SBIA 2020

U.S. FOOD & DRUG ADMINISTRATION

FDA's Overview of the Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs

David Keire, Ph.D. and Dongmei Lu, Ph.D.

Office of Pharmaceutical Quality

CDER/U.S. FDA

October 2, 2020

Advancing Pharmaceutical Quality: Nitrosamines in Drugs

David Keire

Deputy Director

Office of Testing and Research

Office of Pharmaceutical Quality

US FDA Center for Drug Evaluation and Research

October 2, 2020

Pharmaceutical Quality

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

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

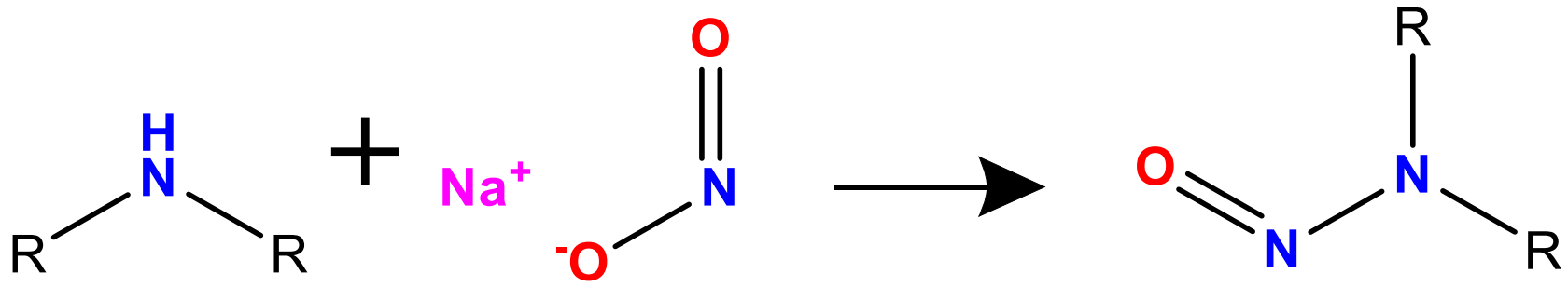
assuring *every* dose is safe and effective, free of contamination and defects.


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

www.fda.gov

Nitrosamines are everywhere.

- 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.

ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk

- Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like, N-nitroso-, and alkyl-azoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guidance.

ICH M7 (2)

- **Other Considerations for <u>Marketed Products</u>:** Application of this guidance to marketed products may be warranted if there is specific cause for concern. The existence of impurity structural alerts alone is considered insufficient to trigger follow-up measures, unless it is a structure in the cohort of concern (Section III (3)). However, a specific cause for concern would be new relevant impurity hazard data (classified as Class 1 or 2, Section 6) generated after the overall control strategy and specifications for market authorization were established.

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

Timeline of US Drug Nitrosamine Issues (2)

- Nov 2018 – losartan recalled due to NDEA
- Dec 2018 – FDA posted interim limits for NDMA/NDEA in ARBs
- Feb 2019 – FDA posted interim limit for NMBA in ARBs
- March 2019 – NMBA detected in losartan
  - Temporary drug shortage mitigation: “FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market.”

Timeline of US Drug Nitrosamine Issues (3)

- 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 (4)

- Dec 2019 – NDMA detected in some metformin products but recalls not warranted as the amounts were below AI
- 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

Timeline of US Drug Nitrosamine Issues (5)

- May 2020 – metformin extended-release recalled due to NDMA
- May 2020 – 1-cyclopentyl-4-nitrosopiperazine (CPNP) reported in rifapentine
- **Numerous information requests to industry from FDA and responses from industry throughout this entire time period**

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**

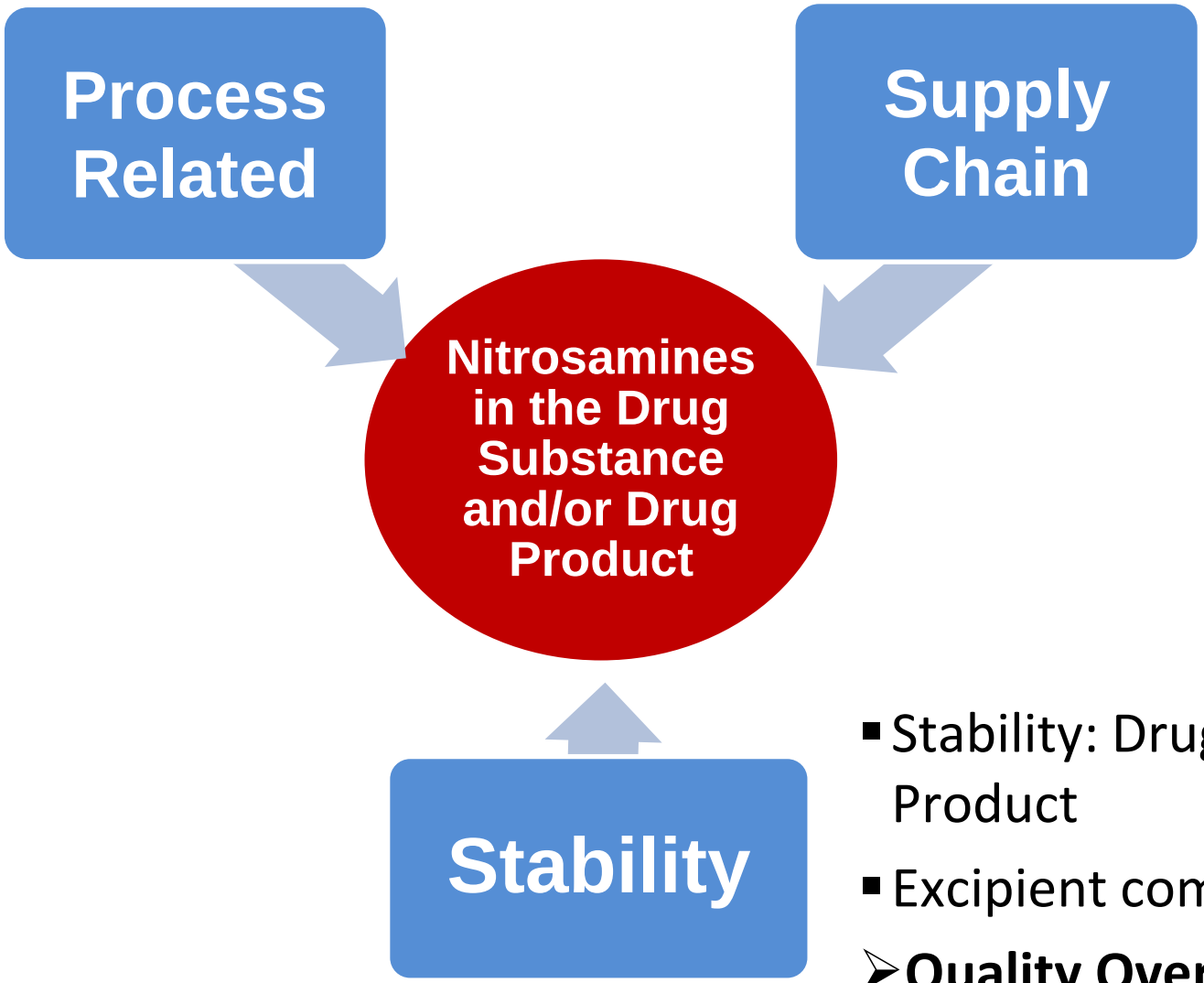
Outcome:

Over the past 2 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**



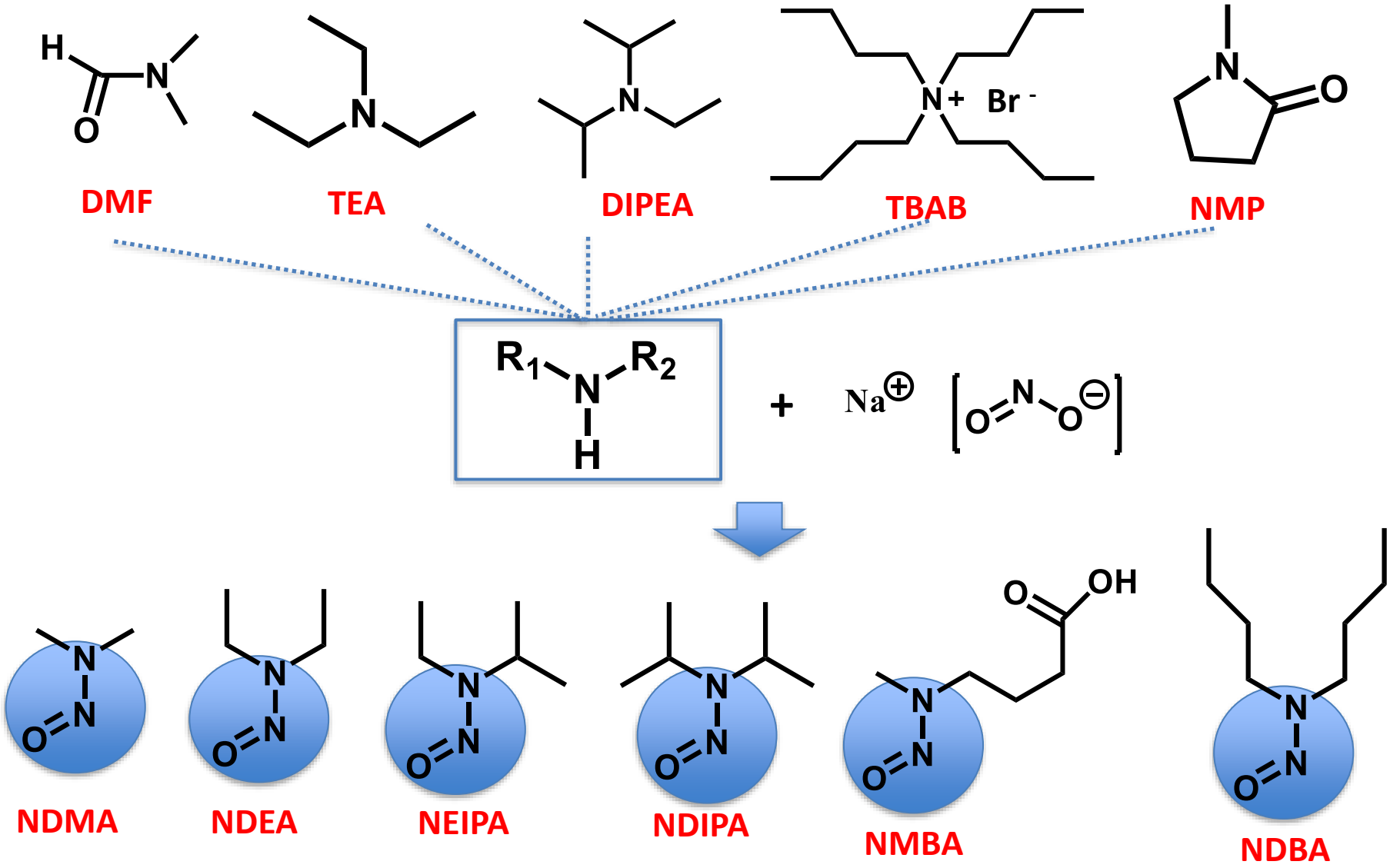
- Use of recovered or recycled materials or other intermediates contaminated with nitrosamines
- Cross-contamination in multi-purpose facilities

➢ **Quality Oversight**

- Stability: Drug Substance or Drug Product
- Excipient compatibility

➢ **Quality Oversight**

Potential Nitrosamine Impurities Generated During the Synthesis of ARB Drug Substances



Nitrosamine Risk Assessment

- Assess stages of API or Drug Product manufacturing
  - Are there API or formulation steps that have the potential to have reactive amines in the presence of nitroso compounds?
  - Are there reagents (*e.g.,* catalysts, solvents) that may have components that could form nitroso-compounds in side reactions?
  - What about intermediates or reagents sourced from suppliers?
- Is there nitrosamine risk?

If nitrosamine risk is present

- Is the nitroso-compound a known mutagen as per ICH M7?
  - Determine a drug-specific acceptable intake (AI) based on the maximum daily dose (MDD) of the drug.
  - Establish an analytical target based on the AI and MDD.
- Develop and validate an analytical procedure sensitive enough to track and trace nitroso-compounds in the manufacturing process.
  - Conduct an assessment of the nitrosamine formation and purge capacity of the synthetic route.

Stability

- Is the nitrosamine content stable over time in the API?
- Does the nitrosamine content increase during formulation?
- Is the nitrosamine amount stable under “real world” conditions in the drug product?

Based on these data, an appropriate control strategy can be proposed to regulators.

Challenges

- Root cause for nitrosamine impurities
  - Investigation(s) ongoing
  - Not one source (but some common factors)
- Where recalls were warranted,
  - Is the drug medically necessary?
  - Will a recall lead to a drug shortage?
  - If a recall occurs, are there safe and effective alternatives that patients can switch to?
- Ongoing communications with patients, healthcare providers, media, industry and international regulators
- Rapid development of validated laboratory testing methods

FDA sampling and testing of the US Drug Supply for Nitrosamines

- The US FDA analytical procedure development approach has been to have two validated orthogonal tests (primary and confirmatory) for each drug.
  - Typically, developed and validated on one API and a single dosage form.
- However, the FDA is testing many different dosage forms
  - The second orthogonal test (if the value measured is similar) provides assurance that no matrix interference has occurred with the primary measurement.
  - Spike recovery checks are key steps across products

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

Suitable Analytical Measurements on Trace Amounts (ppm to ppb) of Nitrosamines

- Key to detection of nitrosamines in each drug is the application of appropriate measurement technology focused on detecting amounts of nitrosamines in solvents, intermediates, APIs and across finished dosage forms.
  - LOQs should be appropriately below AI amounts (Guidance!)
- Many analytical procedures developed by regulatory labs have been made publicly available to speed the risk-based screening of manufacturing processes for nitrosamines (FDA.gov).

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.

FDA Expectations of Industry

"Manufacturers are responsible for understanding their processes, which includes preventing the presence of unacceptable impurities. Manufacturers are also responsible for developing and using suitable methods to detect and limit unacceptable impurities, including any new impurities that may arise when they make changes to their manufacturing processes."

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

What industry should know about nitrosamine impurities.

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."

https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

Can we trust FDA and its approvals and drug surveillance?

FDA Guidance
Control of Nitrosamine Impurities in Human Drugs

FDA Recommendations

Dongmei Lu, Ph.D.

Office of Policy for Pharmaceutical Quality

Office of Pharmaceutical Quality | CDER | U.S. FDA

October 2, 2020

FDA Guidance
Control of Nitrosamine Impurities in Human Drugs

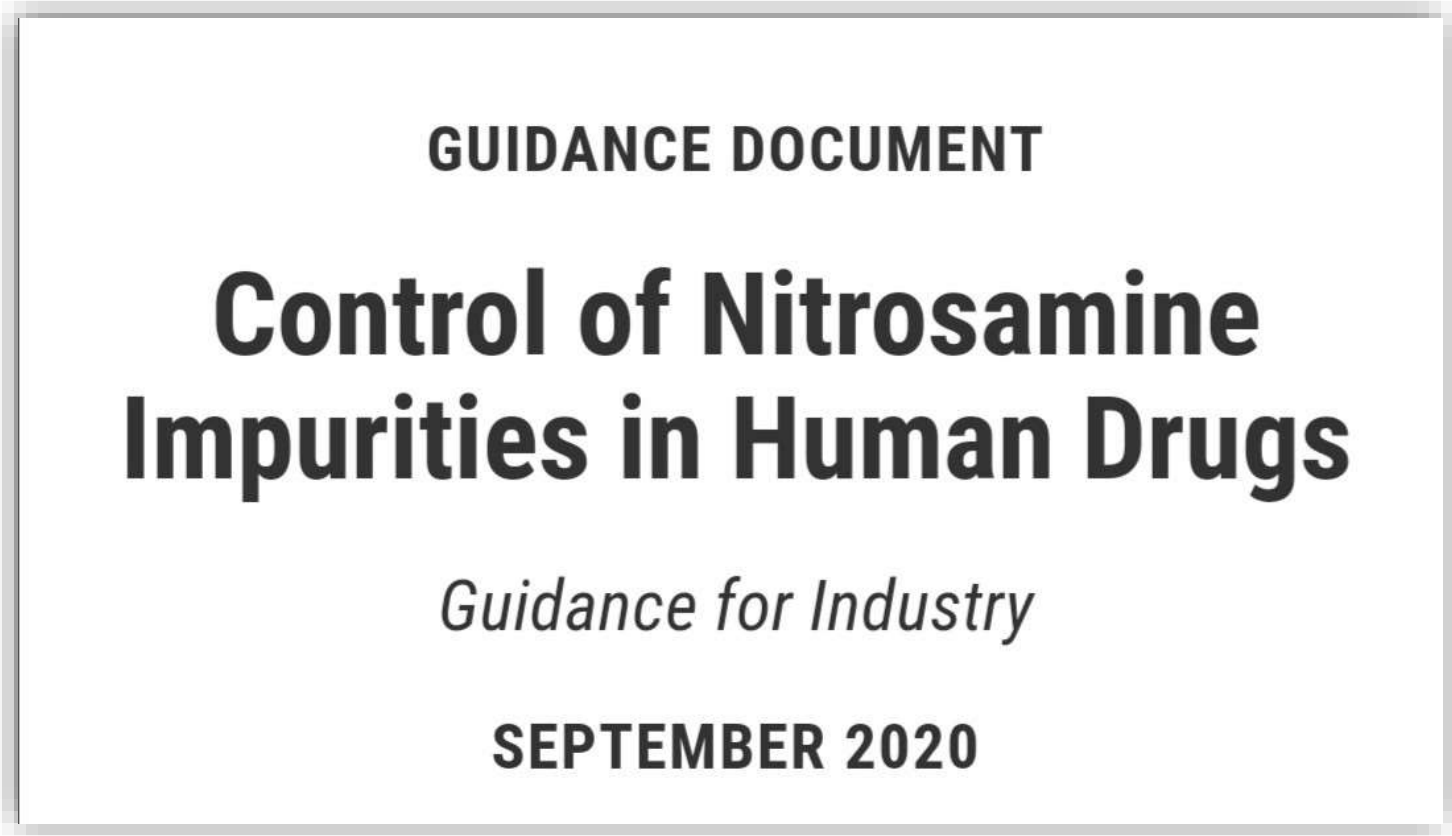
FDA Recommendations

Dongmei Lu, Ph.D.

Office of Policy for Pharmaceutical Quality

Office of Pharmaceutical Quality | CDER | U.S. FDA

October 2, 2020



Guidance was published on Sept 1st, 2020

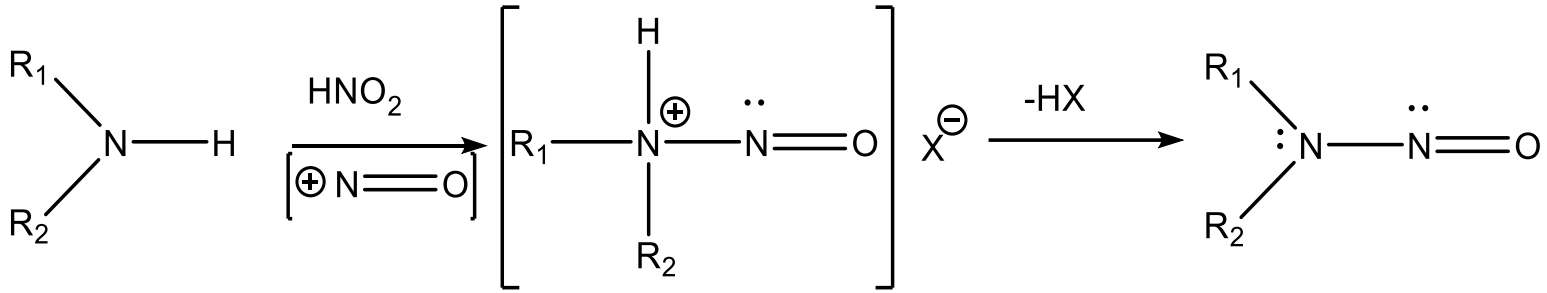
Guidance link: https://www.fda.gov/media/141720/download
Comment submission (Docket ID: FDA-2020-D-1530):
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

Outline

- Background
- Root Causes of Nitrosamines
- FDA Recommendations to Manufacturers
- Reporting Changes to FDA

What are Nitrosamines?

- What are Nitrosamines?



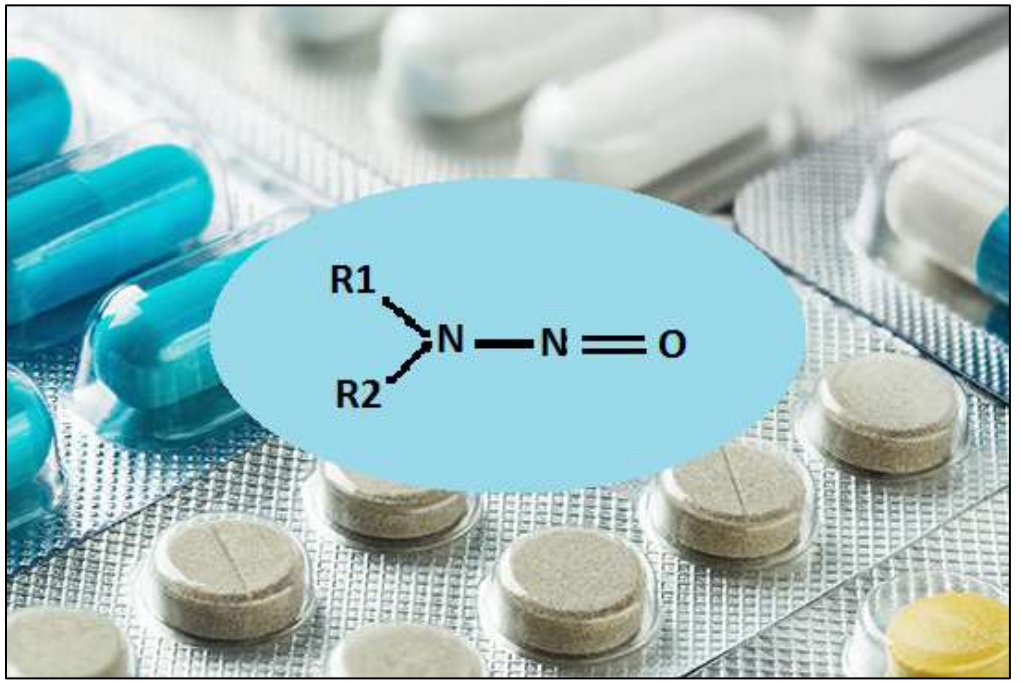
Secondary, tertiary,
or quaternary amines

- 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.

Nitrosamines Detected

- 7 possible nitrosamines could form (NDMA, NDEA, NMBA, NMPA, NIPEA, NDIPA, NDBA) and 5 actually have been found in APIs and drug products
- More are under investigation…



Impacts

- Drug Shortages:
  - ➢ valsartan, olmesartan, eprosartan, nizatidine
- Withdrawals/recalls:
  - ➢ ranitidine (all products)- withdrawal
  - ➢ sartans (certain product lots)
  - ➢ metformin (certain extended-release product lots)

https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and.
https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine
https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin

Industry Needs

- Urgent Need: for API and drug product manufacturers
  - ➢Assess potential nitrosamines in any pharmaceutical product at risk for their presence
  - ➢Develop a prevention strategy

FDA Efforts

- FDA:
  - investigated intensively
  - communicated with public via announcements
  - worked with industry to remove affected products from market
  - coordinated with international regulators
  - developed guidance/instructions to industry

What is Covered in Guidance

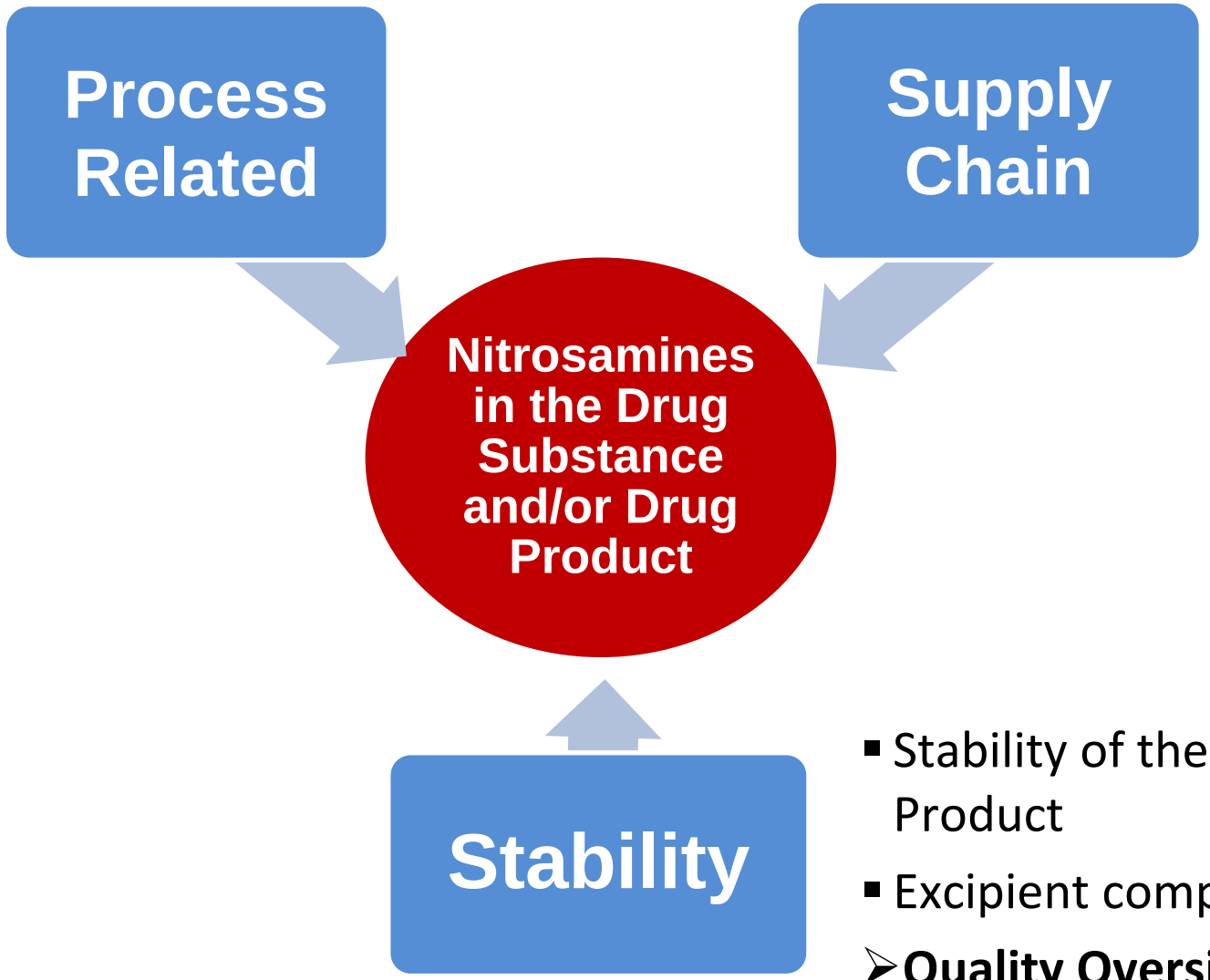
- Root causes
  - In APIs
  - In drug products other than API contamination
- Recommendations
  - Acceptable Intake Limits
  - To API manufacturers
  - To drug product manufacturers
- Three- step Mitigation Strategy
- Reporting Changes

  Timeline for three-step actions

Root Causes of Nitrosamine Impurities in APIs and Drug Products

- 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 Recommendations

Nitrosamine 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)).

Implementation of AI

- AI is only applicable if a single nitrosamine is found - Table 1
- If >1 nitrosamines:
  - Total quantity ≤ AI of the most potent one (26.5 ng/day) based on MDD
  - otherwise contact FDA*
- Analytical methods:
  - LOQ ≤ 0.03 ppm
  - If MDD is high (e.g., > 1g), LOQ and LOD as low as reasonably practical
- API manufacturers should control nitrosamine level to ensure Drug Product meets these criteria

* FDA Contact: CDER-OPQ-Inquiries@fda.hhs.gov

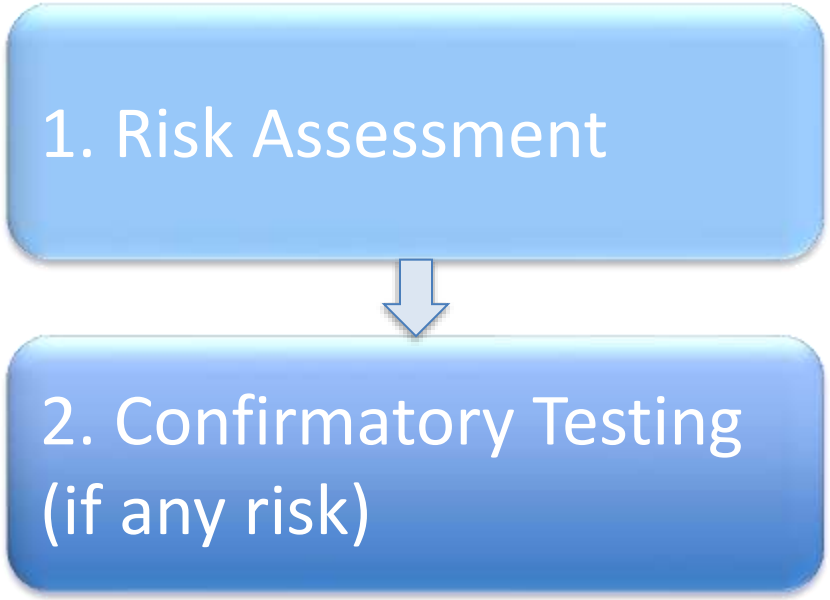
Three Steps for Mitigation Strategy

Three Steps for Mitigation Strategy

1. Risk Assessment

- APIs, marketed products, and products under approved/ pending applications.
- Conduct in a timely manner based on the prioritization of drugs:
  - MDD
  - treatment duration
  - therapeutic indication
  - number of patients treated
- FDA may recommend certain drug products as higher priority based on understanding
- If no risk, no further action.

Three Steps for Mitigation Strategy



Analytical methods need to have specificity, excellent chromatographic separation, and highly sensitive detection capability.

Three Steps for Mitigation Strategy

Report changes implemented to prevent or reduce nitrosamines. This includes DMF amendments and changes to approved/pending applications.

All risk assessment reports stay at manufacture site, available upon request

Recommendations to API Manufacturers

- Optimize design of process in ROS
  - Related reaction conditions
  - Amine bases
  - Amide solvents – use caution
  - Replace nitrites with other quenching agents for azide decomposition processes
  - Control reaction sequence/conditions
- Audit/monitor supply chain
- Avoid cross-contamination

Recommendations to API Manufacturers

- Control of Nitrosamine impurity in APIs
  - ➢ LOQ< nitrosamine level ≤AI
    - control strategy (including specifications)
  - ➢Nitrosamine level > AI
    - The batches should not be released unless with FDA agreement to prevent/mitigate drug shortages

Recommendations to Drug Product Manufacturers

- Collaborate with API manufacturers
  - ➢ If risk is detected, continuously test API lots until verified to be without unacceptable levels of nitrosamines
- Evaluate all pathways (including degradation) during manufacture and storage

Recommendations to Drug Product Manufacturers

- Control of nitrosamines in drug products
  - ➢ LOQ< nitrosamine level ≤AI:
    - control strategy (specification); also necessary if risk is inherent from API or drug product
  - ➢ nitrosamine level > AI:
    - batches should not be released;
    - contact FDA regarding batches on the market
    - FDA may exercise regulatory discretion when warranted to prevent/mitigate drug shortages.

Timeline: Three-Step Implementation

- Approved/marketed drug products
  1. Risk assessment

     6 months from guidance publication (March 1st, 2021)
  2. Confirmatory testing

     Start once risk is identified; Immediately for high risk products
  3. Submission of changes to FDA

     Last two steps concluded within 3 years of guidance publication (September 1st, 2023)

Implementation for Pending Applications

- Pending applications
  - ➢ Pre-submission:
    - Risk assessment, confirmatory testing if at risk
    - Changes may be submitted in amendment if not included in the original submission
  - ➢ Pending with FDA:
    - Risk assessment, confirmatory testing if at risk
    - Report to FDA if nitrosamine level >AI
    - If LOQ< nitrosamine level ≤AI, amendment with control strategy (including specifications)

Summary

This guidance describes

- Potential root causes of nitrosamine impurities in APIs and drug products
- Established AI limits
- Recommendations on the steps to take for prevention or mitigation of this issue
- Timeline for the implementation
- Expectations in DMFs/applications at various stages

Harmonization

- Harmonization with other international regulators
  - Systemic approaches of three-step mitigation strategy
  - Timeline for implementation of three-step strategy (EMA)
  - Acceptable Intake Limits
  - Analytical methods and criteria
- Benefits - APIs/drug product manufacturers and applicants can evaluate and address risks in consistent approaches globally

Acknowledgements

- Colleagues from OPQ (7 sub-offices)
- Colleagues from OND, OGD, ORA
- OPQ Nitrosamine Workgroup
- CDER Task Force Workgroup
- EMA/EDQM/OMCL
- HSA/TGA/HC

Thank You!