈ H ₁₇ N ₂ O
Nitrosodiphenylamine N-Methyl-N-nitrosophenylamine	NMPA	614-00-6		C ₇ H ₉ N ₂ O
Nitrosomethylaminobutyric acid 4-Methyl(nitrosamino)butanoic acid	NMBA	61445-55-5		C ₅ H ₉ N ₂ O ₃

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FORUM PF 46(2) 02-Mar-2020 to 31-May-2020	FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022	FORUM PF 46(2) 02-Mar-2020 to 31-May-2020	FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022	FORUM PF 46(2) 02-Mar-2020 to 31-May-2020	FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022
IA	62-75-9	IA	62-75-9	IA	62-75-9
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₂ H ₇ N ₂ O		C ₂ H ₇ N ₂ O		C ₂ H ₇ N ₂ O
	74.08		74.08		74.08
	55-18-5		55-18-5		55-18-5
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₆ H ₁₃ N ₂ O		C ₆ H ₁₃ N ₂ O		C ₆ H ₁₃ N ₂ O
	102.14		102.14		102.14
	601-77-4		601-77-4		601-77-4
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₁₂ H ₁₉ N ₂ O		C ₁₂ H ₁₉ N ₂ O		C ₁₂ H ₁₉ N ₂ O
	130.19		130.19		130.19
	16329-04-1		16329-04-1		16329-04-1
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₇ H ₁₅ N ₂ O		C ₇ H ₁₅ N ₂ O		C ₇ H ₁₅ N ₂ O
	116.16		116.16		116.16
	924-18-3		924-18-3		924-18-3
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₈ H ₁₇ N ₂ O		C ₈ H ₁₇ N ₂ O		C ₈ H ₁₇ N ₂ O
	158.25		158.25		158.25
	614-00-6		614-00-6		614-00-6
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₇ H ₉ N ₂ O		C ₇ H ₉ N ₂ O		C ₇ H ₉ N ₂ O
	136.15		136.15		136.15
	61445-55-5		61445-55-5		61445-55-5
	CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE		CLICK IMAGE TO ENLARGE
	C ₅ H ₉ N ₂ O ₃		C ₅ H ₉ N ₂ O ₃		C ₅ H ₉ N ₂ O ₃
	146.15		146.15		146.15

3. SOURCES OF NITROSAMINES
There are a number of pathways by which nitrosamines can be introduced into pharmaceutical drug products. Specifically, nitrosamines are formed in chemical reaction of secondary or tertiary amines with nitrites (the latter via intermediate degradation) under acidic conditions (see 3.1. Nitrosamine Formation Reaction). Some examples of the reported sources or pathways leading to the generation of nitrosamines identified empirically or reported in literature (2.2) include (but are not limited to) the following:
• Drug substance processing under specific conditions and in the presence of certain reagents, solvents, raw materials, and processing aids. There is evidence that, despite processing and purification steps, reactive species, whether intentionally added to or formed during the process/reaction sequence (e.g., nitrites and secondary amines in the presence of acidic conditions), can carry over to subsequent steps (see 3.1. Nitrosamine Formation Reaction). Special attention should be given to the formation of nitrosamines containing heterocycles by employing acids followed by quenching with nitrous acid to remove excess acids.
• The drug substance itself, which may degrade under some conditions resulting in the formation of nitrosamines (e.g., valmidine).
• Degradation of solvents (e.g., dimethylformamide (DMF) leading to the formation of dialyl amines).
• Impurities in raw materials, solvents (including recycled solvents), reagents, or analytes.
• Impurities in materials and intermediates, reagents, and solvents used to prepare the starting materials or intermediates.
• Impurities in water, excipients, or processing aids used in the production of the finished drug product.
• During drug product manufacturing under certain reaction conditions and in the presence of requisite processing necessary for the formation of nitrosamines.
• Impurities in the container-closure system for the finished drug product, which may include impurities capable of forming nitrosamines, especially if associated with materials containing amines and potential sources of a nitrating agent (e.g., nitrite, nitrocellulose).
A risk assessment should be conducted to determine the materials that contribute to the potential for inclusion of nitrosamines in the drug product. All potential sources for the introduction of nitrosamines should be considered in the risk assessment including, for example, the drug substance, excipients, water, solvents, the manufacturing process, packaging components, and formation on stability. See Figure 1 for a diagram of some potential sources to be considered.

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FORUM PF 47(6) 01-Nov-2021 to 31-Jan-2022 Revisions Off Reference Standards Document Info

[General Chapters](#) ▶ [General Information](#) ▶ [1469 Nitrosamine Impurities](#)

<1469> Nitrosamine Impurities

1. INTRODUCTION

The presence of nitrosamine impurities has been detected recently in several drug substances and drug products. In 2018, *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) were detected in some valsartan drug substances and the drug products manufactured from drug substances using specific synthetic routes. This observation triggered extensive synthetic route assessments and development of analytical procedures to quantify these two nitrosamine impurities. As additional pharmaceuticals were evaluated and, in some cases tested, other nitrosamines beyond NDMA and NDEA were added as impurities of concern. 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; and b) analytical procedure performance characteristics for procedures used to monitor nitrosamine levels.

2. NITROSAMINE IMPURITIES

Nitrosamines addressed in this general chapter are listed in [Table 1](#) by their common names and chemical names. This list is a compilation of the information shared by multiple global health authorities. 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. The potential presence of any one or more of these impurities is dependent on the reaction chemistries and processes. The list of nitrosamines 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.

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 (1)*, a designation that carries with it a recommendation to control the impurities at or below the acceptable cancer risk. 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.

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FORUM PF 46(2) 02-Mar-2020 to 31-May-2020

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$C_{14}H_{22}N_2O_3$ 266.34
Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]-;
2-[p-[2-Hydroxy-3-(isopropylamino)propoxy]-phenyl] acetamide [29122-68-7]; UNII: 50VV3VW0T1.

DEFINITION
Atenolol contains NLT 98.0% and NMT 102.0% of $C_{14}H_{22}N_2O_3$, calculated on the dried basis.

IDENTIFICATION
Change to read:

- A. **SPECTROSCOPIC IDENTIFICATION TESTS** <197>, **Infrared Spectroscopy: 197K** (CN 1-MAY-2020)

Change to read:

- B. **SPECTROSCOPIC IDENTIFICATION TESTS** <197>, **Ultraviolet-Visible Spectroscopy: 197U** (CN 1-MAY-2020)

Sample solution: 20 µg/mL in methanol

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Nitrosodimethylamine N-Methyl-N-nitrosomethanamine	NDMA	62-75-9	 CLICK IMAGE TO ENLARGE	C ₂ H ₇ N ₂ O
Nitrosodiethylamine N-Ethyl-N-nitrosoethanamine	NDEA	55-18-5	 CLICK IMAGE TO ENLARGE	C ₄ H ₁₁ N ₂ O
Nitrosodiisopropylamine N-Isopropyl-N-nitrosoisopropylamine	NDIPA	601-77-4	 CLICK IMAGE TO ENLARGE	C ₆ H ₁₅ N ₂ O
Nitrosoethylisopropylamine N-Ethyl-N-nitroso-2-propanamine	NEIPA	16339-04-1	 CLICK IMAGE TO ENLARGE	C ₇ H ₁₇ N ₂ O
Nitrosodibutylamine N-Butyl-N-nitroso-1-butanamine	NDBA	924-16-3	 CLICK IMAGE TO ENLARGE	C ₁₀ H ₂₃ N ₂ O
Nitrosomethylphenylamine			 CLICK IMAGE TO ENLARGE	C ₇ H ₉ N ₂ O

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EXPERT COMMITTEE
(SM22020) Small Molecules 2

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The screenshot displays the USP-NF search interface. At the top left is the USP-NF logo. A search bar contains the text "197", with an orange arrow pointing to it. To the right of the search bar are navigation links: "Hi," with a dropdown arrow, "Bookmarks" with a dropdown arrow, "EN" with a dropdown arrow, and "Help" with an external link icon. Below the search bar, there are navigation links: "START HERE" with a dropdown arrow, "GENERAL" with a dropdown arrow, "REAGENTS AND REFERENCE TABLES" with a dropdown arrow, and "RESOURCES" with a dropdown arrow. The search results are displayed in a dropdown menu. At the top of the menu is a checkbox labeled "Search by document title only". Below this is the text "Search official documents for '197' (1,763 results)". The results are categorized into three sections: "MONOGRAPHS (2,252 results)", "GENERAL CHAPTERS (61 results)", and "REAGENTS (9 results)". Each section lists specific search results and a link to view all results for that category. The background of the page shows various USP-NF content, including a "Supporting health resp" banner, a "STAY CONNECTED DURING COVID-19" banner, and a "COVID-19 Vaccine Handling Toolkit" banner.

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MONOGRAPHS (2,252 results)

Procarbazine Hydrochloride

Testosterone Propionate

Bromodiphenhydramine Hydrochloride

Sulfisoxazole Acetyl

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GENERAL CHAPTERS (61 results)

(197) Spectroscopic Identification Tests

Chapter Charts

(2) Oral Drug Products—Product Quality Tests

(2251) Screening for Undeclared Drugs and Drug Analogu...

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REAGENTS (9 results)

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Octyl Sulfate, Sodium Salt

COVID-19 Vaccine Handling Toolkit

COVID-19 VACCINE HANDLING TOOLKIT

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What you need to know about USP-NF versions and official status

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Your Recent Activity

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- 📄 Acetaminophen Tablets, Monograph
- 📄 Acetaminophen Capsules, Monograph
- 📄 Acetaminophen Suppositories, Monograph
- 📖 (227) 4-Aminophenol in Acetaminophen-Containing Drugs, General Chapter
- 📖 (858) Raman Spectroscopy, General Chapter
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 - Acetate**, Suggestion (3 Results)
 - Acetic Acid**, Suggestion (112 Results)
 - Acetyl Chloride**, Suggestion (15 Results)
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▶ **MONTHLY POSTING**

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 Never Official (7)

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Acetaminophen
 Monographs Official as of 1-May-2020
Acetaminophen. C8H9NO2 151.16 Acetamide, N-(4-hydroxyphenyl)-; 4'-Hydroxyacetanilide 103-90-2

Acetaminophen Tablets
 E **Monographs** Official as of 1-Oct-2021
Acetaminophen Tablets. 4-Aminophenol. C6H7NO 109.13. Detector: UV 272 nm. Column temperature: 40

Acetaminophen Capsules
 Monographs Official as of 1-Dec-2014
Acetaminophen Capsules. USP Reference Standards 11 USP **Acetaminophen** RS. B. Thin-Layer

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<711> Dissolution
 General Chapters Official as of 1-May-2016
<711> **Dissolution. Dissolution** medium: Proceed as directed for Immediate-Release Dosage Forms

<711> Dissolution
 General Chapters To be Official on 1-May-2022
<711> **Dissolution. Dissolution** medium: Prepare as directed for Immediate-Release Dosage Forms

<1087> Intrinsic Dissolution—Dissolution Testing Procedures for Rotating Disk and Sta
 General Chapters Official as of 1-Dec-2020
<1087> Intrinsic **Dissolution—Dissolution** Testing Procedures for Rotating Disk and Stationary Disk

ICON KEY ?
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ORIGIN OF CHANGE KEY ?
E: Errata
IRA: Interim Revision Announcements
RB: Revision Bulletin
H: Harmonization

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<711> Dissolution
🕒 General Chapters To be Official on 1-May-2022
<711> **Dissolution. Dissolution** medium: Prepare as directed for Immediate-Release Dosage Forms

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