Identification and control of harmful impurities in pharmaceutical products: Nitrosamine as an example

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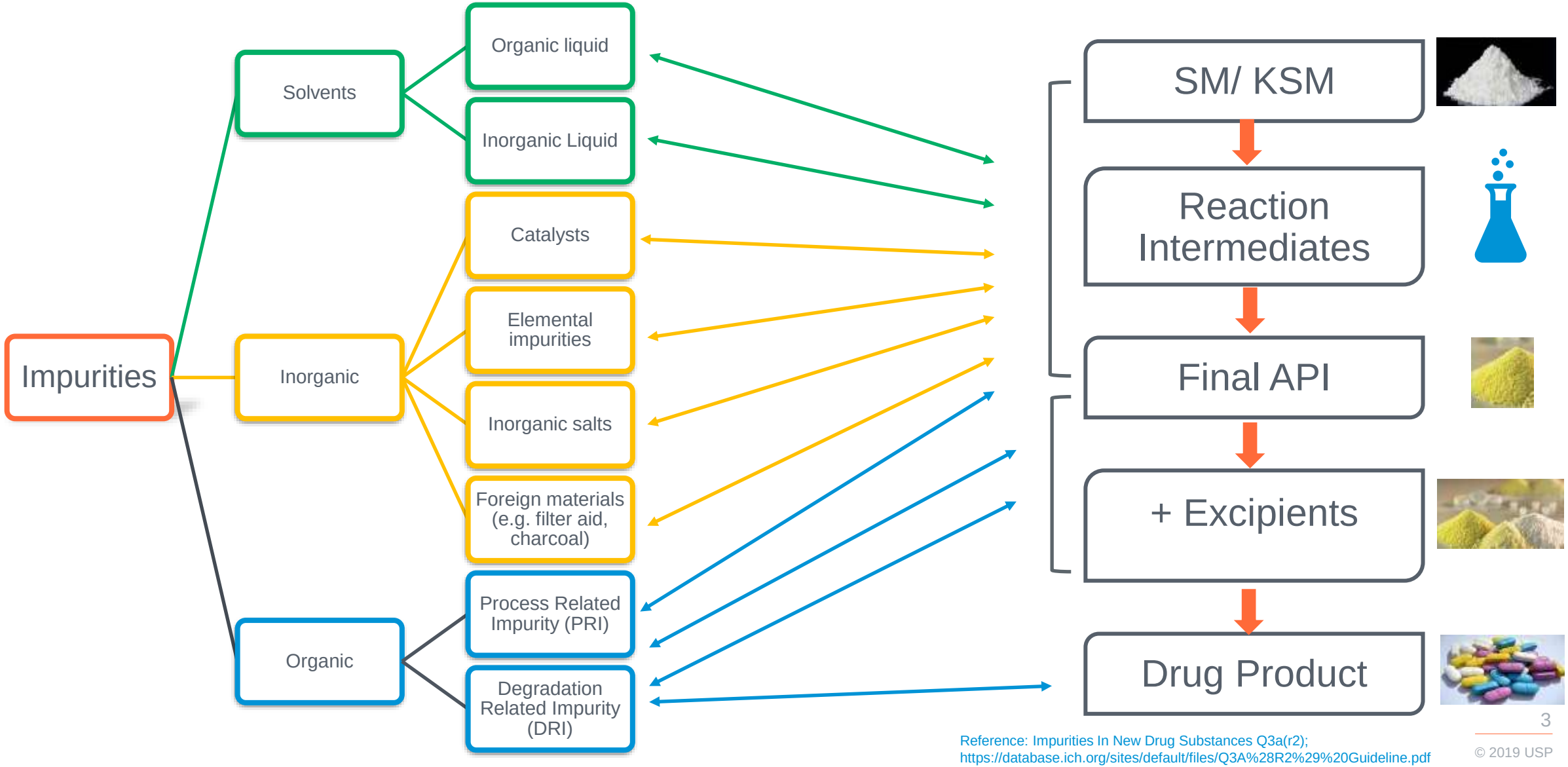
August 18, 2022

Outline

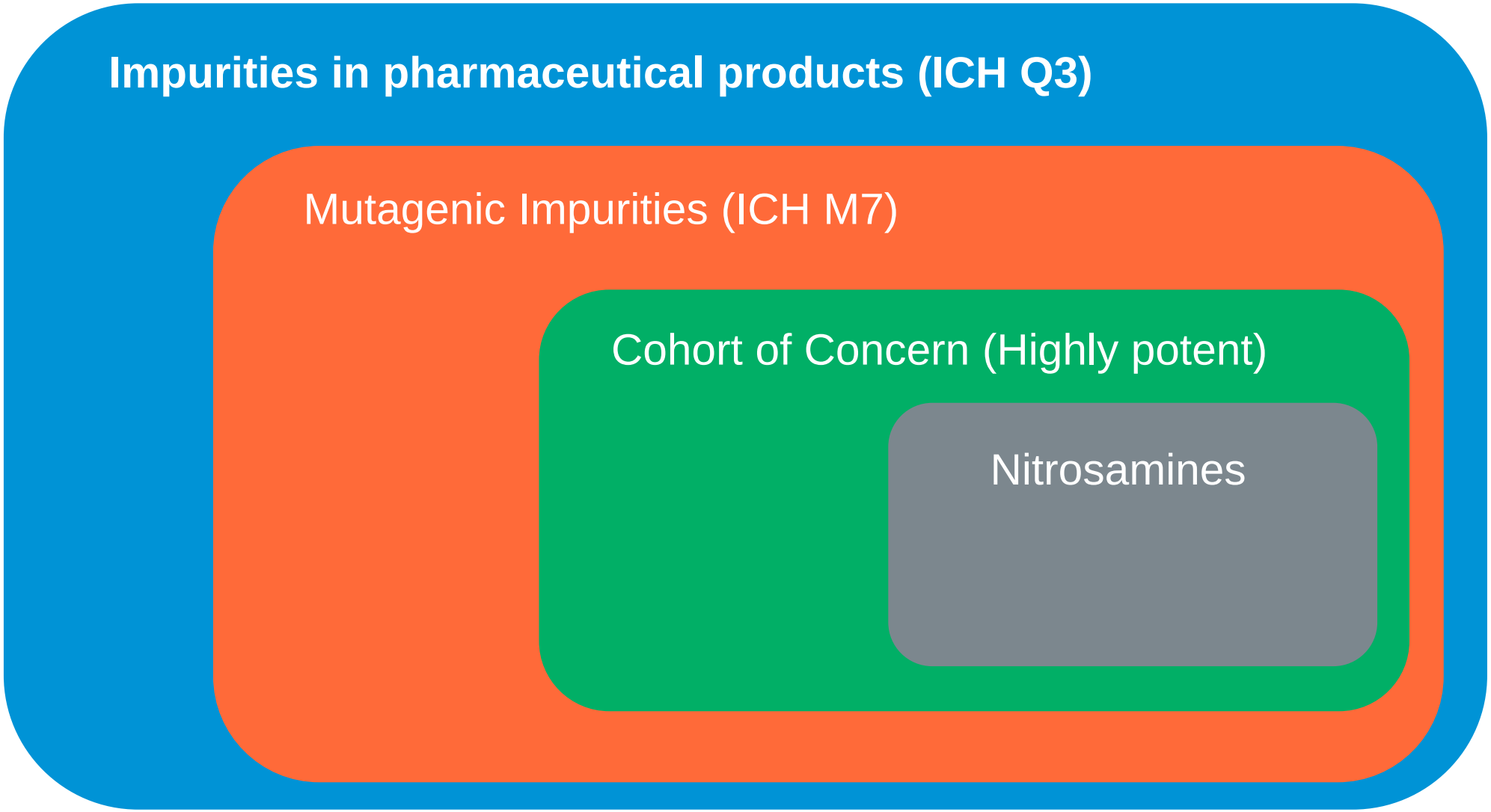
- Impurities in pharmaceutical products
  - Impurities in Drug Substance and Drug Products
  - Mutagenic Impurities
  - Cohort of Concern
  - Nitrosamines
- USP’s response to Nitrosamines
- Current Challenges
- Way forward..

Impurities in Pharmaceutical Products



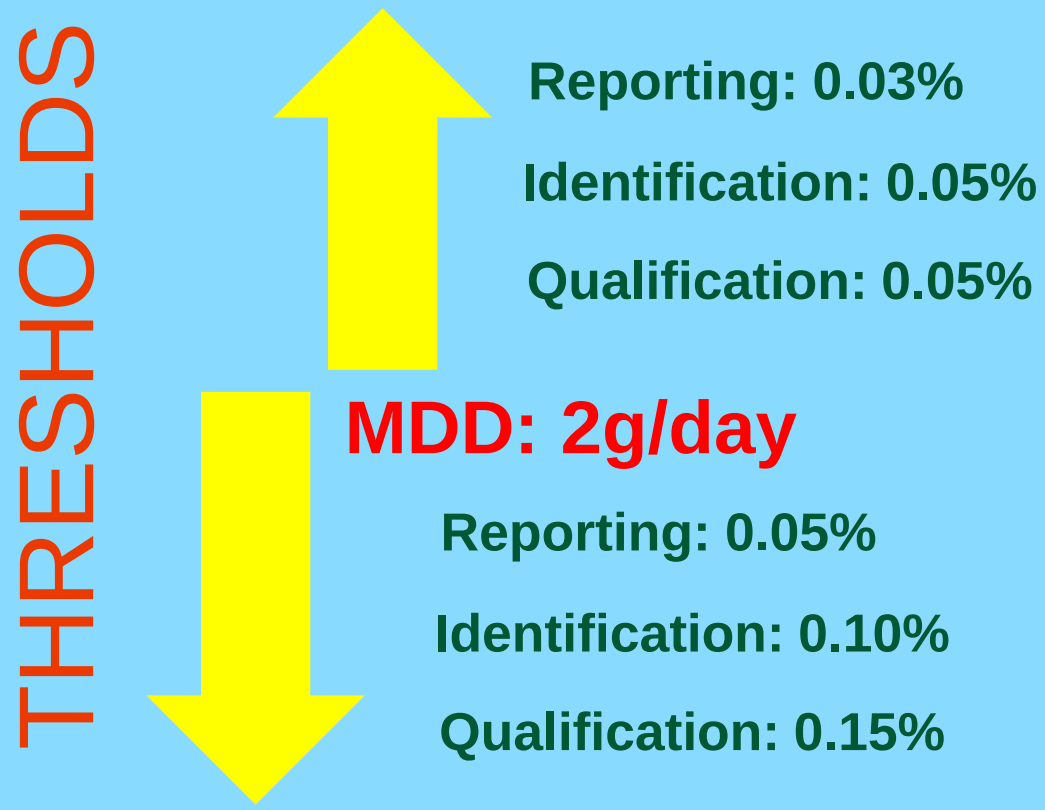
Reference: Impurities In New Drug Substances Q3a(r2); https://database.ich.org/sites/default/files/Q3A%28R2%29%20Guideline.pdf

Impurities in Pharmaceutical Products



Impurities in Pharmaceutical Products

Drug Substances ICH Q3A (R2)



MDD: The **amount** of **drug substance** administered **per day**

Higher reporting thresholds should be **scientifically justified**

Lower thresholds can be **appropriate** if the impurity is **unusually toxic**

Qualification: The process of acquiring and evaluating data that establishes the **biological safety** of an individual impurity or a given impurity profile at the level(s) specified.

Impurities in Pharmaceutical Products

Drug Products ICH Q3B (R2)

Reporting: 0.05%

MDD: 1g/day

Reporting: 0.1%

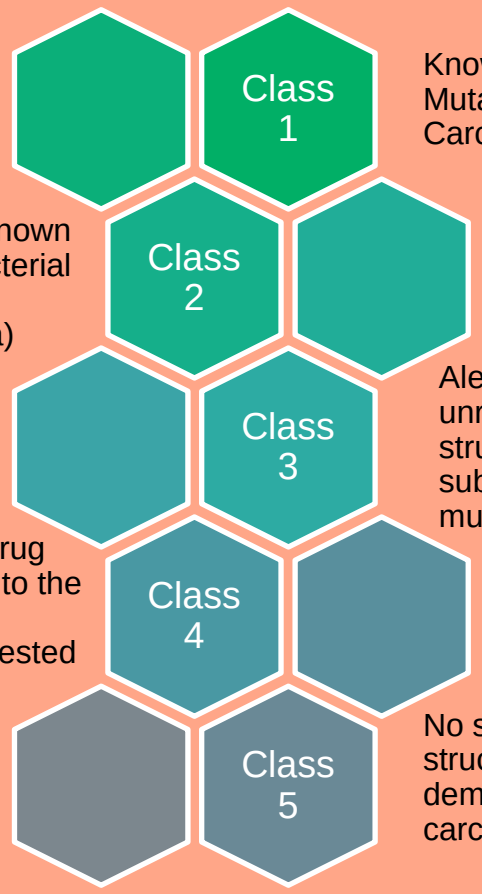
Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

	Identification: 0.10%
2 g/day	
	Identification: 0.2% or 2 mg TDI whichever is lower
10 mg/day	
	Identification: 0.5% or 20 µg TDI whichever is lower
1 mg/day	
	Identification: 1% or 5 µg TDI whichever is lower

	Qualification: 0.15%
2 g/day	
	Qualification: 0.2% or 3 mg TDI whichever is lower
100 mg/day	
	Qualification : 0.5% or 200 µg TDI whichever is lower
10 mg/day	
	Qualification: 1% or 50 µg TDI whichever is lower

Impurities in Pharmaceutical Products

Mutagenic Impurities (ICH M7)



Class 1: Known Mutagenic Carcinogens — Control at or below compound specific acceptable limit

Class 2: Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data) — Control at or below acceptable limits (appropriate TTC)

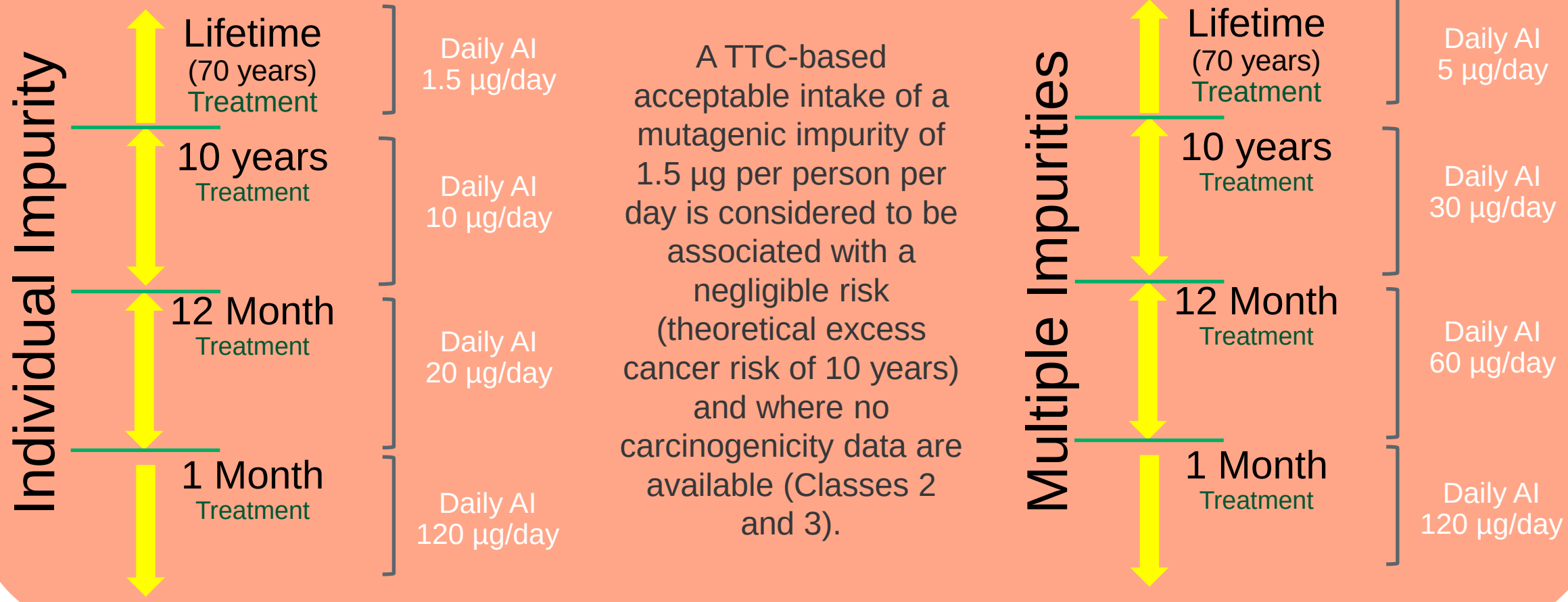
Class 3: Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data — Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2

Class 4: Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non mutagenic — Treat as non-mutagenic impurity

Class 5: No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity — Treat as non-mutagenic impurity

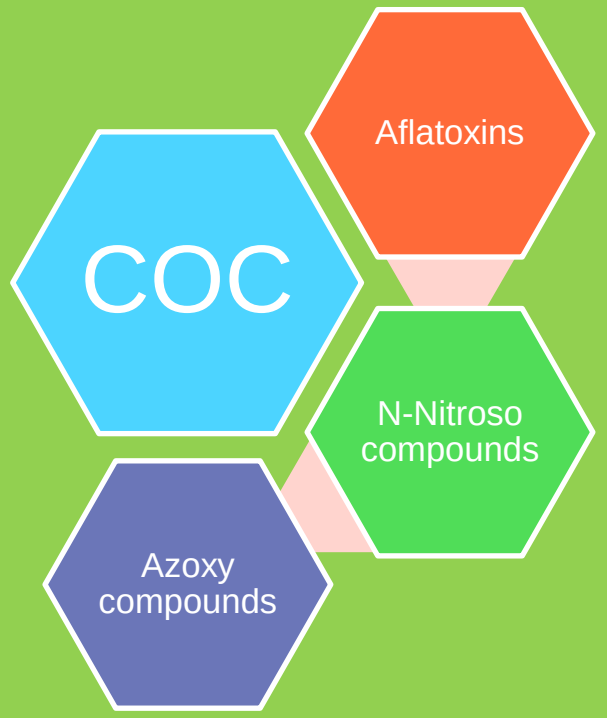
Impurities in Pharmaceutical Products

Mutagenic Impurities (ICH M7)



Impurities in Pharmaceutical Products

Cohort of Concern (Highly potent) – ICH M7 (R1)

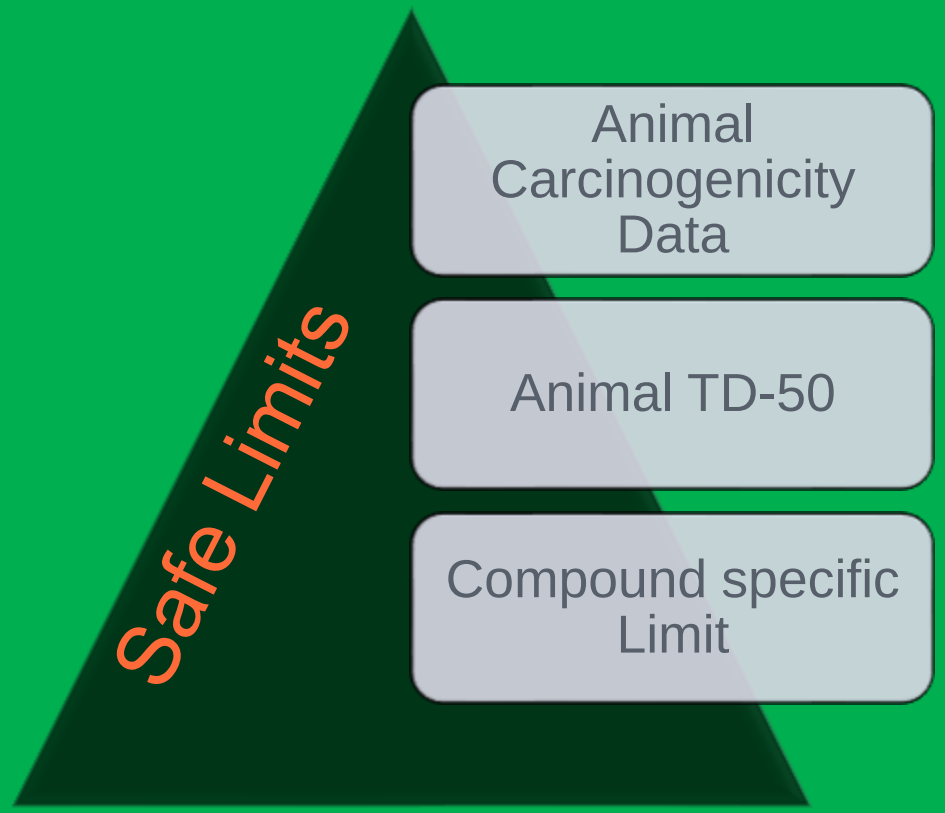


Certain structural groups have been identified to be of such high mutagenic potency that the TTC approach is not justified for these compounds. This group is comprised of aflatoxin-like-, N-nitroso, and alkyl-azoxy compounds and is referred to as the **Cohort of Concern (CoC).**

Reference: Assessment And Control Of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf

Impurities in Pharmaceutical Products

Cohort of Concern

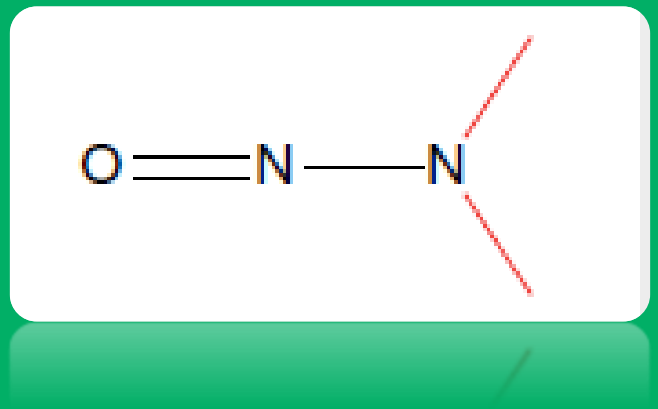


- TD50 – dose level showing 50% tumor incidence in animal study
- Accepted life-time cancer risk level: 1 in 100’000 patients
- Dividing TD50 by 50’000
- Calculated acceptable NDMA life-time limit
  - TD50 of 0.0959 mg/kg / 50’000 = 0.000001918 mg/kg
  - To derive a total human daily dose: 0.000001918 mg/kg x 50 kg = 0.0000959 mg/day (= 96 ng/day)

Reference: Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, USFDA, September 2020
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

Impurities in Pharmaceutical Products

Cohort of Concern



The acceptable concentration in the material can be calculated as

Acceptable nitrosamine content = AI / MDD

Where, AI = Acceptable daily intake of the nitrosamines, ng/day; MDD = maximum daily dose of the API, mg/day

Acceptable concentration, ng/g			
0.050 g (50 mg dose)	0.100 g (100 mg dose)	0.250 g (250 mg dose)	1.00 g (1000 mg dose)
1920	960	384	96

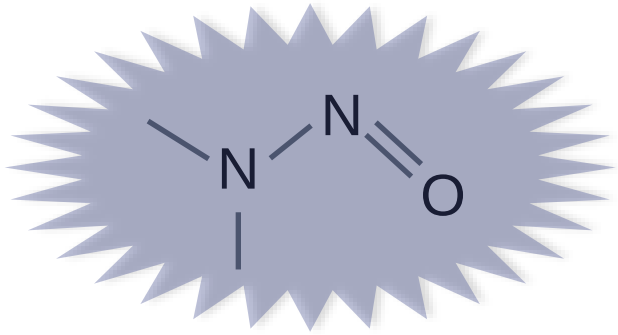
**The example uses AI of a 96 ng/day for target nitrosamine*

Reference: USP GC <1469> Nitrosamine Impurities

Numerous FDA Recalls

Recalls

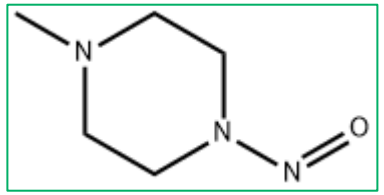
Genotoxic Impurity



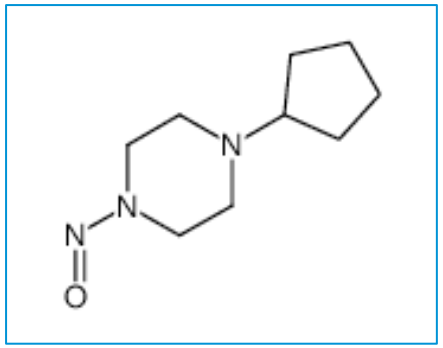
References:
1. https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and
2. https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

Nitrosamines in Rifapentine and Rifampin

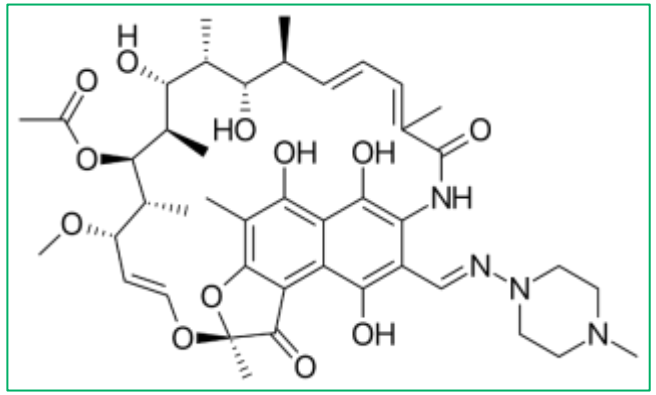
- Rifampin and Rifapentine are antibacterial drugs used to treat **tuberculosis**; rifampin is also used to treat or prevent other serious infections
- The **acceptable intake limits (in terms of concentration in ppm) are 0.16 ppm for MNP** in rifampin and **0.1 ppm for CPNP in rifapentine**.
- The agency will not object to certain manufacturers temporarily distributing **rifampin containing MNP below 5 parts per million (ppm).** The agency also will not object to certain manufacturers temporarily distributing **rifapentine containing CPNP below 14 ppm**..
- Update [10/29/2020] To continue to mitigate or avoid a shortage and to help ensure patients have access to rifapentine, FDA will not object to certain manufacturers temporarily distributing the medicine containing **1-cyclopentyl-4-nitrosopiperazine (CPNP) above the acceptable intake limit of 0.1 parts per million (ppm) and at or below 20 ppm** until they can reduce or eliminate the impurity.



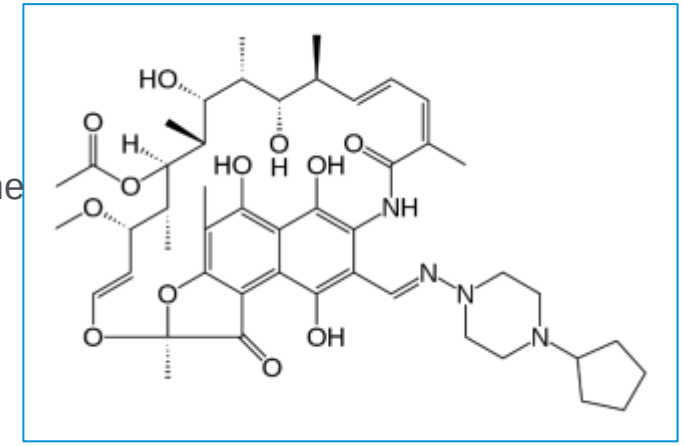
1-methyl-4-nitrosopiperazine (MNP)



1-Cyclopentyl-4-nitrosopiperazine (CPNP)



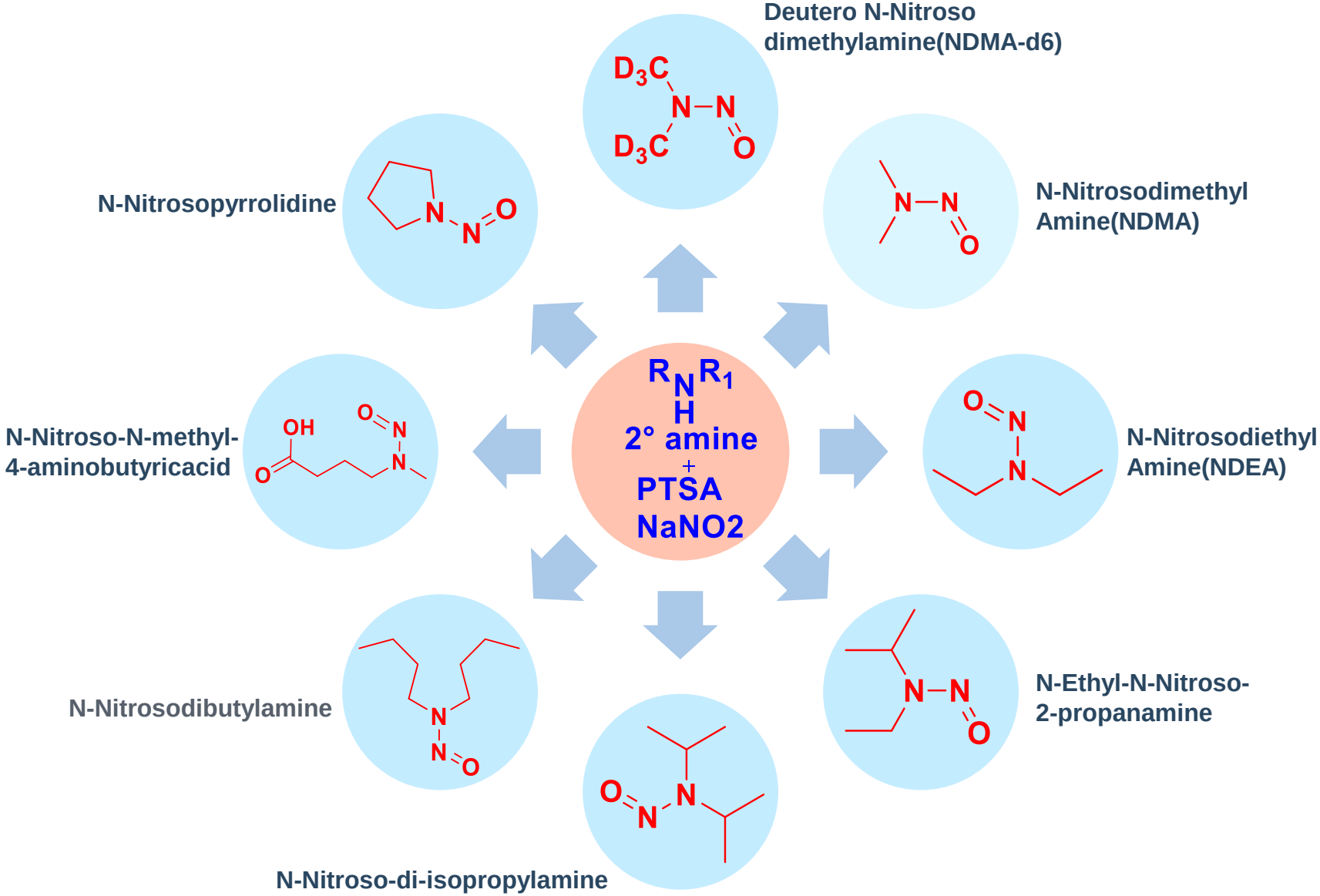
Rifampin



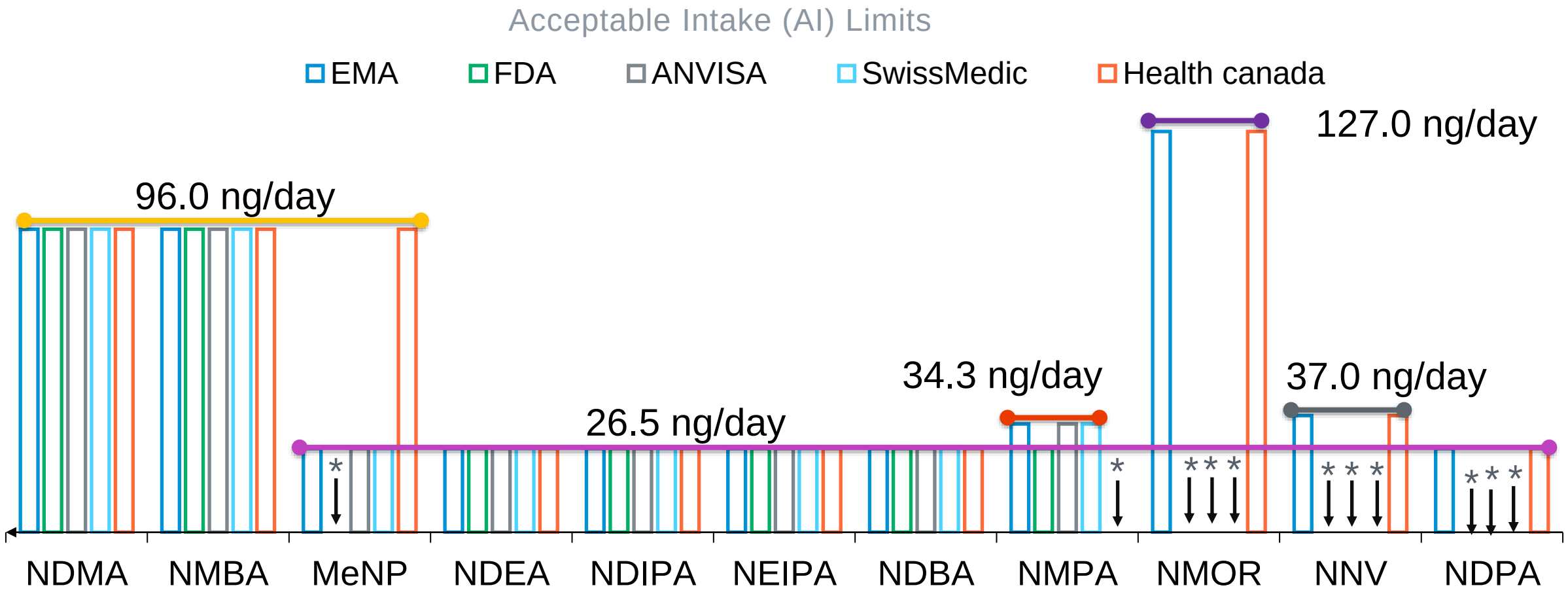
Rifapentine

Reference: FDA Updates and Press Announcements on Nitrosamines in Rifampin and Rifapentine
https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine#:~:text=8%2F26%2F2020%3A%20FDA,or%20prevent%20other%20serious%20infections.

Nitrosamines: General method of Synthesis



Nitrosamines: Acceptable Intakes



N-Nitrosodimethyl amine (NDMA), N-Nitroso-4-(methylamino)-butyric acid (NMBA), MeNP (1-methyl-4-nitrosopiperazine), N-Nitrosodiethyl amine (NDEA) , N-Nitrosodiisopropylamine (NDIPA), NEIPA (N-Nitrosoethylisopropylamine), N-Nitrosodibutylamine (NDBA), NMPA (N-Nitrosomethylphenylamine), N-Nitrosomorpholine (NMOR), N-Nitrosovarenicline (NNV), N-Nitrosodipropylamine (NDPA)

* No limits specified

Limits in ppm = Acceptable intake (ng/day) / Maximum Daily Dose (MDD) in mg/day

USP's response to Nitrosamine

2020 – 2025 Mission

Strengthen the global supply of quality medicines

Impurities Taskforce

USP 2025 Goal: Develop proactive, risk-based, and flexible approaches that predict, identify, evaluate and control impurities throughout the supply chain

Nitrosamine impurities: A global challenge

- To respond quickly to this urgent need, USP decided to support pharmaceutical industry and regulators by working in below areas:
  - Developed standards (documentary and physical RS) to provide solutions to our stakeholders.
  - Raised awareness about USP's offerings.
  - Supported our stakeholders for effective use of tools.
  - Delivered education course and training programs on analytical and regulatory requirements.

GC <1469> Nitrosamines Impurities

Timeline

1

01 Sep 2020

GC <1469> publication in the PF

<1469> published in Pharmacopeial Forum 46 Issue 5, available on-line

2

30 Nov 2020

End commentary

Comments period ended (all stakeholders were encouraged to participate)

3

JSC addressed comments and reviewed proposal

Sub-committee addressed public comments and revised the chapter as found appropriate

4

Standard is balloted

GC was balloted and approved by Chemical Analysis General Chapter Expert committee

5

Published to USP-NF 1st Jun '21

6

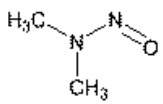
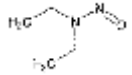
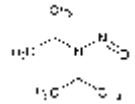
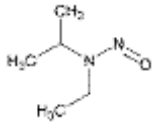
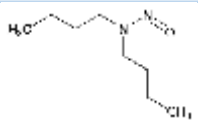
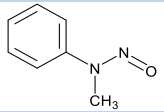
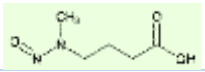
GC <1469> became official 1st Dec '21

GC <1469> Nitrosamines Impurities

Content

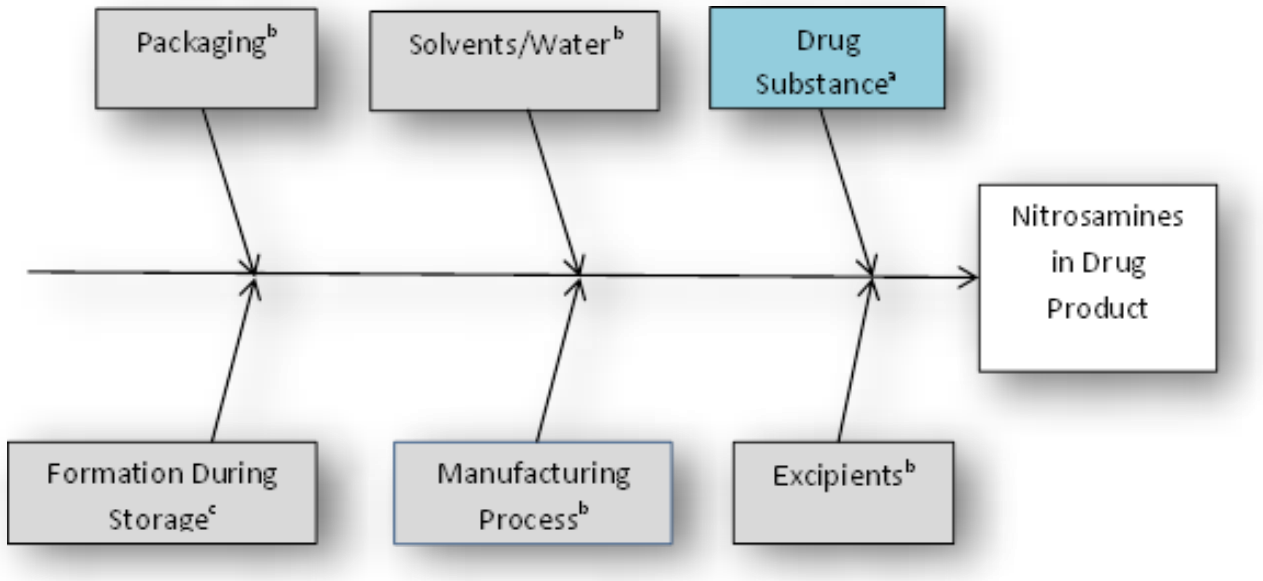
1. INTRODUCTION
2. NITROSAMINE IMPURITIES
3. SOURCES OF NITROSAMINES
4. NITROSAMINE RISK ASSESSMENTS – DEVELOPMENT OF A CONTROL STRATEGY
5. LIMITS OF NITROSAMINE
6. TESTING FOR THE PRESENCE OF NITROSAMINES
7. TEST METHOD PERFORMANCE CHARACTERISTICS OF NITROSAMINE METHODS
8. ANALYTICAL PROCEDURES
9. ADDITIONAL SOURCES OF INFORMATION

GC <1469> Nitrosamines Impurities

Common Name and Chemical Name	Acronym	CAS #	Structure	Chemical Formula	Molecular Weight
Nitrosodimethylamine/ N-Methyl-N-nitrosomethanamine	NDMA	62-75-9		$C_2H_6N_2O$	74.08
N-Nitrosodiethylamine/ *N*-Ethyl-*N*-nitrosoethanamine	NDEA	55-18-5		$C_4H_{10}N_2O$	102.13
N-Nitrosodiisopropylamine/ N-Isopropyl-N-nitrosoisopropylamine	NDIPA	601-77-4		$C_6H_{14}N_2O$	130.19
N-nitrosoethyisopropylamine/ N-Ethyl-N-nitroso-2-propanamine	NEIPA	16339-04-1		$C_5H_{12}N_2O$	116.16
N-nitrosodibutylamine/ N-Butyl-N-nitroso-1-butanamine	NDBA	924-16-3		$C_8H_{18}N_2O$	158.24
N-Nitrosomethylphenylamine/ N-Methyl-N-nitrosophenylamine	NMPA	614-00-6		$C_7H_8N_2O$	136.15
N-Nitrosomethylaminobutyric acid / 4-[Methyl(nitroso)amino] butanoic acid	NMBA	61445-55-4		$C_5H_{10}N_2O_3$	146.14

Nitrosamines: Sources

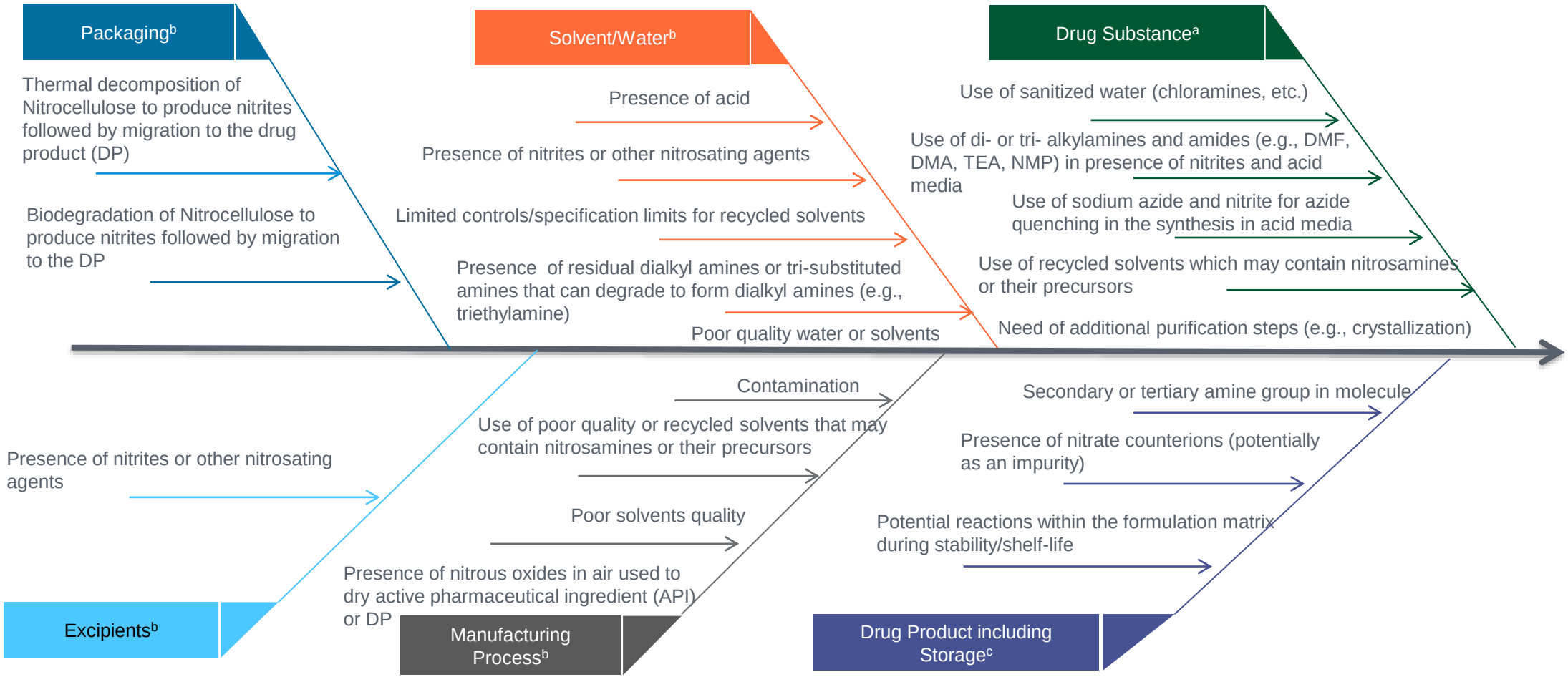
This section, with its fish-bone (Ishikawa) diagram, includes a summary on how nitrosamine impurities are formed and could end up in pharmaceuticals. The summary is followed by a bulleted list of examples of sources/pathways compiled from the literature or identified empirically.



Potential sources of nitrosamine impurities in drug products.

[a] Primary/ Predominant source of potential nitrosamines
[b] Secondary source of potential nitrosamines
[c] Formed by a mechanism other than degradation of the drug substance

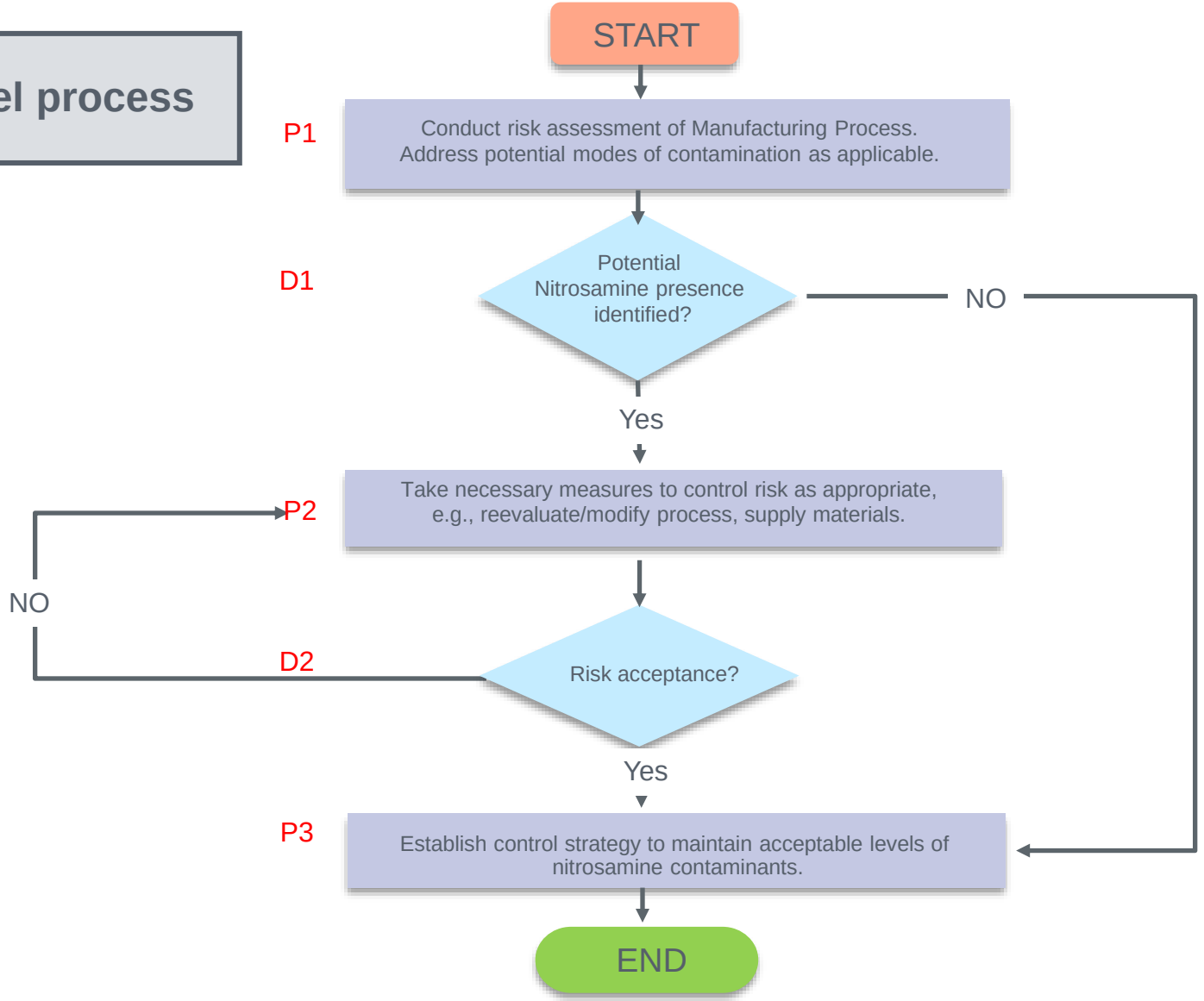
Nitrosamines: Risk Assessment



[a] Primary/predominant source of potential nitrosamines, [b] Secondary sources of potential nitrosamines, [c] Formed by a mechanism other than degradation of the drug substance

Nitrosamines: Control Strategy

High-level process



P1, P2, P3 = Process 1, 2, 3;
D1, D2 = Decision 1, 2

Nitrosamines: Limits

The limits published by FDA were based on the *TD_{50} values for NDMA and NDEA with a 1:100,000 safety factor applied (decreasing the potential cancer risk to 1 in 100,000)

The acceptable concentration in the material can be calculated using the equation below:

Acceptable nitrosamine content = AI / MDD

Where AI = Acceptable daily intake of the nitrosamines, ng/day;
MDD = maximum daily dose of the API, mg/day

Calculation of Acceptable nitrosamine concentration**, ng/g (ppb) or ng/mg (ppm):

Nitrosamine	Acceptable concentration, ng/g (ppb) or ng/mg (ppm):			
	0.050 g (50 mg dose)	0.100 g (100 mg dose)	0.250 g (250 mg dose)	1.000 g (1000 mg dose)
Nitrosamine 1	1920 ng/g	960 ng/g	384 ng/g	96 ng/g

*TD_{50} refers to doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2

**The example uses AI of 96 ng/day for target nitrosamine

Nitrosamines: Method Performance Characteristics

- Application of sensitive and selective analytical procedures (e.g., HPLC-MS/MS, GC-MS/MS).
- This section covers ‘Considerations for sample preparation’ in certain circumstances (e.g., In situ formation of nitrosamines as an artifact, especially in GC analysis and Total solubilization versus selective extraction).
- The recommended method performance characteristics that need to be evaluated for
  - For quantitative analysis of nitrosamines: range of linearity, accuracy, repeatability, intermediate precision, and limit of quantitation.
  - For limit test of nitrosamines: specificity, recovery, detectability, and solution stability.
- The acceptance criteria for these performance characteristics should be properly set and confirmed through validation (refer to USP GC <1225>) Higher variability may be tolerated or acceptable at lower concentrations such as LOQ while lower variability would be expected at higher concentrations.

Nitrosamines: Analytical Procedures

The analytical procedures that have been verified by USP can be found in Section 8.1: Quantitative procedures:

- Procedure 1: HPLC-High Resolution (HR) Mass Spectrometry (MS) method for quantitation of NDMA, NDEA, NDIPA, NEIPA, NMBA, NMPA, and NDBA in selected sartans.
- Procedure 2: Headspace (HS) GC-MS/MS (triple-quad) method for quantitation of NDMA, NDEA, NDIPA, and NEIPA in selected sartans.
- Procedure 3: Quantitation of NDMA, NDEA, NDIPA, NEIPA, NMBA, and NDBA in selected sartans by HPLC–MS/MS (triple-quad).
- Procedure 4: Quantitation of NDMA, NDEA, NDIPA, NEIPA, NMPA, and NDBA in selected sartans by GC–MS/MS (triple-quad)

GC <1469> Nitrosamines Impurities Procedures

Procedure sensitivity/ Limit of Quantification

	LC–HRMS	GC–HS-MS/MS (Triple-Quad)	LC–MS/MS (Triple-Quad)	GC–MS/MS (Triple-Quad)
Impurities	NDMA,NDEA, NEIPA,NDIPA, NMBA, NMPA, NDBA.	NDMA,NDEA, NEIPA,NDIPA.	NDMA,NDEA, NEIPA,NDIPA, NMBA, NDBA.	NDMA,NDEA, NEIPA,NDIPA, NMPA, NDBA.
Sample Concentration	20 mg/mL	100 mg/mL	66.67mg/mL	100 mg/mL
LOQ as such Concentration	0.001 µg/mL	0.002 µg/mL	0.00066(NDEA), 0.002 (other impurities) µg/mL	0.0005 µg/mL
LOQ w.r.t sample Concentration	0.05 ppm	0.02 ppm	0.01 (NDEA), 0.03 (other impurities) ppm	0.005 ppm

Overview of USP Nitrosamine activities

Documentary Standards

<1469>- Nitrosamine Impurities

Nitrosamine USP Reference Standards

- NDIPA
- NDMA
- NDBA
- NDEA
- NMBA
- NEIPA
- NMPA
- D6-NDMA

Nitrosamine Training material/ Education course

Developed a tutorial and education course on Nitrosamine impurities to train industry stakeholders

USP Workshops / Webinars / Conferences

Scientific Webinars/ Workshops

Round table discussions/ stakeholder forums

Industry connect forums

Global Public Health

Training and guidance for global regulators

Nitrosamine test methods for essential tuberculosis drugs

USP Reference Standards – Nitrosamine Impurities

Nitrosamine Impurities

N-Nitrosodimethylamine (NDMA)

(1 mg/mL in methanol)
(*Label value: 1.00 mg/mL)

N-Nitrosodiethylamine (NDEA)

(1 mg/mL in methanol)
(*Label value: 1.00 mg/mL)

N-Nitrosodiisopropylamine (NDIPA)

(1 mg/mL in methanol)
(*Label value: 0.98 mg/mL)

N-Nitrosodibutylamine (NDBA)

(1 mg/mL in methanol)
(*Label value: 0.99 mg/mL)

*Label value: For quantitative applications use a value of *mg* of nitrosamine per *mL* of solution on the as is basis

USP Reference Standards – Nitrosamine Impurities

Nitrosamine Impurities

N-Nitrosoethylisopropyl (NEIPA)

(1 mg/mL in methanol)
(*Label value: 1.00 mg/mL)

N-Nitrosoethylaminobutyric (NMBA)

(1 mg/mL in acetonitrile)
(*Label value: 1.00 mg/mL)

N-Nitrosomethylphenylamine (NMPA)

(1 mg/mL in methanol)
(*Label value: 1.00 mg/mL)

d6-*N*-Nitrosodimethylamine (NDMA-d6)

(1 mg/mL in methanol)
(*Label value: 1.00 mg/mL)

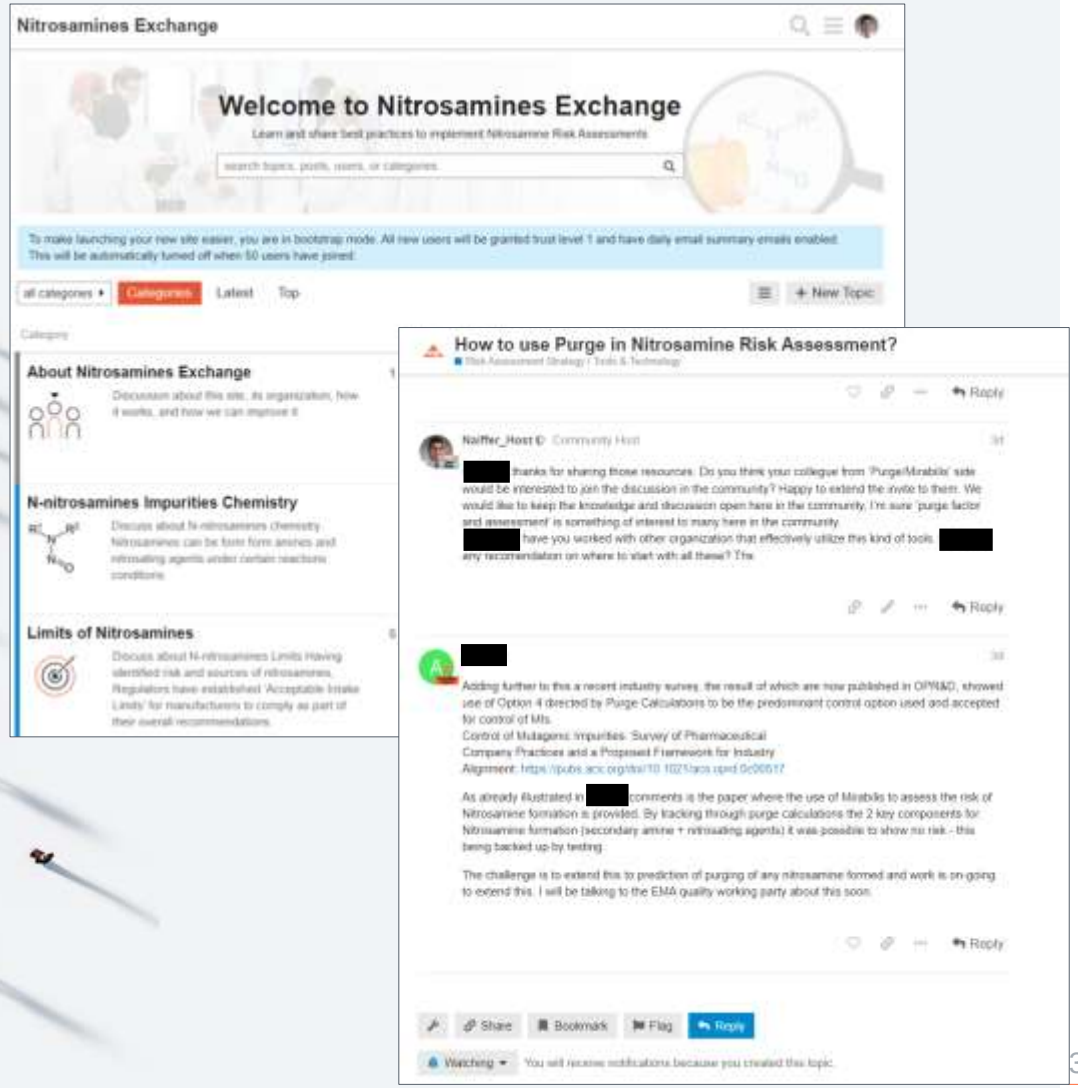
*Label value: For quantitative applications use a value of *mg* of nitrosamine per *mL* of solution on the as is basis

Proposed Nitrosamine PAIs

RFI CAS	Short Description	Impurity name or Chemical formula	API	Molecular Formula
621-64-7	NDPA	N-Nitrosodipropylamine	Metformin	C6H14N2O
61379-66-6	CPNP	1-Cyclopentyl-4-nitrosopiperazine	Rifapentine	C9H17N3O
16339-07-4	MeNP (MNP)	1-Methyl-4-nitrosopiperazine	Rifampin	C5H11N3O
NA	AZBT	N-nitroso-varenicline	Varenicline	C13H12N4O

Nitrosamine Exchange Community

Nitrosamine Exchange Knowledge Community



Join http://nitrosamines.usp.org

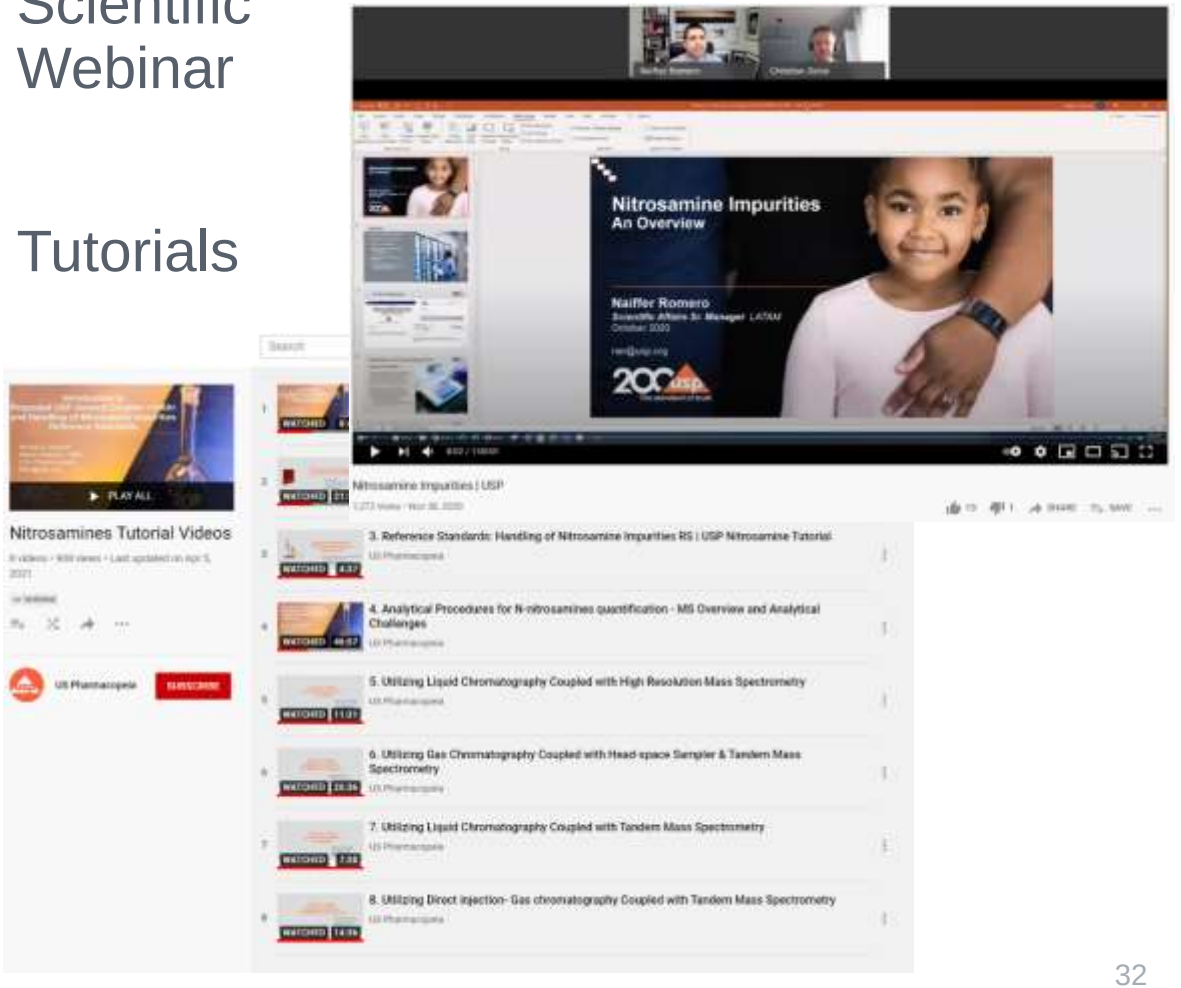
USP Website & Resources

https://www.usp.org/chemical-medicines/nitrosamine-impurities

USP Education

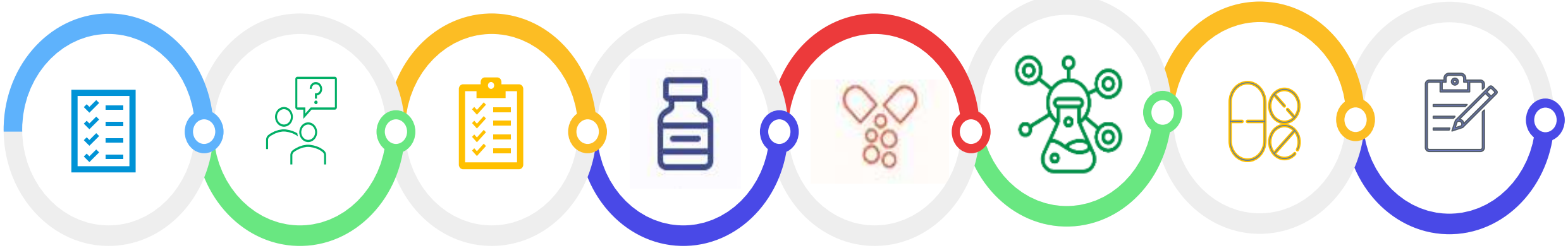
Resources in YouTube

- Scientific Webinar
- Tutorials



Current Industry Challenges

Mission Impact



Different regulatory requirements (recommended AIs) for nitrosamines

MSMEs do not have expertise/ skills for advanced equipment (complex analysis)

Need to verify the analytical procedures for new nitrosamines (NDSRIs) or develop new procedures if needed

Availability of new nitrosamine RS/ materials

No support from excipient manufacturers for risk assessment

Complex nitrosamines getting added to the list

Toxicity data not available for some of the nitrosamines

No AIs recommended for Nitrosamine drug substance related impurities (NDSRIs)

Abbreviations :
AI – Acceptable Intakes
NDSRI – Nitrosamine Drug Substance Related Impurities
MSME – Micro Small & Medium Enterprises

Way-forward

Reference Standards/ PAI

- Evolving nitrosamine impurities
- Nitrosamine Drug Substance Related Impurities (NDSRIs)

Documentary Standards

- Identify specific need based on current trends (e.g.,: Product-specific monographs, New General chapter < 1000, etc.)

Nitrosamine Toolkit

- Nitrosamine analytical hub (additional procedures developed by USP)
- Risk Assessment tools

Training courses

- Video tutorials to demonstrate analysis and trouble-shooting of instrument

Excipients Strategy

- To be determined based on data and discussion with Expert Committee

Thank You

Stay Connected

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