Control of Nitrosamine Impurities in Human Drugs

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

www.fda.gov

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

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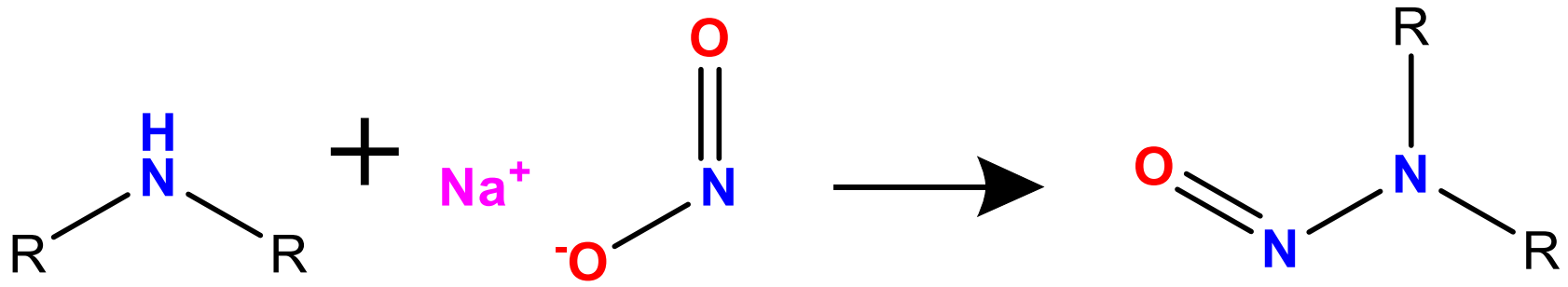
Nitrosamines

- NDMA and other nitrosamines are common contaminants in low amounts (ppm) in foods, beverages, cosmetics, water, tobacco products and consumer goods (1-4).



1. Gushgari AJ, Halden RU. Critical review of major sources of human exposure to N-nitrosamines. Chemosphere. 2018;210:1124-36.
2. Kocak D, Ozel MZ, Gogus F, Hamilton JF, Lewis AC. Determination of volatile nitrosamines in grilled lamb and vegetables using comprehensive gas chromatography - nitrogen chemiluminescence detection. Food Chem. 2012;135(4):2215-20.
3. Park JE, Seo JE, Lee JY, Kwon H. Distribution of Seven N-Nitrosamines in Food. Toxicol Res. 2015;31(3):279-88.
4. Lim DS, Roh TH, Kim MK, Kwon YC, Choi SM, Kwack SJ, et al. Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics. J Toxicol Environ Health A. 2018;81(12):465-80.

Timeline of US Drug Nitrosamine Issues

- June 2018 – FDA informed of the presence of NDMA from a valsartan manufacturer
- July 2018 – voluntary recall of valsartan due to NDMA
- Sept 2018 – NDEA detected in a previously recalled valsartan
- Oct 2018 – irbesartan recalled due to NDEA
- Nov 2018 – losartan recalled to due to NDEA
- Dec 2018 – FDA posted interim limits for NDMA/NDEA in ARBs

Timeline of US Drug Nitrosamine Issues (2)

- Feb 2019 – FDA posted interim limit for NMBA in ARBs
- March 2019 – NMBA detected in losartan
- “FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market.”
- June 2019 – FDA became aware of laboratory testing that detected NDMA in ranitidine
- Aug 2019 – General Advice letter to ARB applicants and DMF holders posted to FDA.gov
- Root causes for nitrosamines in ARBs discussed
- Sept 2019 – ranitidine recalled due to NDMA

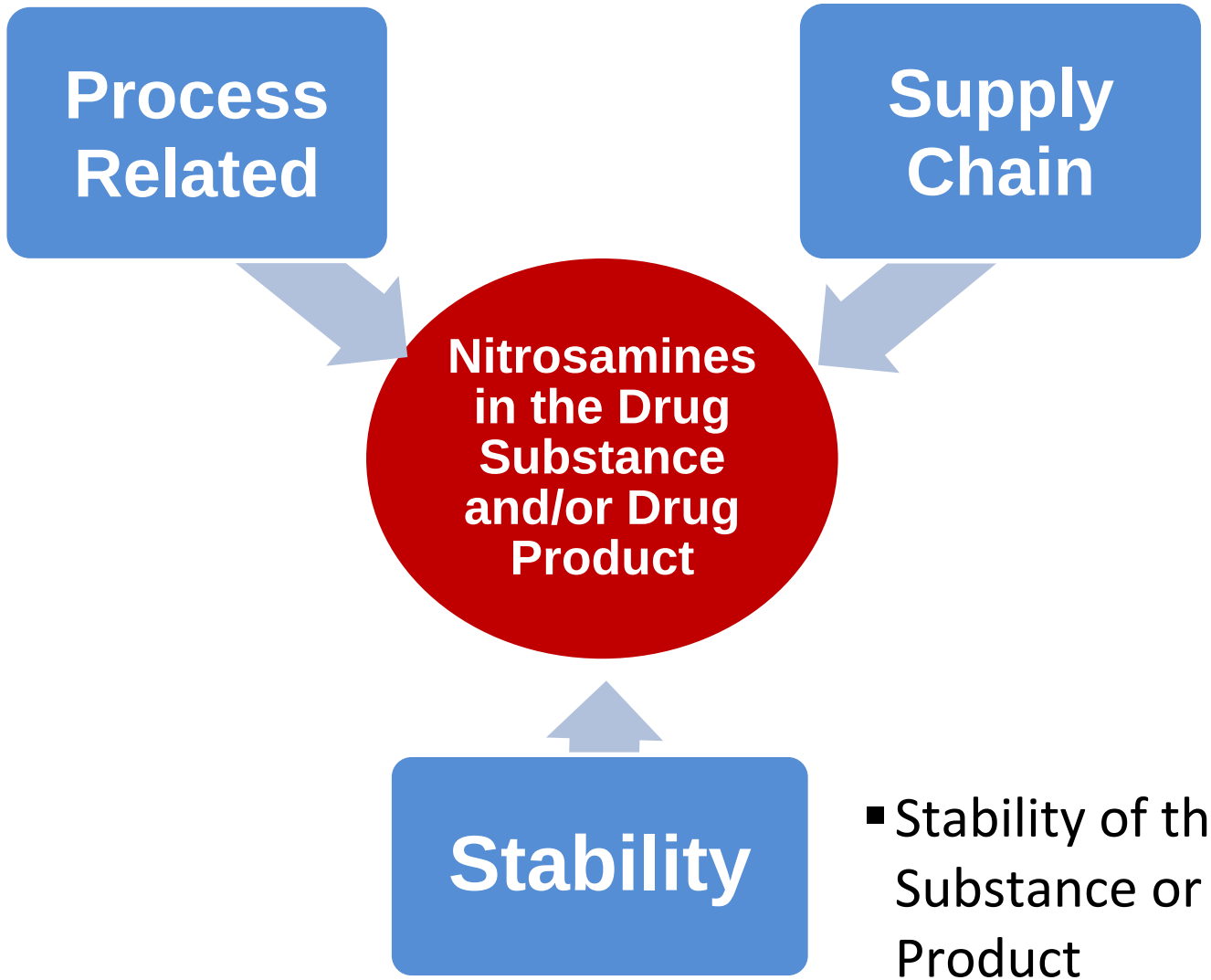
Timeline of US Drug Nitrosamine Issues (3)

- Dec 2019 – NDMA detected in metformin but recalls not warranted
- Dec 2019 – 1-methy-4-nitrosopiperazine (MNP) reported in rifampin
- Jan 2020 – nizatidine recalled due to NDMA
- April 2020 – FDA requested withdrawal of all ranitidine from the U.S. market
- May 2020 – metformin extended-release recalled due to NDMA
- May 2020 – 1-cyclopentyl-4-nitrosopiperazine (CPNP) reported in rifapentine

Outcome:

Over the past 3 years industry and regulators have learned a lot about what *factors* lead to the risk of nitrosamine impurities in pharmaceuticals

Root Causes of Nitrosamine Contamination



- Physicochemical properties of the starting materials, intermediates or Drug Substance
- Specific process conditions
- Impurities in or reactions with raw materials

➢ **Development and Control Strategies**

- Use of recovered or recycled materials or other intermediates contaminated with nitrosamines
- Cross-contamination in multi-purpose facilities

➢ **Quality Oversight**

- Stability of the Drug Substance or Drug Product
- Excipient compatibility

➢ **Quality Oversight**

Guidance was published on Sept 1st, 2020 last revised February 2021.

Guidance link: https://www.fda.gov/media/141720/download
Comment submission (Docket ID: FDA-2020-D-1530):
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

Laboratory Testing Methods-An Example

- Once a signal for nitrosamines in a specific drug is reported, a **fit for purpose technique** is chosen
- Testing API first and then finished products
- Method validation
  - ICH Q2(R1) Validation of Analytical Procedures
- Orthogonal technique(s)
  - Primarily used to confirm positive results
- Dissemination of methods
  - A guide-each lab should develop and validate fully

Picking the Right Platform

Target of quantitation limit for NDMA

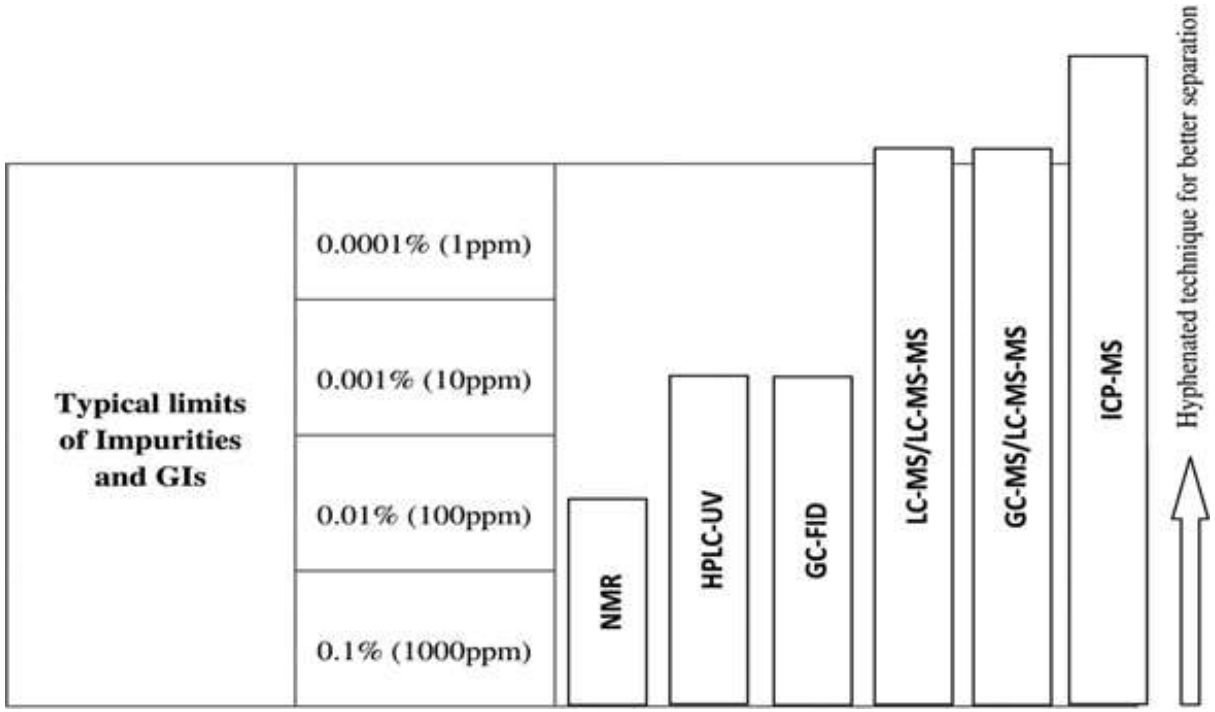
Drug	Maximum Daily Dose (mg/day)	NDMA	
		ADI (ng)	ng/mg (ppm)
Valsartan	320	96	0.3
Ranitidine	300	96	0.32
Metformin ER	2550	96	0.038

ADI: acceptable daily intake

NDMA: N-nitrosodimethylamine

$$(\text{ng/mg (ppm)} = \frac{W_{nitrosamine}\,(ng)}{W_{API}\,(mg)})$$

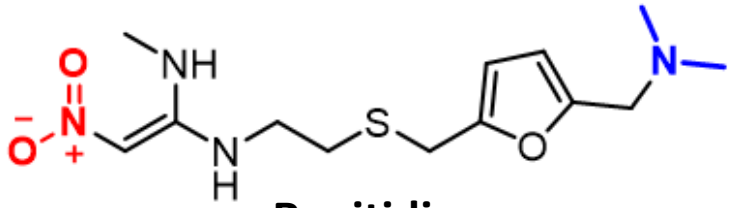
Detection limit of common instruments



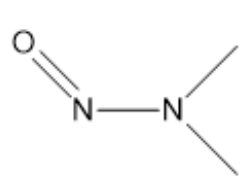
Evolution of regulatory aspects of genotoxic impurities in pharmaceuticals: Survival of the fittest; Journal of Liquid Chromatography & Related Technologies, 2017, vol 40, issue 15, 759 - 769

Mass Spectrometry-Based Methods are Needed for Trace Level Analysis

Picking the Right Platform (con't)



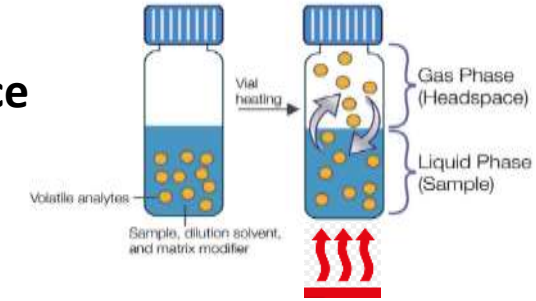
Ranitidine



NDMA

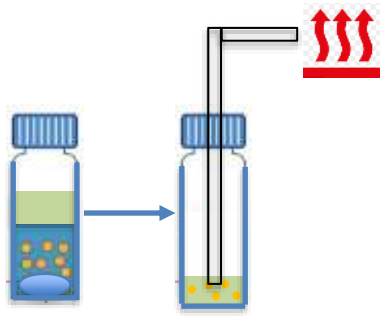
Levels of NDMA in Ranitidine Cannot Be Accurately Determined by GC/MS Due to Thermal Degradation of Ranitidine to NDMA

Headspace GC/MS



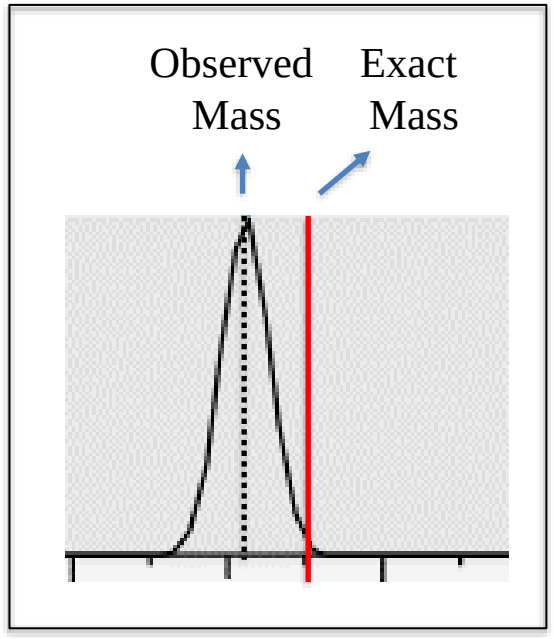
Sample	NDMA (ppm)
sub1	**2255**
sub2	**2203**
sub3	**2299**
sub4	**2215**

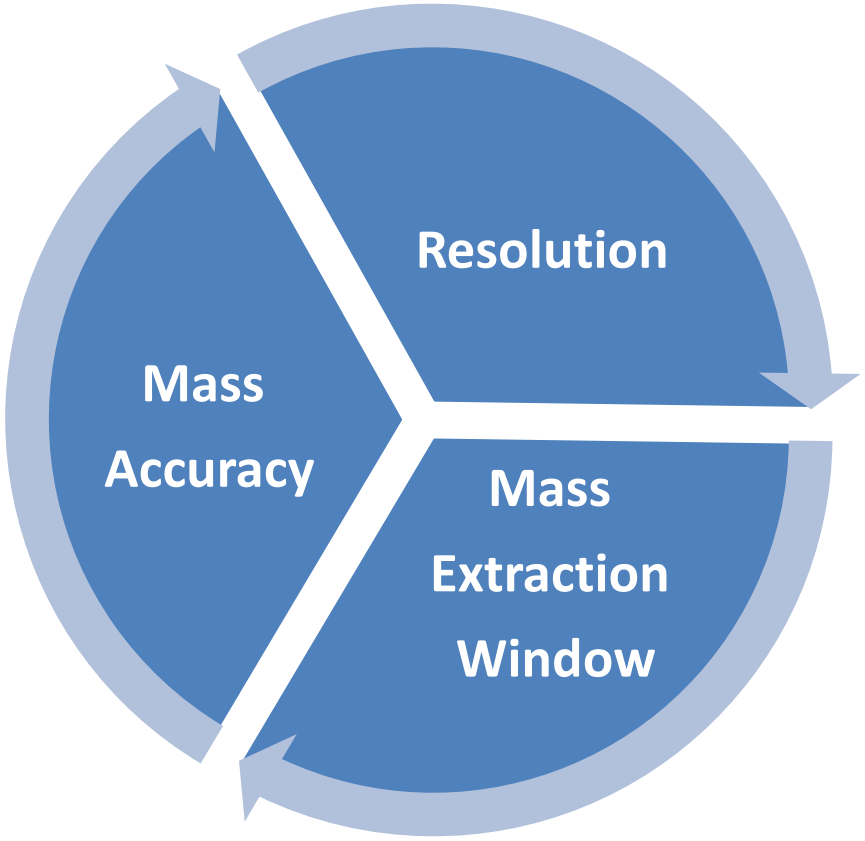
Direct injection GC/MS

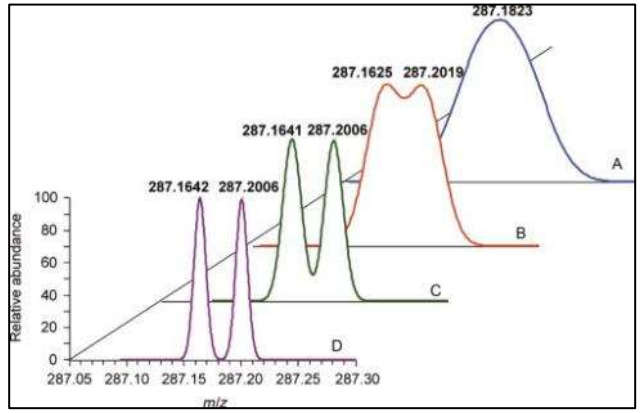


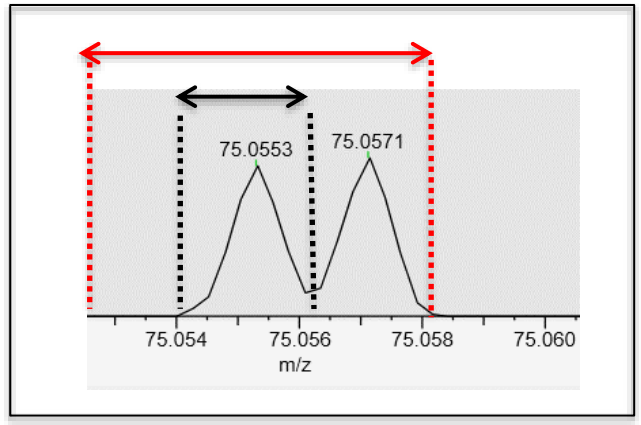
	GC/MS/MS			LC/HRMS
Name	$CHCl_3$ Extraction	One HCl/$CHCl_3$ Extraction	Two HCl/$CHCl_3$ Extraction	
	NDMA (ppm)	NDMA (ppm)	NDMA (ppm)	NDMA (ppm)
Ranitidine	3.232	1.692	1.432	1.021
Ranitidine	5.634	0.340	0.127	0.067
Ranitidine	6.419	3.477	3.758	2.382
Avg. (3):	5.095	1.836	1.772	1.157
Nizatidine	10.839	0.089	ND	0.054
Nizatidine	11.268	0.179	0.147	0.088
Nizatidine	13.267	0.202	0.180	0.106
Avg. (3):	11.791	0.157	0.109	0.083

Critical Factors for LC-HRMS Quantitation

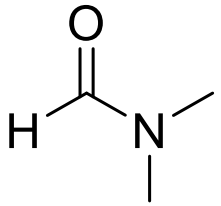






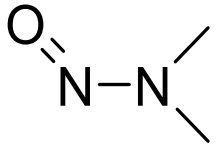


Enhanced Selectivity Improves Accuracy



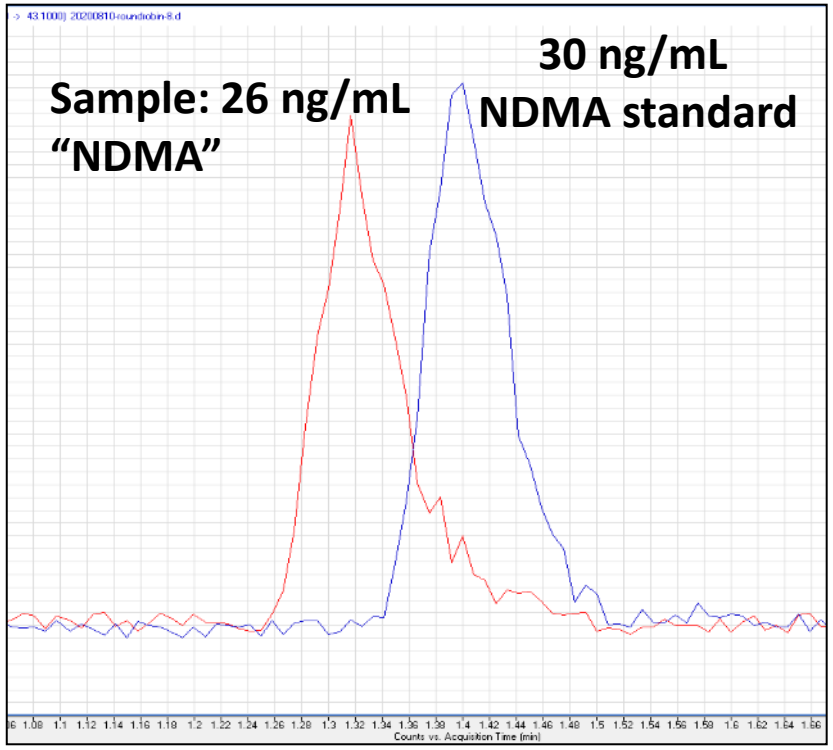
***N*,*N*-Dimethylformamide (DMF)**

Chemical Formula: C_3H_7NO
Monoisotopic Mass: 73.0528

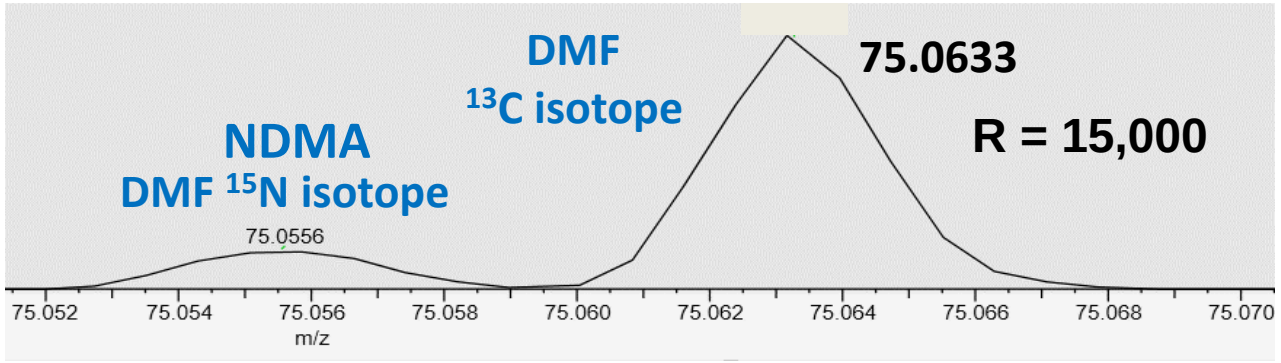


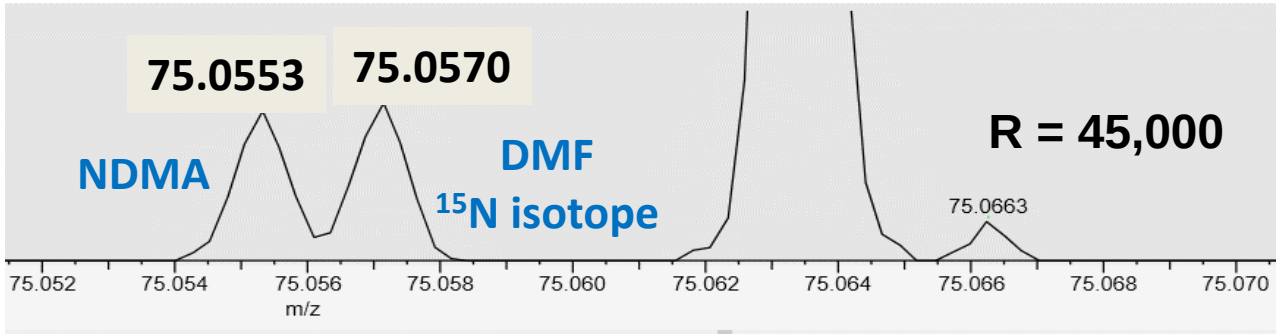
NDMA

Chemical Formula: $C_2H_6N_2O$
Monoisotopic Mass: 74.0480



MRM (75.1 → 43.1)





Yang, J, Marzan, TA, Ye, W, Sommers, CD, Rodriguez, JD, Keire, DA, A Cautionary Tale: Quantitative LC-HRMS Analytical Procedures for the Analysis of N-Nitrosodimethylamine in Metformin, AAPS J. 2020; 22(4) 89

Method Validation Considerations

- **ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology**

Type of analytical procedure characteristics	IDENTIFICATION	TESTING FOR IMPURITIES quantitat.	 limit	ASSAY - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

Method Validation Plan (Sample)

Validation Characteristic	Range	Acceptance Criteria
Linearity	0.5 – 200 ng/mL (6 Levels)	R2 ≥ 0.990
Accuracy	Placebo, 0.5, 1.0, 3.0, 10.0, 100.0 & 200 ng/mL	% Recovery = 80 - 120%
Precision		
Instrument Precision (n=10)	1 & 3 ng/mL	% RSD (n=10) ≤ 10%
Repeatability (n=3)	Level 1 – Level 6	% RSD (n = 3) ≤ 10%
Specificity	API peak should be resolved from nitrosamine peaks	
Limit of Quantitation (LOQ)	Should meet the accuracy and precision criteria	
Limit of Detection (LOD)	% RSD (n=5) should be < 15 %; S/N should be ≥ 3	
Range	Should meet the accuracy, linearity and precision criteria	

FDA and USP Posted Testing Methods

- ARBs – 6 methods
  - NDMA, NDEA, NMBA, NDBA, NDIPA, NEIPA
- Ranitidine – 2 methods
  - NDMA
- Metformin – 2 methods
  - NDMA
- Rifampin and Rifapentine – 1 shared method
  - MNP, CPNP
- USP Chapter <1469> Nitrosamine Impurities went to PF (link below). Four methods described. Out for Comment.
  - 6 USP reference standards are available

Any method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

https://online.usppf.com/usppf/document/GUID-C97F817C-A383-4693-8E0C-2F0A0A371977_10101_en-US

International Regulators

- This included (under established confidentiality agreements):
  - Scientific discussions about acceptable intake limits
  - Sharing of laboratory methods and test results
  - Coordination of joint inspections where appropriate
  - Sharing of inspectional findings

- Essential to future global drug safety/quality investigations

1. FDA/CDER. FDA Updates and Press Announcements on NDMA in Metformin FDA.gov2020 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin.
2. FDA/CDER. FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan) 2020 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.
3. FDA/CDER. FDA Updates and Press Announcements on NDMA in Zantac (ranitidine) 2020 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine.
4. CDER/FDA. Laboratory Tests | Metformin 2020 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-tests-metformin.

Drug Quality & the U.S. Market

The FDA is committed to ensuring that the medicines Americans take are safe and effective. When we identify drug quality lapses that pose potential risks for patients, we make every effort to understand the issues and provide our best recommendation to the public as quickly and accurately as possible. We will continue to investigate and work to ensure these types of impurities do not exceed acceptable limits so that patients can continue taking their medicines without concern.

Acknowledgements

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Thank You!