FDA Overview
Control of Nitrosamine Impurities in Human Drugs

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Office Of Lifecycle Drug Products

Office of Pharmaceutical Quality

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.

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.

FDA NEWS RELEASE

FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

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For Immediate Release: July 13, 2018

The U.S. Food and Drug Administration is alerting health care professionals and patients of a voluntary recall of several drug products containing the active ingredient valsartan, used to treat high blood pressure and heart failure. This recall is due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. However, not all products containing valsartan are being recalled. NDMA is classified as a probable human carcinogen (a substance that could cause cancer) based on results from laboratory tests. The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured.

FDA Updates and Press Announcements on Nitrosamines in Rifampin and Rifapentine

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1/28/2021: Laboratory testing results for nitrosamines in rifampin and rifapentine

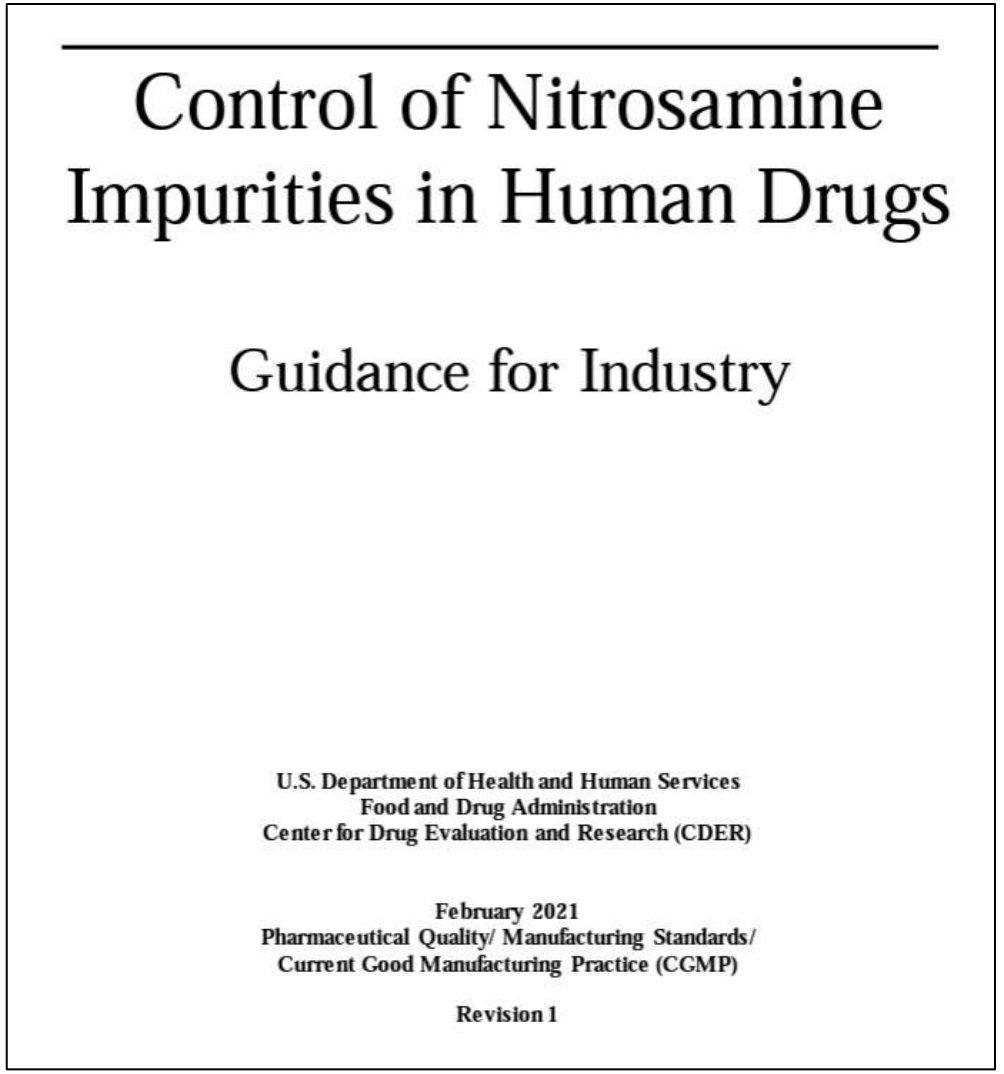
10/29/2020: UPDATE - FDA not objecting to rifapentine with CPNP at or below 20 ppm remaining on the market

8/26/2020: FDA recently became aware of nitrosamine impurities in certain samples of rifampin and rifapentine.

[8/26/2020] These are antibacterial drugs used to treat tuberculosis; rifampin is also used to treat or prevent other serious infections. Patients taking rifampin or rifapentine should continue taking their current medicine and consult with their health care professional about any concerns.

To mitigate or avoid shortages and to help ensure patients have access to these necessary medicines, FDA will not object to certain manufacturers temporarily distributing rifampin containing 1-methyl-4-nitrosopiperazine (MNP) or rifapentine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP) above the acceptable intake limits until they can reduce or eliminate the impurities.

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



Control of Nitrosamine Impurities in Human Drugs

Guidance for Industry

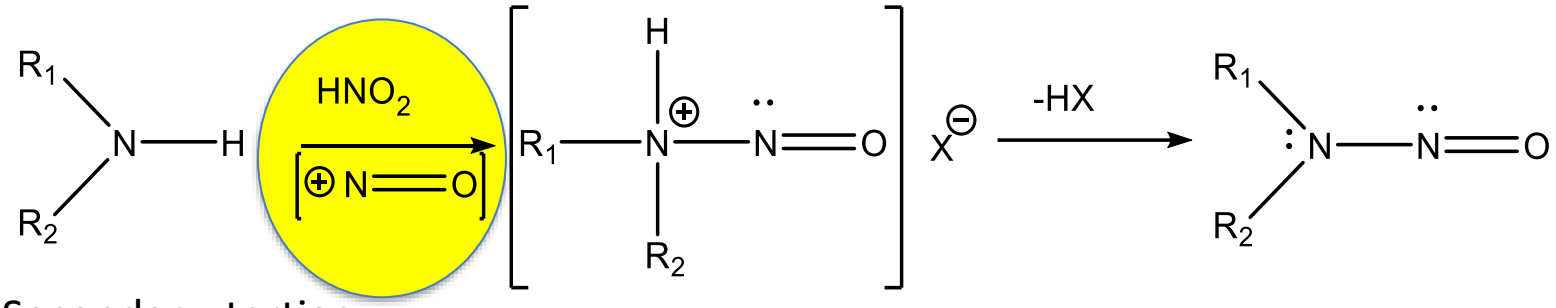
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2021
Pharmaceutical Quality/ Manufacturing Standards/
Current Good Manufacturing Practice (CGMP)

Revision 1

What are Nitrosamines?

- What are Nitrosamines?



Secondary, tertiary,
or quaternary amines

- Nitrosamines are
  - Probable or possible human carcinogens
  - Potent genotoxic agents
  - "Cohort of concern" compounds in the ICH *M7(R1)*

ICH M7 (R1) Guidance: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk (March 2018) https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Cohort of Concern with Stringent Intake Limits

- Acceptable Intake Limits (AI)

Table 1. AI Limits for Nitrosamines in Drug Products

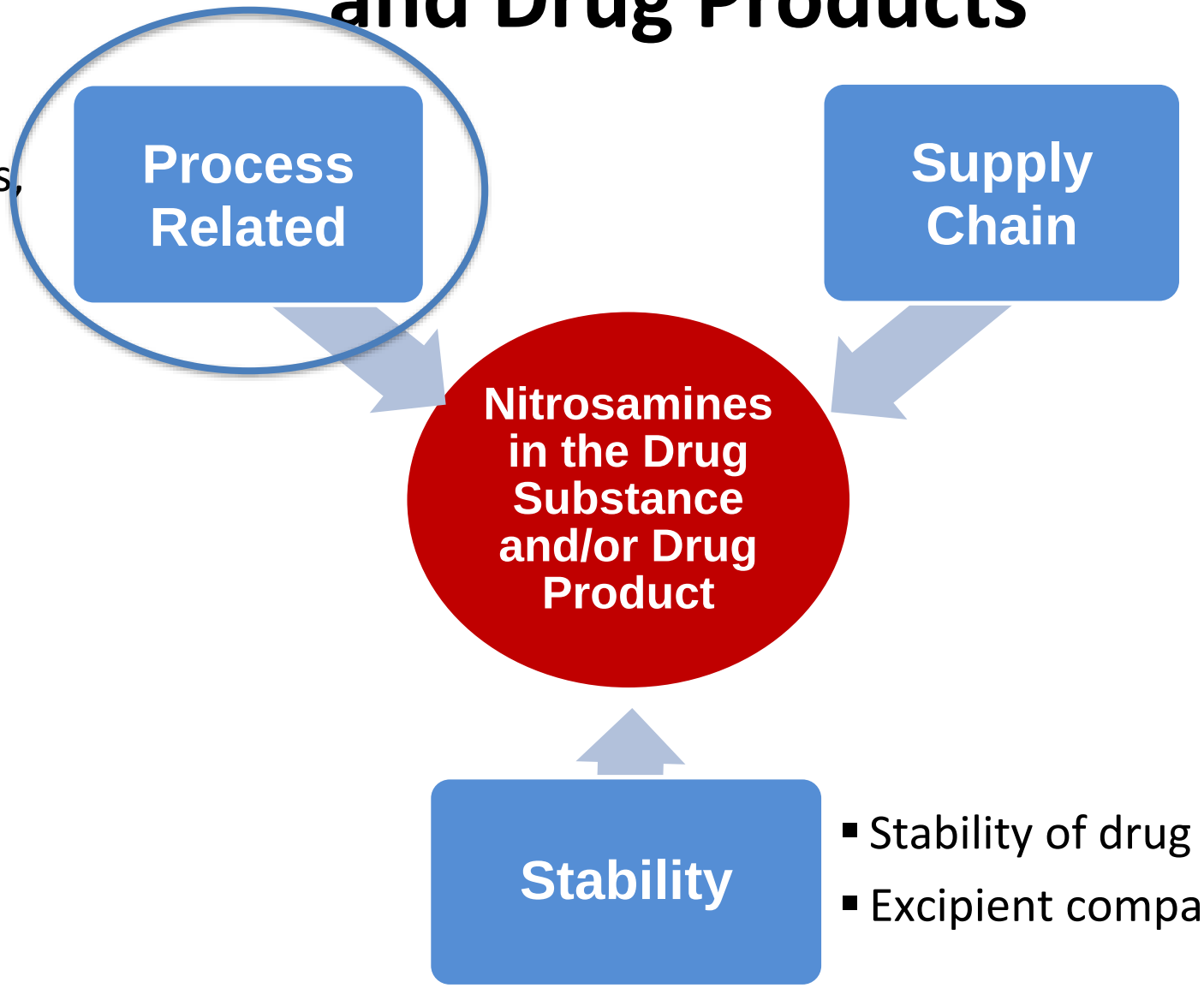
Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[1] The AI limit is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of exposure.

[2] The conversion of the AI limit into ppm varies by product and is calculated based on a drug's maximum daily dose (MDD) as reflected in the drug label (ppm = AI (ng)/MDD (mg)).

Root Causes of Nitrosamine Impurities in APIs and Drug Products

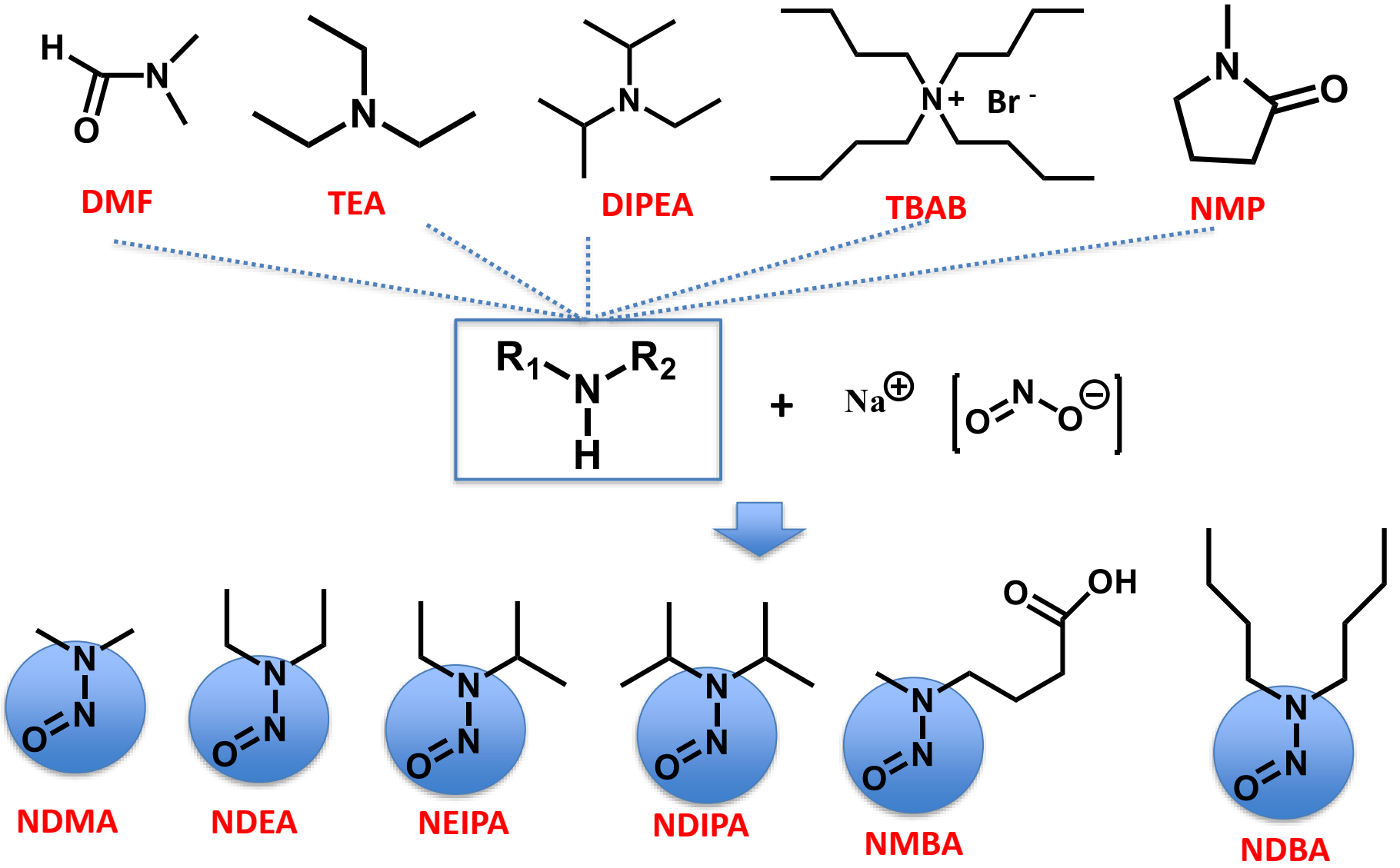
- Properties of the starting materials, intermediates or drug substance
- Specific process conditions
- Impurities in or reactions with raw materials



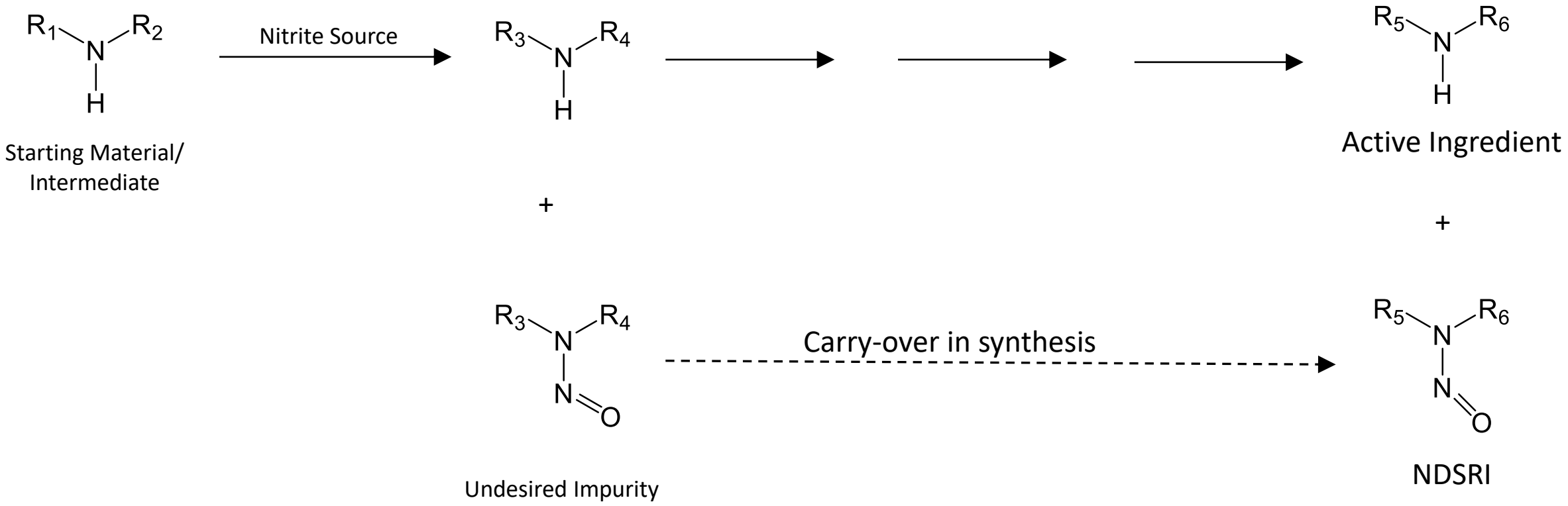
- Use of recovered or recycled materials or other intermediates contaminated with nitrosamines
- Cross-contamination in multi-purpose facilities

- Stability of drug substance or drug product
- Excipient compatibility

Potential Nitrosamine Impurities Generated During the Synthesis of Drug Substances

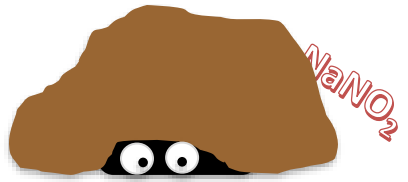


Nitrosamine Drug Substance Related Impurities (NDSRIs) From Synthesis of Drug Substances



Lessons Learned: Hidden sources of precursors

- Substantial quantity of sodium nitrite in sodium azide.
- Contaminating amines in bases/catalysts.
- Degradation of amide solvents that generate secondary amines.
- Amine contaminants present in starting materials or intermediates.
- Secondary and tertiary amine functional groups on intermediates and API molecules.



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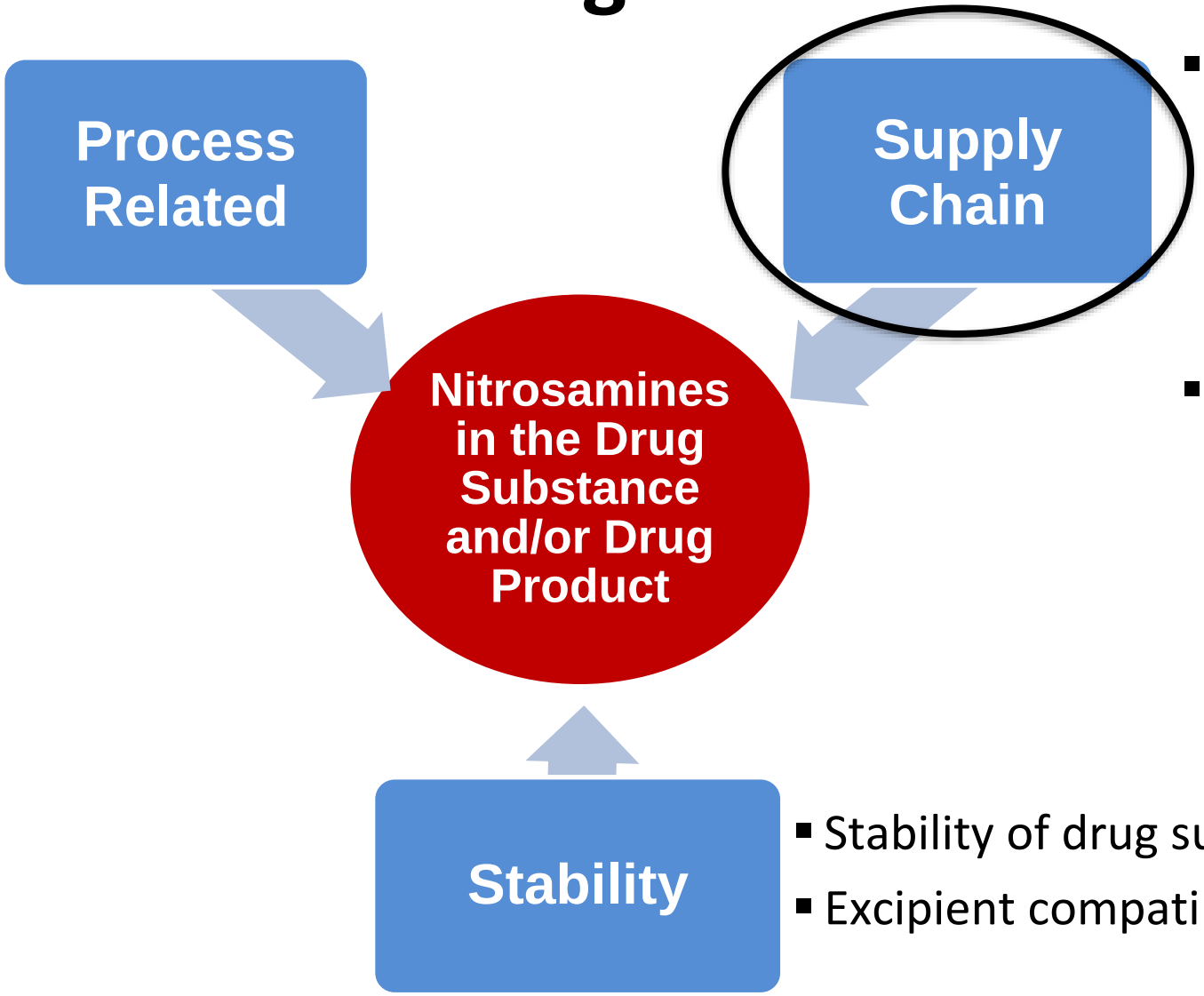

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- Stability of drug substance or drug product
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Lessons Learned: Solvents

- Use solvents of appropriate grade.
  - Exercise due diligence when choosing vendors
  - Is vendor recycling solvents?
  - How are tankers cleaned?

- Process understanding should extend to recovered solvents.

- Analytics: Attention to “new unknown” peaks

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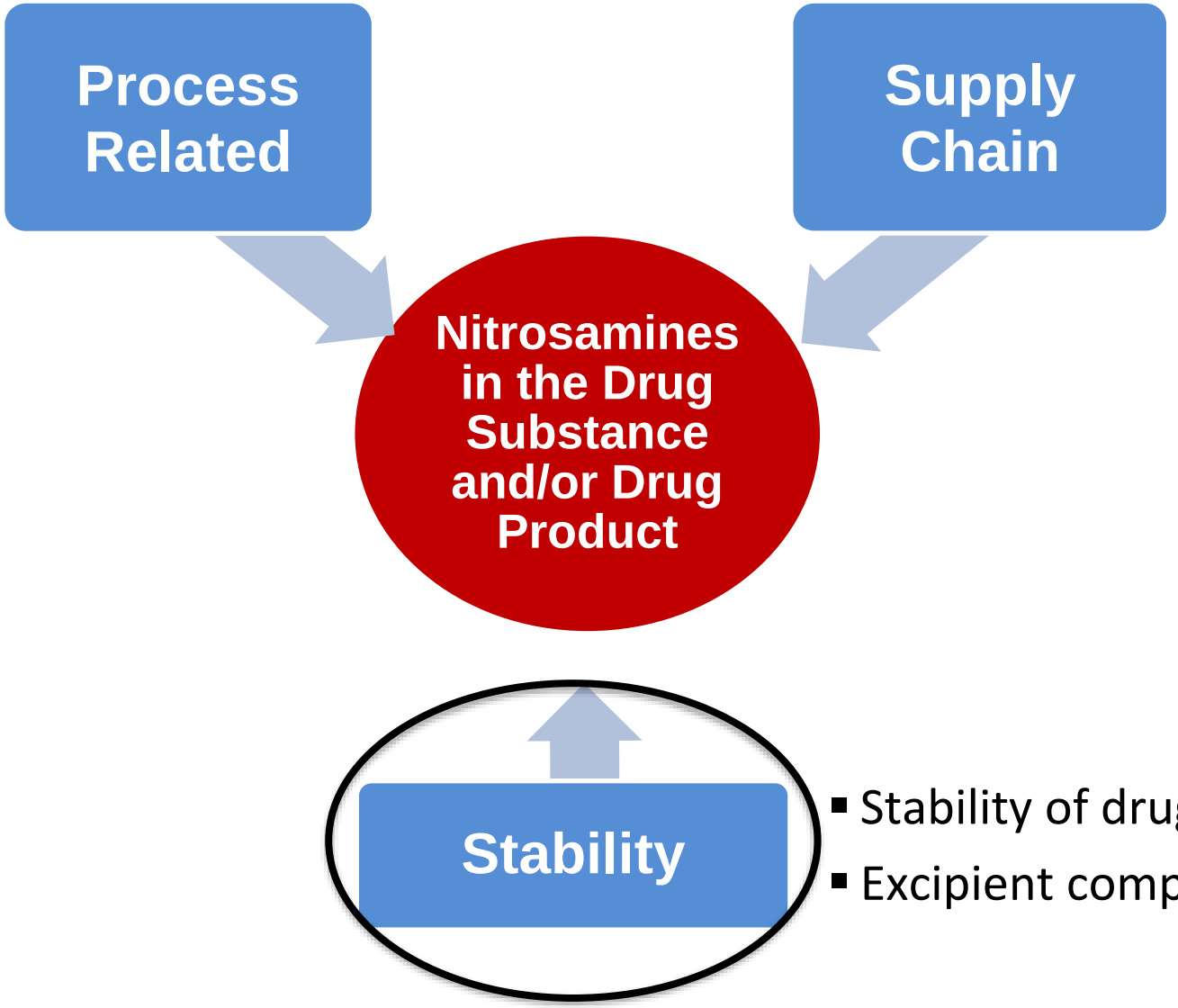

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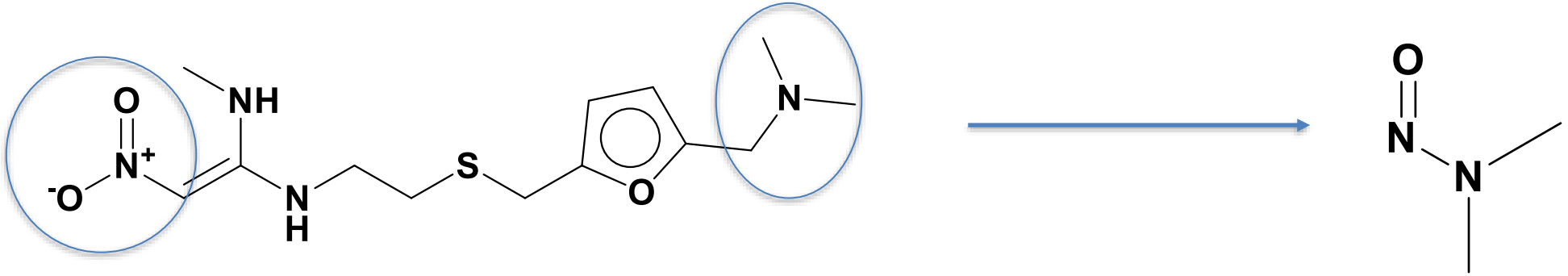
Stability Failure Modes

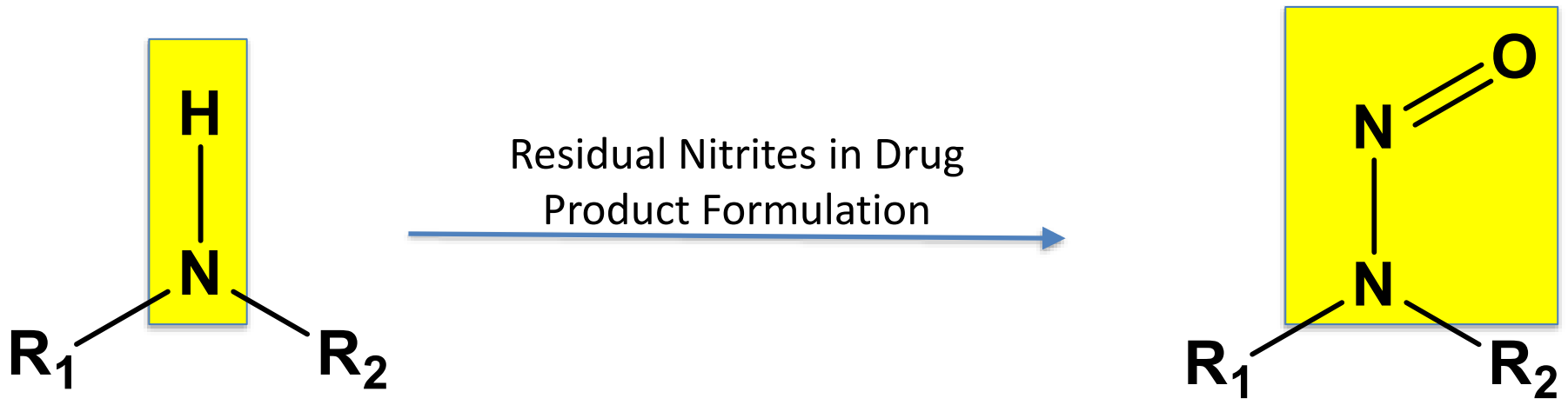
Evaluate Inherent Propensity of the
Active Ingredient to Generate Nitrosamines



Ranitidine **NDMA**

FDA Requests Removal of All Ranitidine Product (Zantac) from the Market
https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

NDSRIs Formed in Drug Product During Manufacturing and/or Shelf-Life



Active Ingredient

NDSRI
Derivative of Active Ingredient Structure

Processing Steps to purge NDSRIs is not possible for those generated in drug products

Excipients/Water: Common Source of Nitrite

Excipients	Sources/lot	Impurity (ppm) Glucose	HCHO	Hydrogen peroxide	NO_2	NO_3	Monochloroacetate
Microcrystalline cellulose, PH102	FMC/1	79.6	4.8	<2	N/A	N/A	N/A
	FMC/2	59.5	5.1	<2	9.4	23.0	0.9
	FMC/3	40.7	4.1	ND	N/A	N/A	N/A
Lactose Fast Flo	Foremost	ND	N/A	<2	10.4	12.4	12.0
Lactose monohydrate	Foremost/1	ND	1.4	<2	5.1	9.1	1.0
	Foremost/2	ND	ND	<2	5.5	8.0	0.9
Lactose anhydrous	Quest/1	ND	7.4	<2	5.4	4.3	0.6
	Quest/2	ND	3.6	<2	3.7	6.0	0.6
Pre-gelatinized starch	Colorcon/1	ND	14.7	<2	14.5	29.2	4.4
	Colorcon/2	ND	10.9	<2	11.8	22.9	2.3
	Colorcon/3	ND	11.1	N/A	N/A	N/A	N/A
Povidone	ISP/1	INC	INC	37	2.2	13.6	ND
	ISP/2	INC	INC	72	1.6	13.1	ND
Crospovidone	ISP/1	ND	40.8	66	17.2	52.4	ND
	ISP/2	ND	8.5	69	10.5	30.4	ND
Sodium starch glycolate	Roquette/1	–	4.6	<2	279.2	183.1	ND
	Roquette/2	–	1.5	<2	285.6	117.3	135.8
Croscarmellose Na	FMC/1	ND	6.5	<2	2.4	23.8	52.2
	FMC/2	ND	6.6	<2	1.4	10.3	21.6
Magnesium stearate	Mallincrodt/1	ND	3.8	<2	2.1	6.0	ND
	Mallincrodt/2	ND	3.7	<2	5.3	12.5	0.7
Stearic acid	Crompton	ND	3.1	<2	3.5	6.6	ND
Hydroxypropyl cellulose	Hercules/1	ND	11.4	13	N/A	N/A	N/A
	Hercules/2	ND	9.4	13	0.9	3.5	ND
Silicone dioxide	Degussa/1	ND	6.1	<2	5.8	12.5	ND
	Degussa/2	N/A	N/A	<2	1.5	8.7	ND

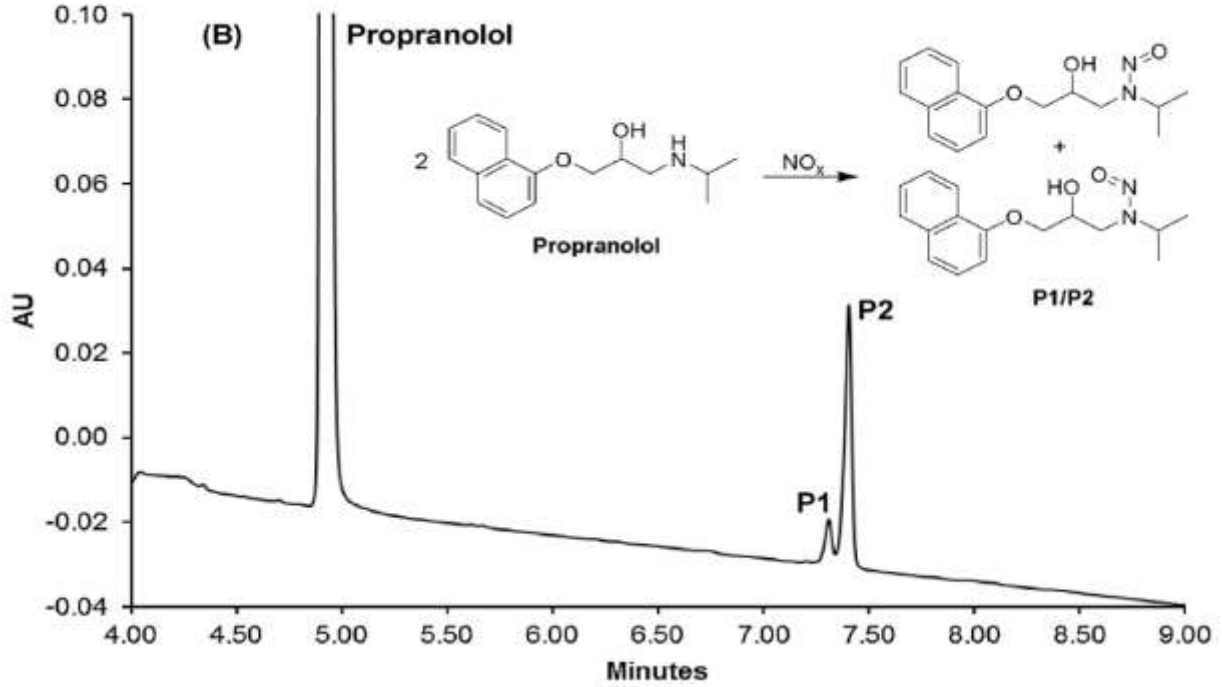
Possible Nitrite Source: Processing water, processing steps requiring acid titration, bleaching, and oxidation of air as excipient is being heated in a drying process

Wu, et al. *AAPS PharmSciTech*, **2011**, 12(4), 1248-1263

NDSRIs Generated in Excipient Compatibility Studies

A B S T R A C T

Accelerated stability studies of pharmaceutical products are commonly conducted at various combinations of temperature and relative humidity (RH). The RH of the sample environment can be controlled to set points using humidity-controlled stability chambers or via storage of the sample in a closed container in the presence of a saturated aqueous salt solution. Herein we report an unexpected N-nitrosation reaction that occurs upon storage of carvedilol- or propranolol-excipient blends in a stability chamber in the presence of saturated sodium nitrite ($NaNO_2$) solution to control relative humidity (~60% RH). In both cases, the major products were identified as the corresponding N-nitroso derivatives of the secondary amine drugs based on mass spectrometry, UV–vis and retention time. These degradation products were



Sluggett et al. *Journal of Phamaceutical and Biomedical Analysis*, **2018**, 149, 206-213.

Risk Assessment Should Consider this Failure Mode that Leads to NDSRIs in Drug Products

From FDA Nitrosamine Guidance

Nitrites are common nitrosating impurities that have been reported in many excipients at ppm levels. Nitrite impurities are found in a range of commonly used excipients, which may lead to nitrosamine impurities forming in drug products during the drug product manufacturing process and shelf-life storage period.

If Risk for Creation of NDSRIs in Drug Product

Considerations for Risk Mitigation based upon Control/Design (Not All-Inclusive List)

Control of Formulation Inputs

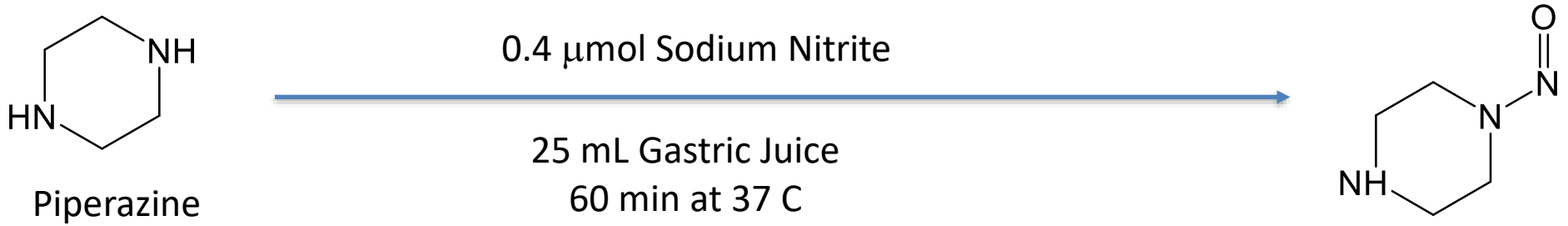
- Work with your excipient supplier to control residual nitrites

  From FDA Nitrosamine Guidance: *The supplier qualification program should take into account that nitrite impurities vary across excipient lots and may vary by supplier. Drug product manufacturers should also be aware that nitrite and nitrosamine impurities may be present in potable water*.

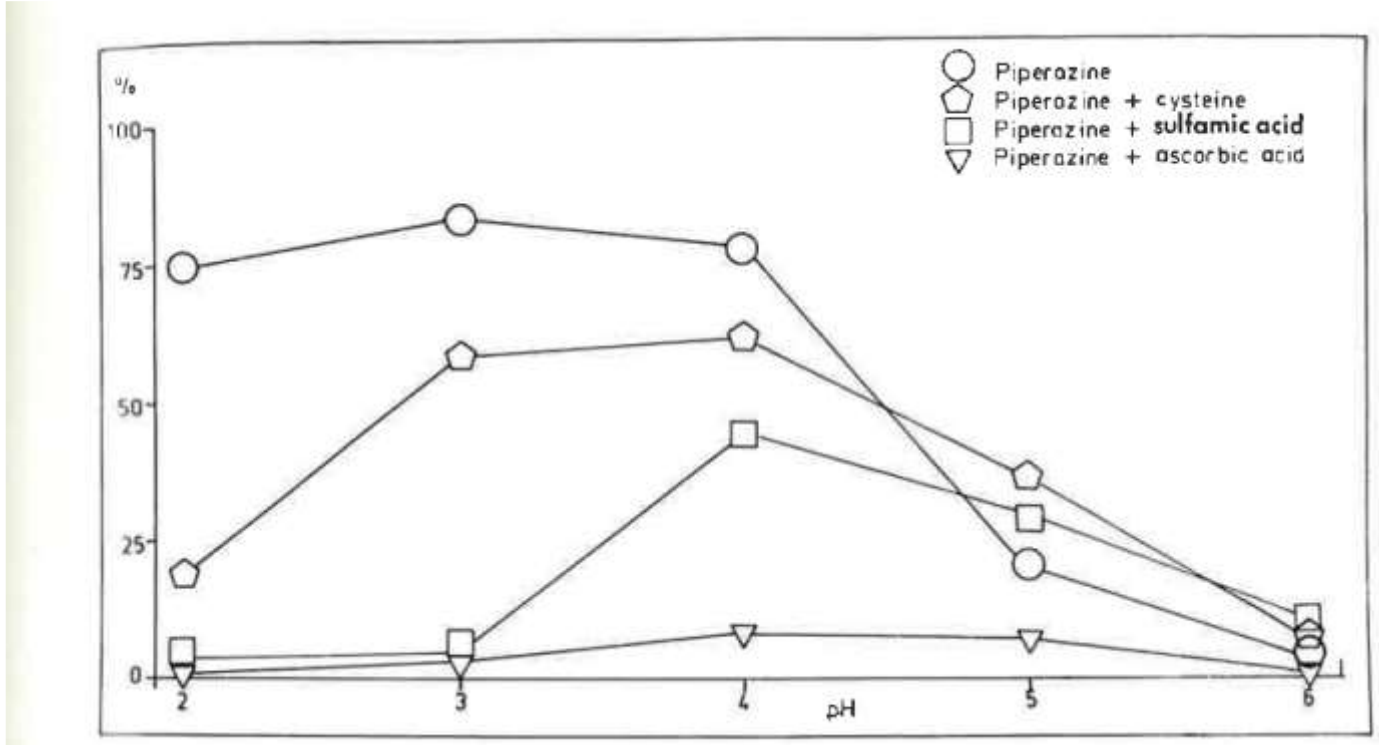
- During Development: Selection of formulation excipients less likely to contain nitrites.

Formulation Design (Additive Inhibitors)

Environmental N-Nitroso Compounds Analysis and Formation
IARC Scientific Publication No. 14 (1976), Ziebarth, D. and Scheunig, G. pages 279-290



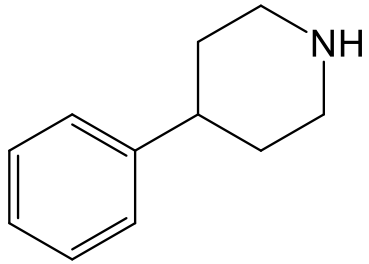
Piperazine



Formulation Design Mitigation

Inhibition of *N*-Nitrosamine Formation in Drug Products: A Model Study

Nanda et al. *Journal of Pharmaceutical Sciences (August 2021)*



4-phenylpiperidine hydrochloride (4-PPHCl)

HCl

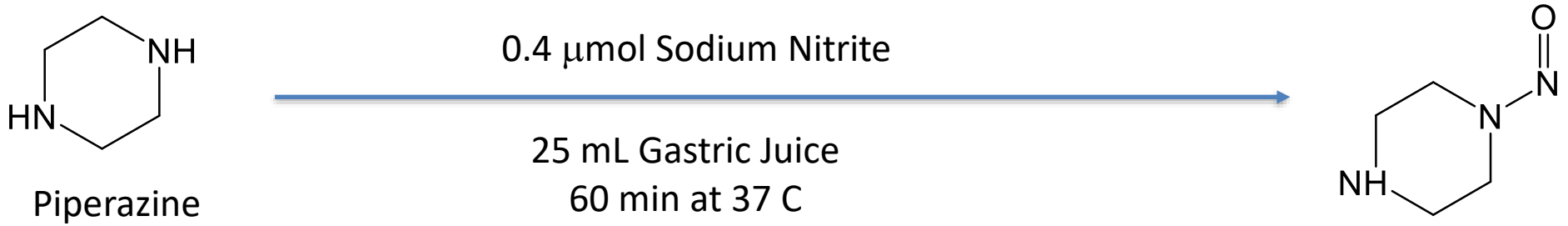
Manufacture Tablets (100 mg with 10% 4-PPHCl)
Common Excipients (known to contain nitrite)
Spike with Anti-Oxidant Inhibitors (0.1% wt, 1 wt%)

Stress at 50 C/75% RH for 1 month

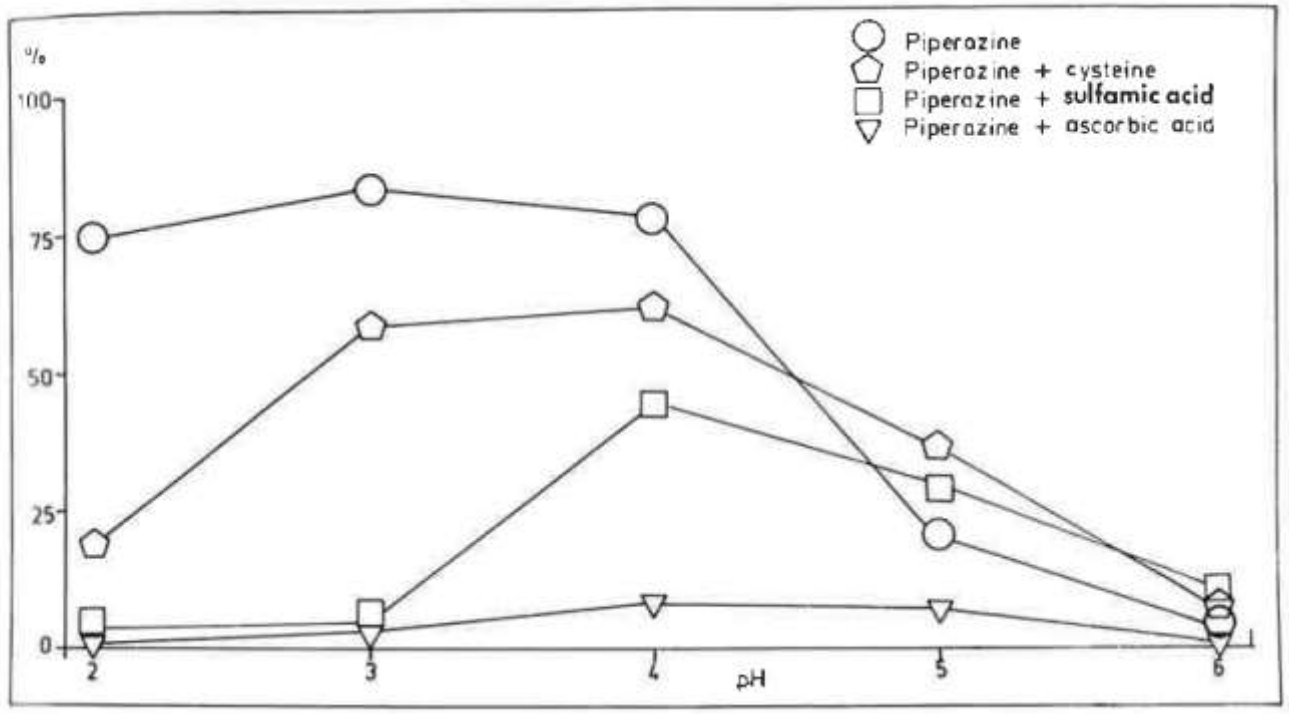
Inhibitor	Level	Growth on nitrosamine (ppb)	Inhibition Efficiency (%)
No inhibitor		345	N/A
Ascorbic Acid	0.57 µmole (0.1 wt%)	283	17.9
	5.7 µmole (1.0 wt%)	-72	120.9
Sodium Ascorbate	0.57 µmole	344	0.3
	5.7 µmole	30	91.3
Ferulic Acid	0.57 µmole	137	60.3
Caffeic Acid	0.57 µmole	129	62.6
	5.7 µmole	-72	120.9
α- Tocopherol	0.57 µmole	148	57.1
	5.7 µmole	64	81.5

Formulation Design (Impact of pH)

Environmental N-Nitroso Compounds Analysis and Formation
IARC Scientific Publication No. 14 (1976), Ziebarth, D. and Scheunig, G., pages 279-290



Piperazine



Formulation Design Mitigation

NDMA Formation in Experimental Batches of Metformin Film Coated Tablets.

	NDMA Inital T =0	NDMA 60 °C/75% RH, 7 days
Control	< LOQ	31 ppb
H_2O_2 (400 ppm)	< LOQ	33 ppb
0.5% Na_2CO_3 + H_2O_2 (400 ppm)	< LOQ	< LOQ
H_2O_2 (400 ppm) + dimethylamine HCl (500 ppm)	< LOQ	43 ppb
0.5% Na_2CO_3 + H_2O_2 (400 ppm) + dimethylamine HCl (500 ppm)	< LOQ	< LOQ

"pH modification of the tablets by the addition of Na_2CO_3 was proven to be effective in terms of removing the DMA precursor from the tablets and stopping N-nitrosation completely, no matter the pathway"

Inhibition of *N*-Nitrosamine Formation in Drug Products: A Model Study
Jires et. al. *Journal of Pharmaceutical and Biomedical Analysis, 218 (2022)*

FDA Communication Nov. 11, 2021

Discusses these Possible Mitigation Strategies for NDSRIs

Acknowledgements

- Colleagues from OPQ (7 sub-offices)
- Colleagues from OND, OGD, ORA
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- CDER Task Force Workgroup

Thank You!