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.

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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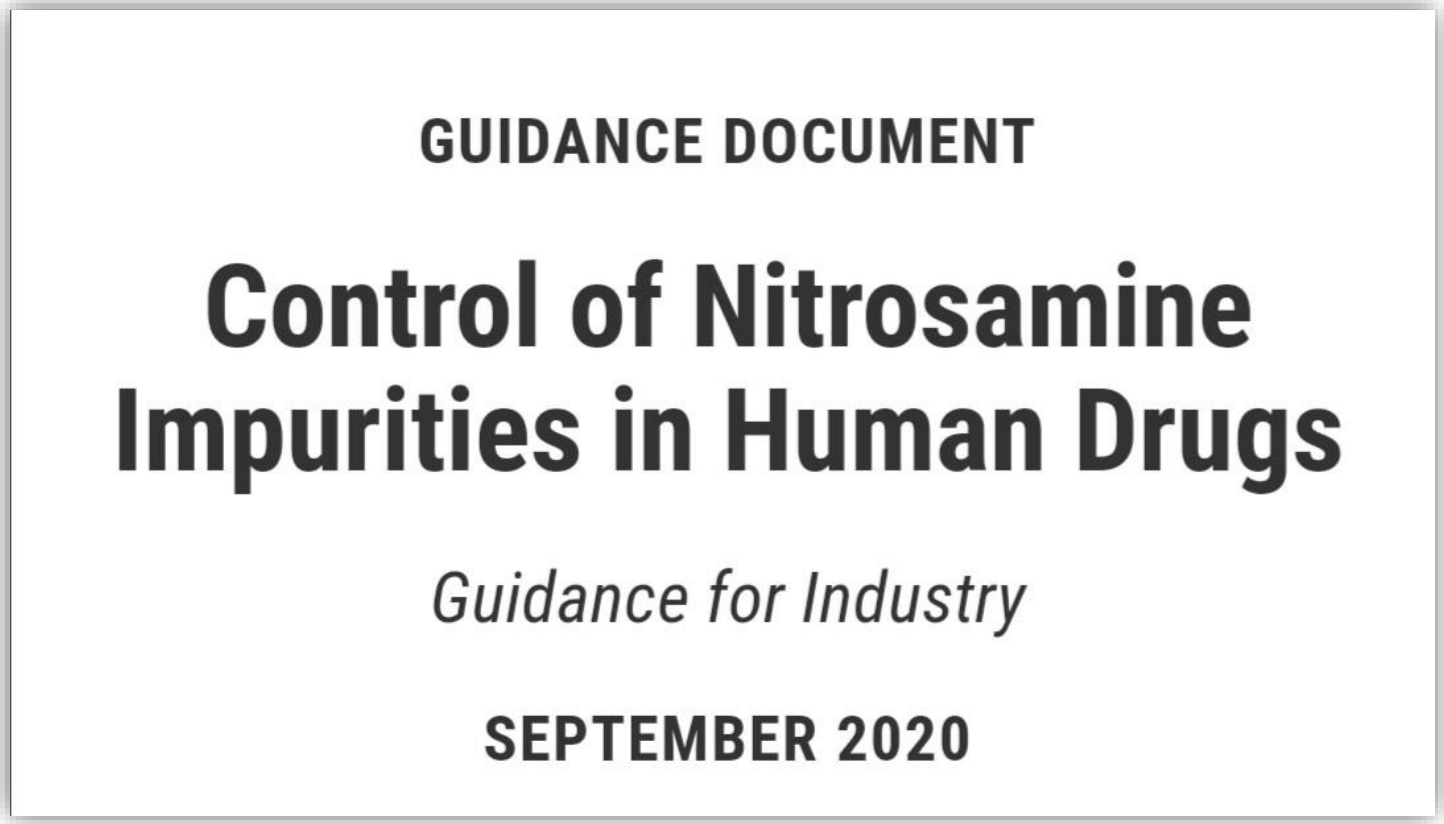

Guidance was published on Sept 1st, 2020, last revised February 2021

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

What are Nitrosamines?

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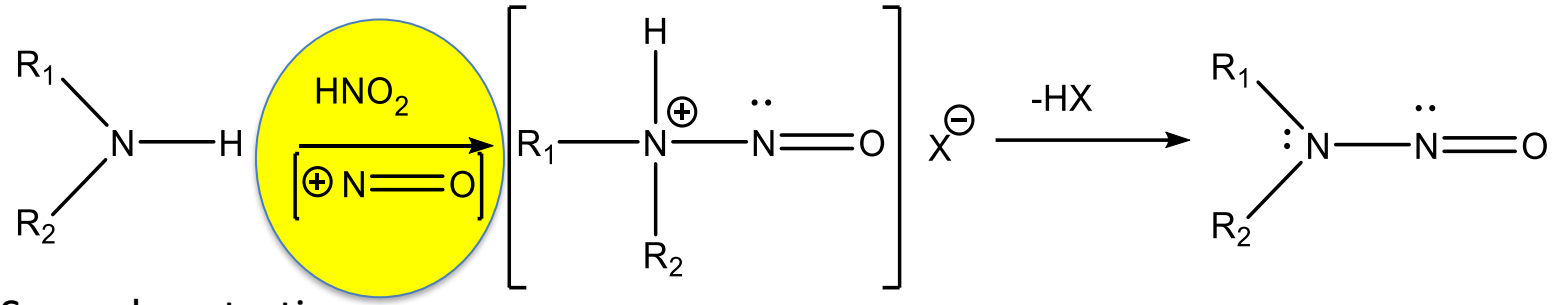


Secondary, tertiary,
or quaternary amines

- 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

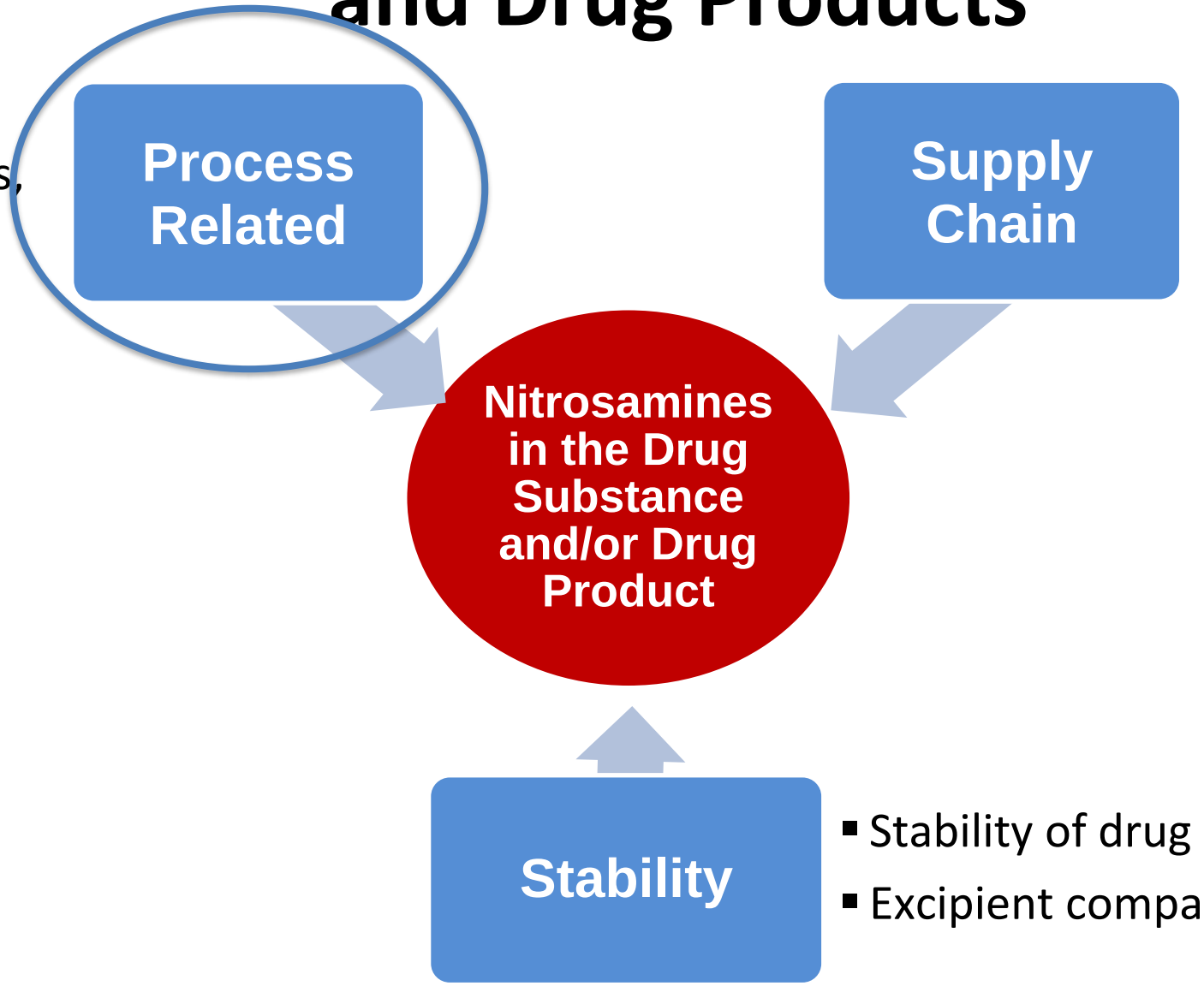
Nitrosamine	AI Limit (ng/day)[1,2]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

[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

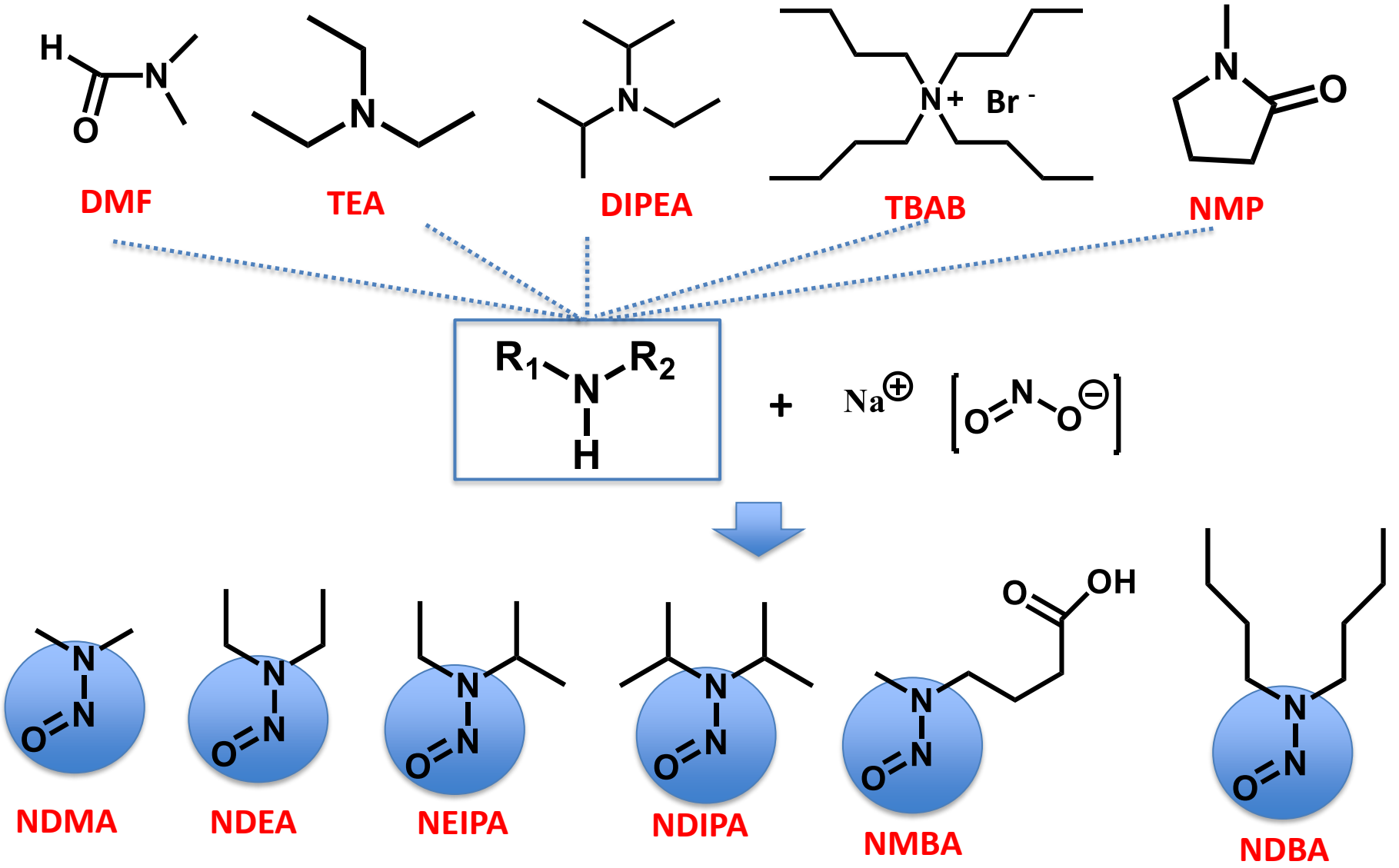
- Properties of the starting materials, intermediates or drug substance
- Specific process conditions
- Impurities in or reactions with raw materials



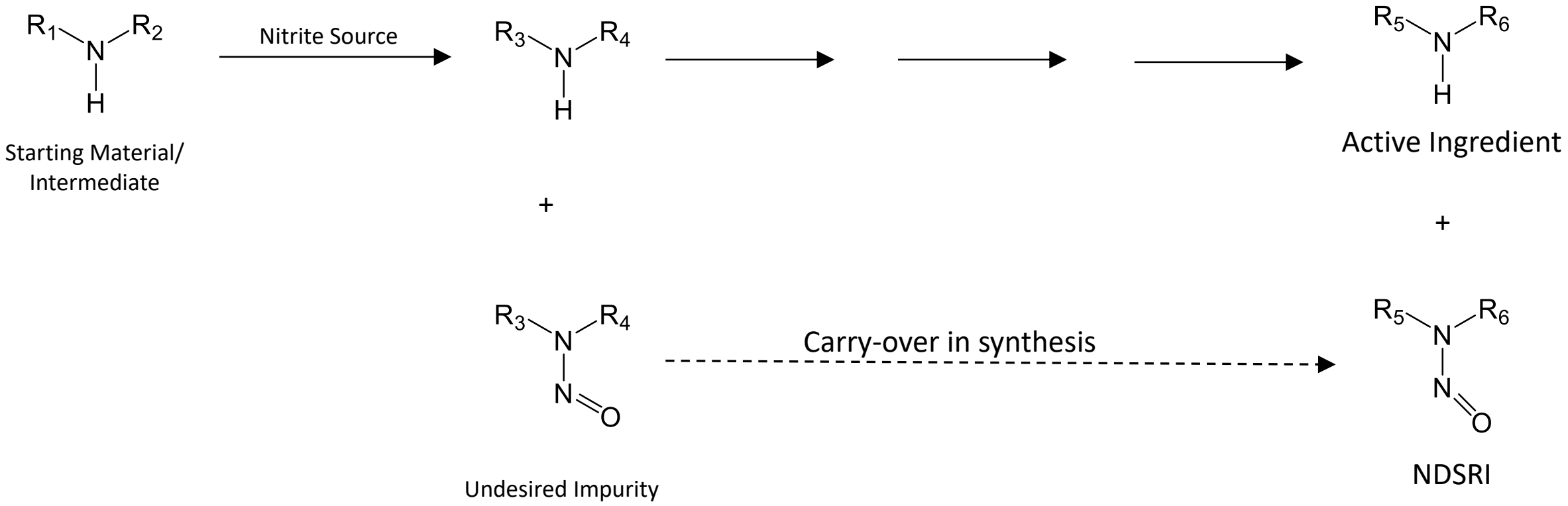
- Use of recovered or recycled materials or other intermediates contaminated with nitrosamines
- Cross-contamination in multi-purpose facilities

- Stability of drug substance or drug product
- Excipient compatibility

Potential Nitrosamine Impurities Generated During the Synthesis of Drug Substances

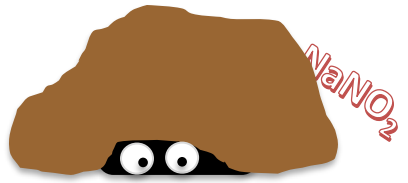


Nitrosamine Drug Substance Related Impurities (NDSRIs) From Synthesis of Drug Substances



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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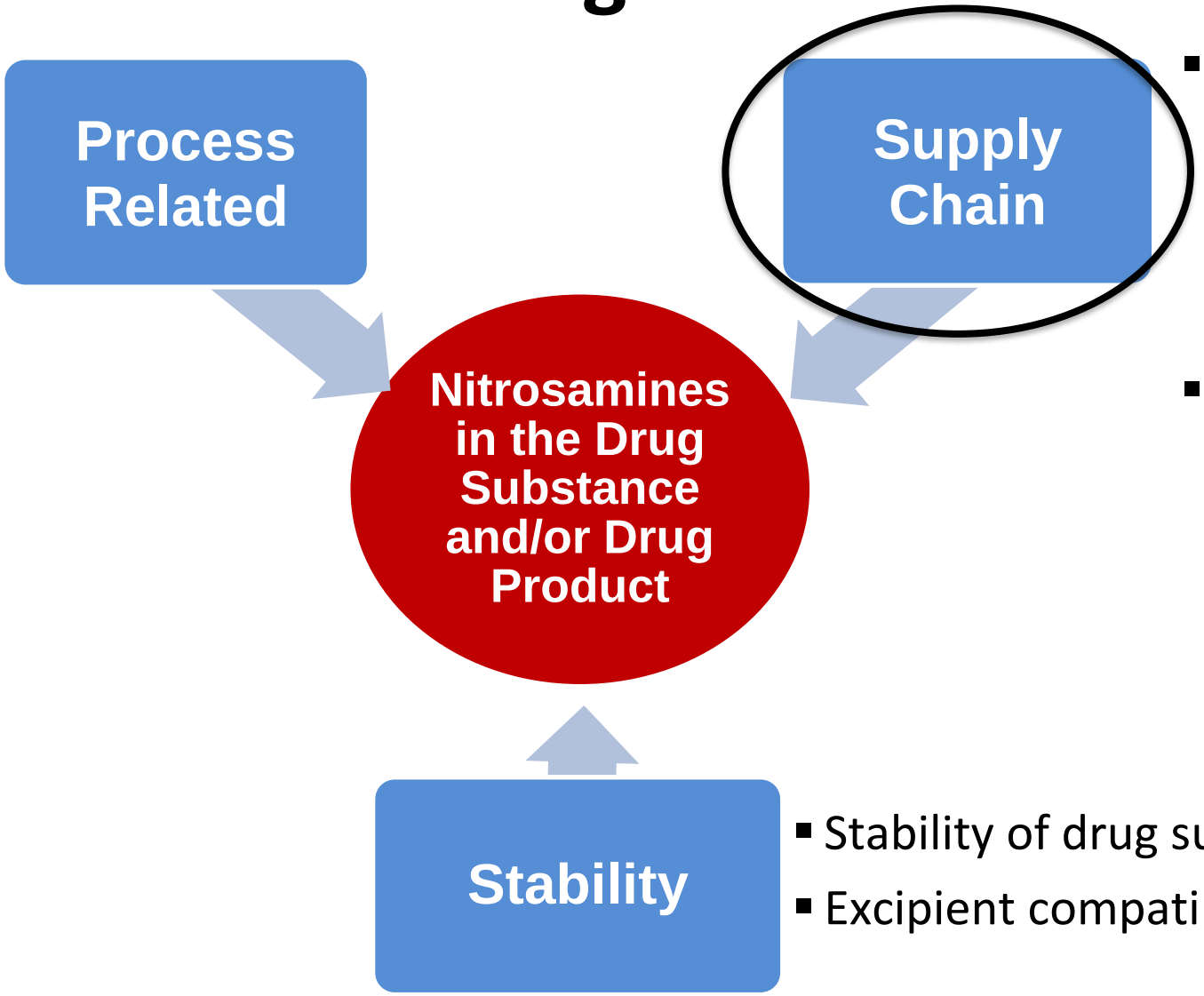

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Lessons Learned: Solvents

- 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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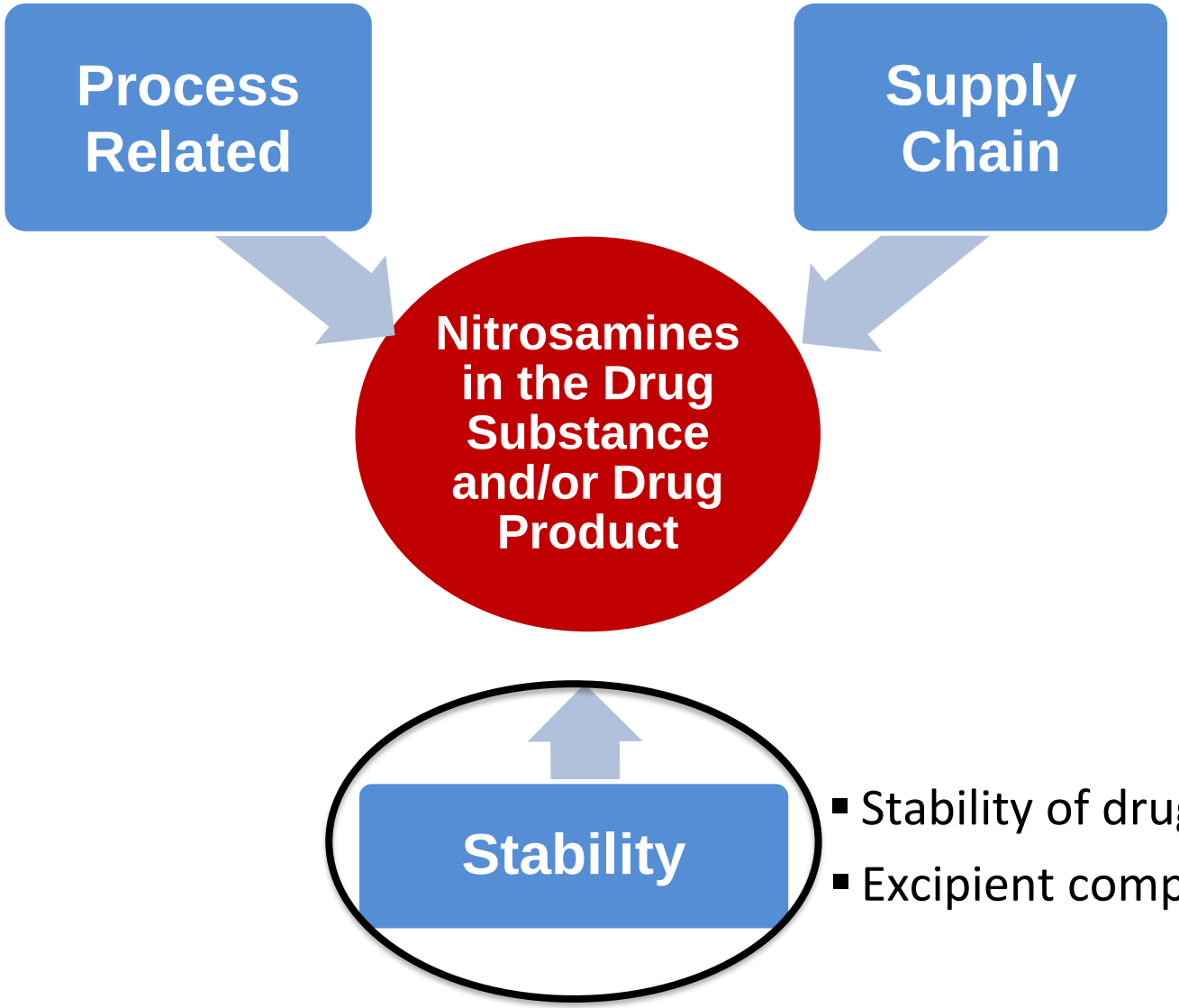

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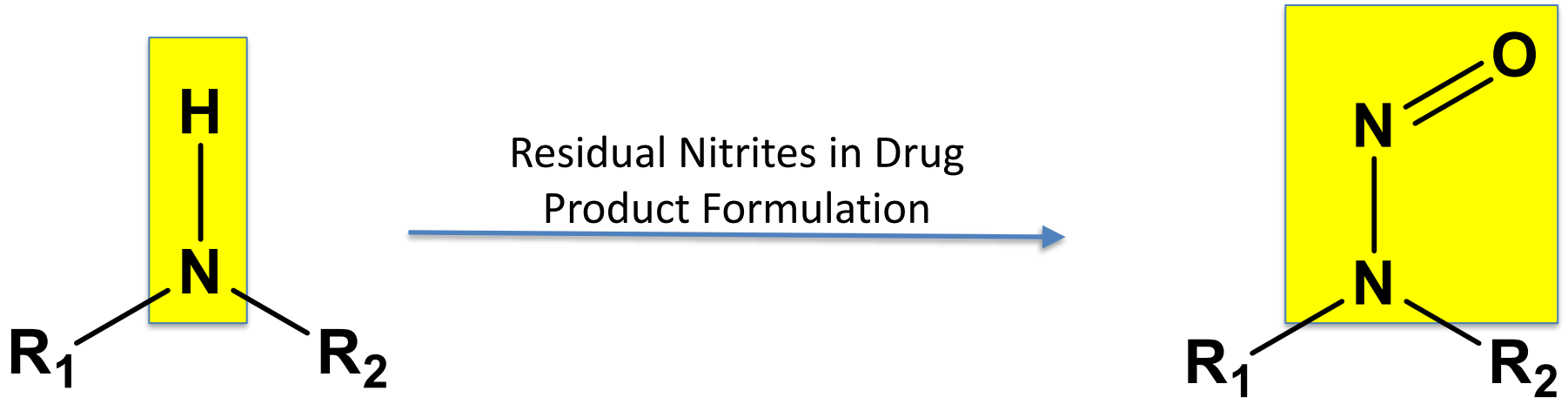
NDSRIs Formed in Drug Product During Manufacturing and/or Shelf-Life



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

		Impurity (ppm)					
Excipients	Sources/lot	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

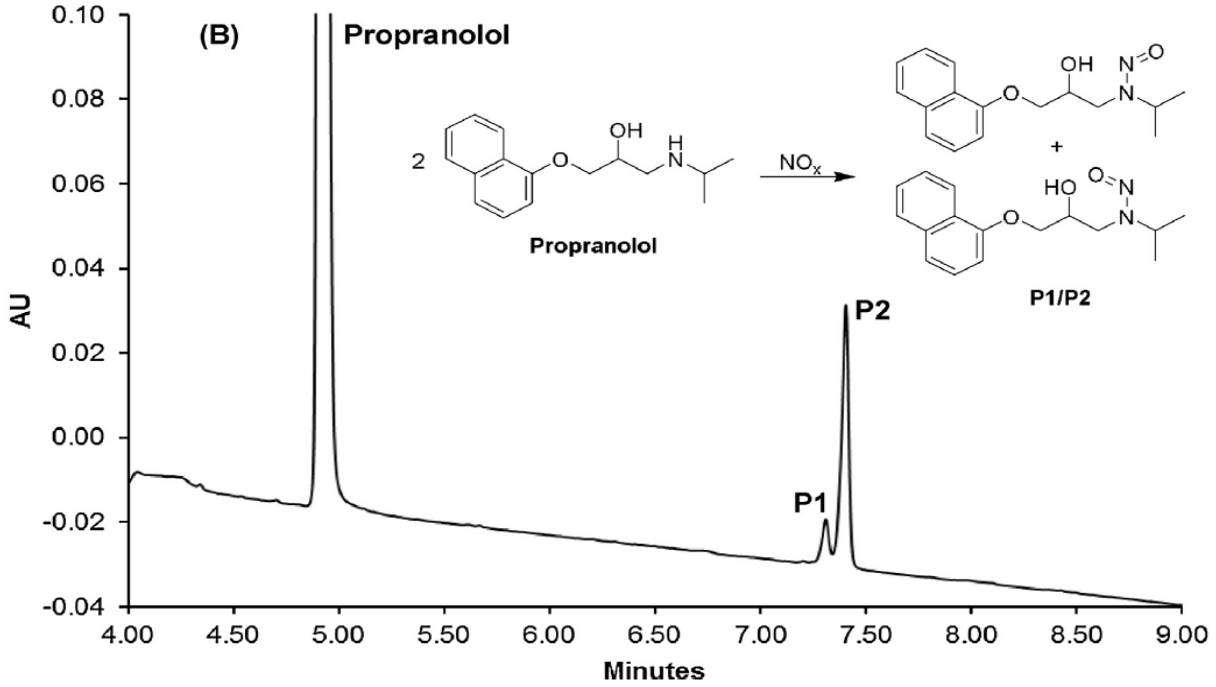
Possible Nitrite Source: Processing water, processing steps requiring acid titration, bleaching, and oxidation of air as excipient is being heated in a drying process

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

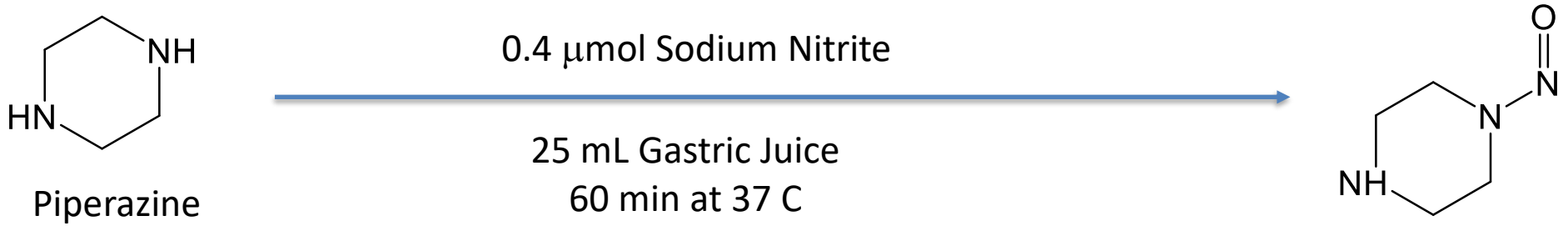
- Work with your excipient supplier to control residual nitrites

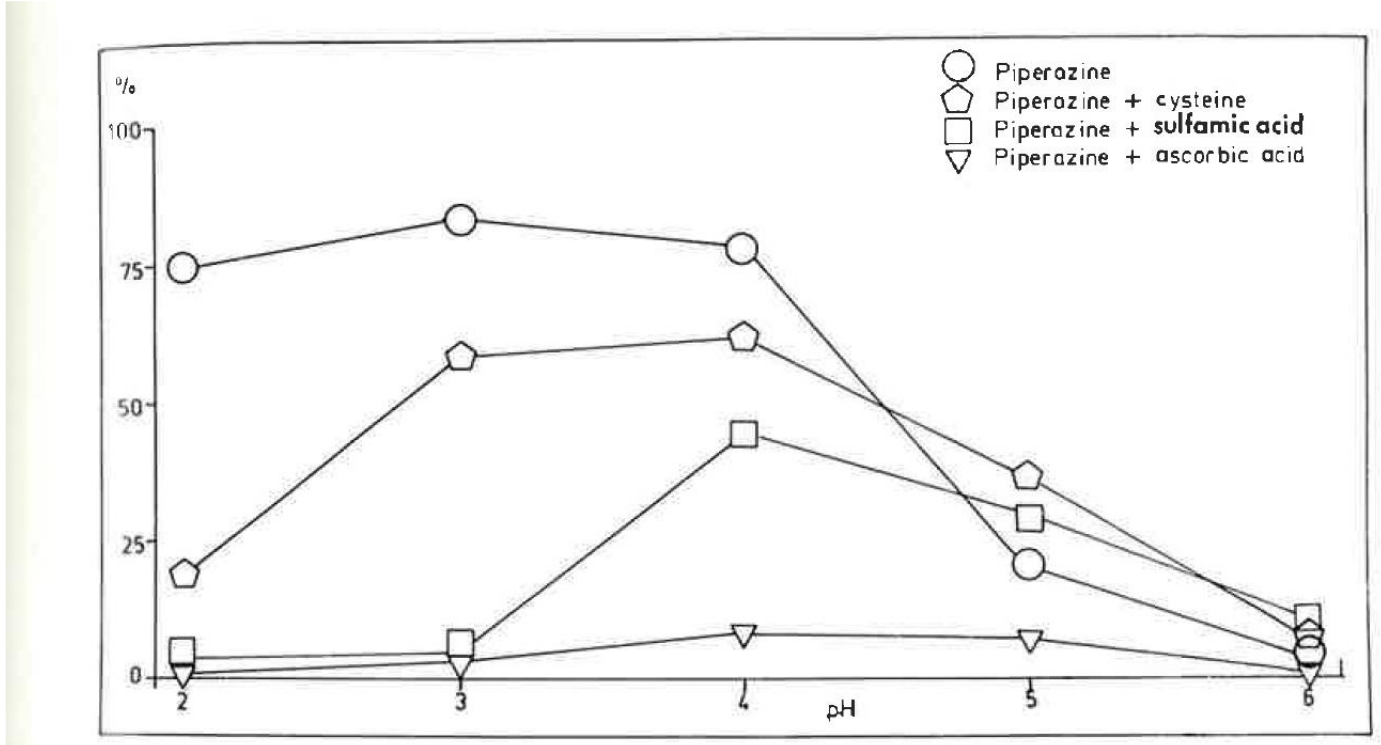
  From FDA Nitrosamine Guidance: *The supplier qualification program should take into account that nitrite impurities vary across excipient lots and may vary by supplier. Drug product manufacturers should also be aware that nitrite and nitrosamine impurities may be present in potable water*.

- 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

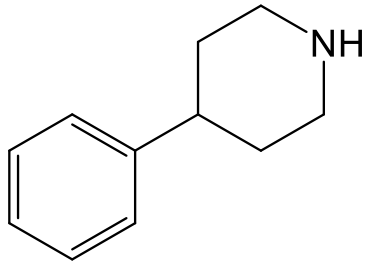




Formulation Design Mitigation

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

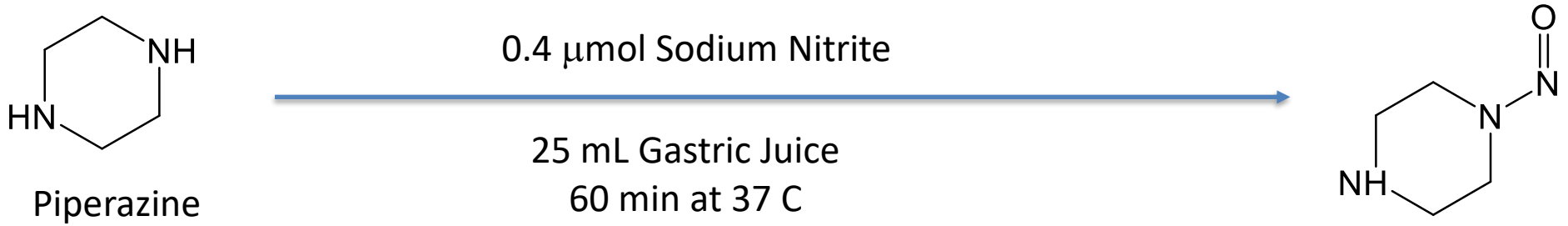
Manufacture Tablets (100 mg with 10% 4-PPHCl)
Common Excipients (known to contain nitrite)
Spike with Anti-Oxidant Inhibitors (0.1% wt, 1 wt%)

Stress at 50 C/75% RH for 1 month

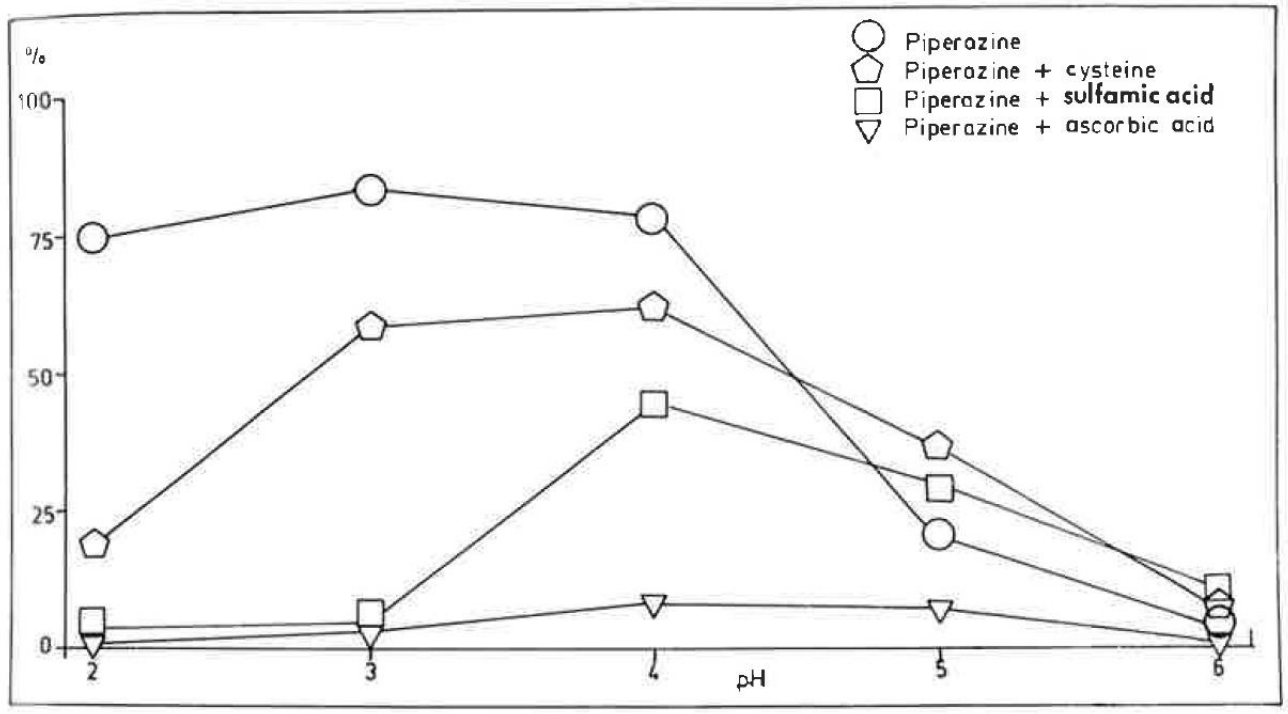
Inhibitor	Level	Growth on nitrosamine (ppb)	Inhibition Efficiency (%)
No inhibitor		345	N/A
Ascorbic Acid	0.57 µmole (0.1 wt%)	283	17.9
	5.7 µmole (1.0 wt%)	-72	120.9
Sodium Ascorbate	0.57 µmole	344	0.3
	5.7 µmole	30	91.3
Ferulic Acid	0.57 µmole	137	60.3
Caffeic Acid	0.57 µmole	129	62.6
	5.7 µmole	-72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

Nitrosamine formation generally requires acidic conditions

Formulations with excipients that modify micro-environment to neutral/ basic pH should theoretically be effective in suppressing NDSRI formation

FDA Communication Nov. 11, 2021

Discusses these Possible Mitigation Strategies for NDSRIs

FDA encourages manufacturers to consider these as well as other innovative strategies to reduce the formation of NDSRIs to acceptable levels in drug products.

FDA will consider meeting requests, as appropriate, to discuss innovative mitigation strategies with prospective applicants or manufacturers.

The data in the NDA/BLA and ANDA meeting package should include, at a minimum, the following:

- Description of the formulation design strategy employed to reduce the formation of NDSRIs in the drug product.

- Supporting manufacturing information and, at a minimum, three months of accelerated stability data demonstrating control of NDSRI.

- For approved NDAs and ANDAs that require reformulation as part of a mitigation strategy, in vitro or in vivo bioequivalence bridging studies.

Acknowledgements

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

Thank You!