Nitrosamine Related Guidance

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Learning Objectives

- Define Nitrosamines and describe the two structural classes of these impurities.
- Describe purpose of predicted carcinogenic potency categorization approach (CPCA) framework introduced with 2023 Guidance.
- Describe four key updates published in 2024 Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs.
- Describe control strategy recommendations described in 2024 Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs.
- List elements of the three-step mitigation strategy.
- Describe recommendations NDSRI mitigation strategies and recommended supporting stability data for reformulation.

Brief Historical Background

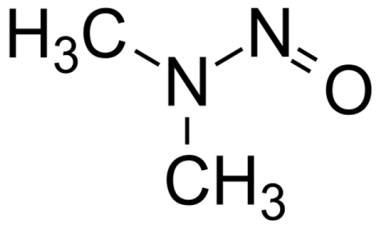
- June 2018, CDER Alerted to presence of NDMA in Valsartan
- Prompted global regulatory response and industry-wide action
- Subsequently, scope expands to include additional drugs and new nitrosamines
- Ongoing investigations into other drug products

What are Nitrosamines?

- N-nitroso compounds: formed by nitrosation of susceptible amines
- Genotoxic, probable human carcinogens
- Commonly found in the environment, rubber, foods (cured meats, beer, and cheese), and pharmaceuticals

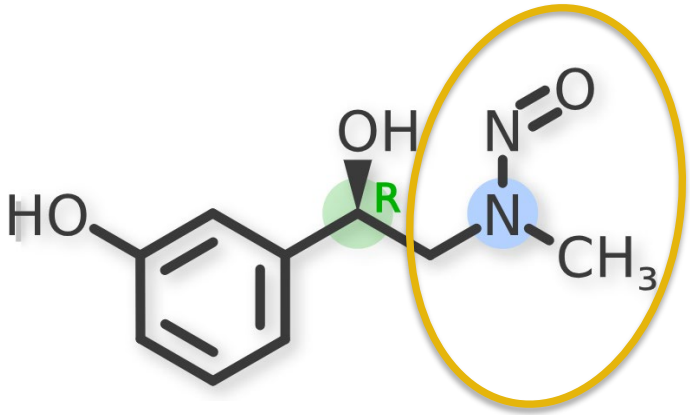
“Small Molecule” vs. “NDSRI”

- Small molecule Nitrosamines (not associated with API. e.g., NDMA, NDEA, NMPA, NDIPA, NDBA, and NBMA etc.)



N-Nitrosodimethylamine (NDMA)

- Nitrosamine drug substance related impurities – NDSRIs (associated with API)



N-nitroso-phenylephrine

Challenge Question #1

FDA's recommended three-step mitigation strategy include all of the following, except:

A. Perform Risk Assessment

B. Submission of Risk Assessment to FDA

C. Perform Confirmatory Testing

D. Report Changes to FDA, as appropriate

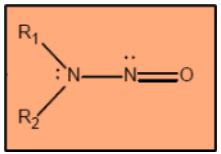
Introduction to Nitrosamine Guidance

- Challenges in Analytical Method Development, Understanding root-cause of nitrosamine contamination, and deriving Acceptable Intake Limits
- Need to communicate Agency observations and understandings
- Outline expectations and provide guidance
- Collaborate to address public health concern

Evolution of FDA Guidance on Nitrosamine Impurities

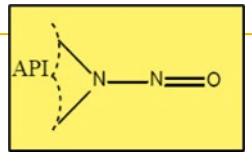
2020/2021 Control of Nitrosamine Impurities in Human Drugs

- Described root causes of nitrosamine impurities
- Focused on small molecule nitrosamines
- Provided API-focused recommendations
- Introduced 3-step mitigation strategy
  - 1. Conduct risk assessments
  - 2. Perform confirmatory testing
  - 3. Report changes to prevent or reduce nitrosamine impurities per applicable requirements*



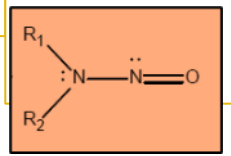
2023 Recommended Acceptable Intake Limits for Nitrosamine

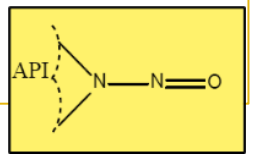
- Provided a framework for predicting acceptable intake (AI) limits
- Addressed nitrosamine drug substance-related impurities (NDSRIs)
- Introduced predicted carcinogenic potency categorization approach (CPCA)



2024 Control of Nitrosamine Impurities in Human Drugs Revision 2

- Broadened scope to both small molecule nitrosamines and NDSRIs
- Added new recommendations for nitrosamine impurity controls
- Provided implementation recommendations
- Included reformulation as a mitigation strategy with CMC and BE recommendations





*For the applicable requirements regarding reporting changes, see 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12 regarding changes to approved applications; 21 CFR 314.60 and 21 CFR 314.96 regarding amendments to pending applications; and 21 CFR 314.420(c) regarding changes to DMFs.

New Recommendations for Nitrosamine Controls: Multiple Nitrosamine Impurities

26.5 ng/day

2020 Guidance Standard Approach

If multiple nitrosamine impurities are detected, total should not exceed 26.5 ng/day (or the AI for the most potent nitrosamine)

$$\sum_{i=2}^{n} \frac{Xi}{AIi} * 100\% \leq 100\%$$

2024 Guidance - Flexible Approach

Levels of the nitrosamine impurities when totaled should result in an exposure level that does not exceed the acceptable cancer risk of 1:100,000 as outlined in ICH M7(R2).[1]

1. M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (July 2023).

New Recommendations for Nitrosamine Controls: Method Sensitivity – Limit of Quantitation (LOQ)

Example: Drug X
MDD = 100 mg/day
AI 1500 ng/day
Control limit[1] = 15 ppm

LOQ = 0.03 ppm

LOQ = 1.5 ppm
Example: LOQ is 10% AI

2020 Guidance – Single Limit

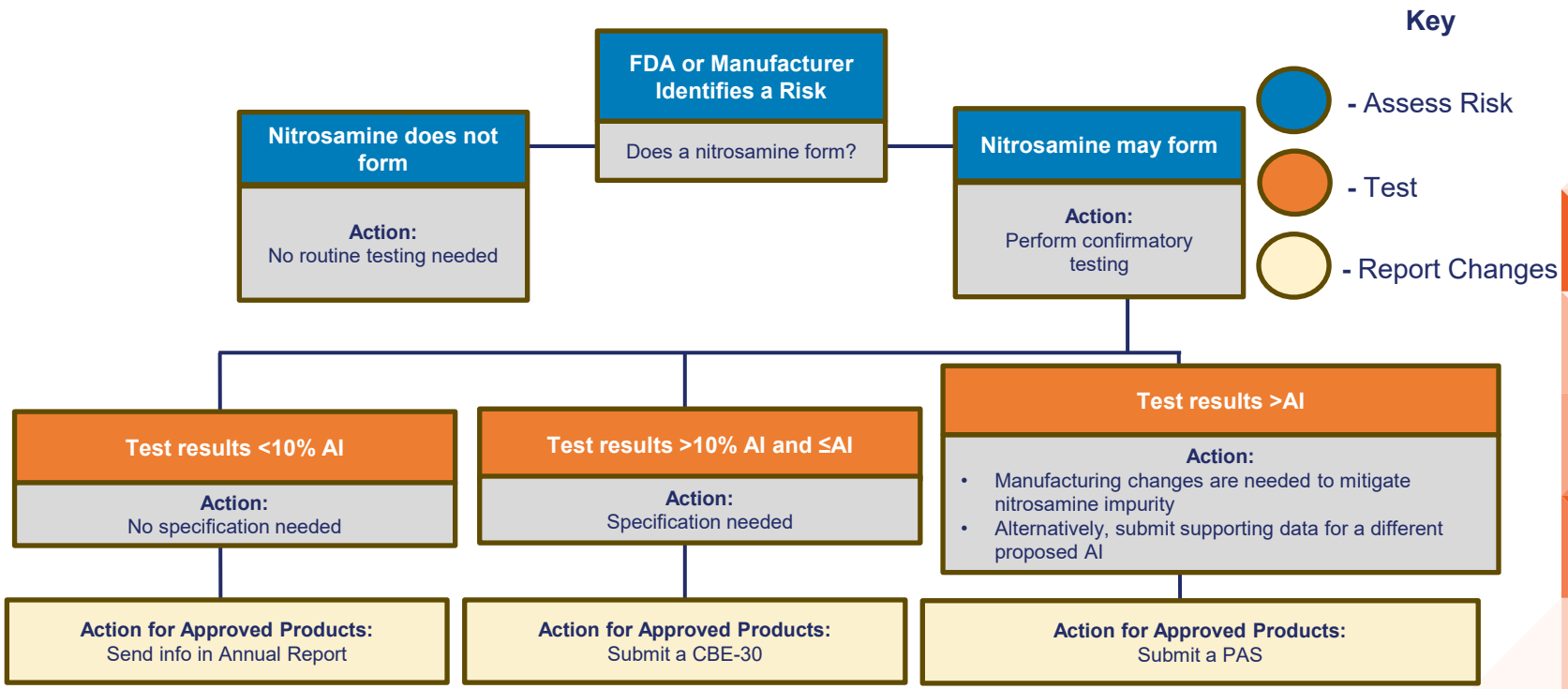
LOQs should be at or below 0.03 ppm

2024 Guidance – Flexible Approach

Limits of Detection and Quantitation should follow ICH Q2(R1) and be commensurate with the level at which the impurities must be controlled.[2]

1. AI (ng/day)/MDD (mg) = limit in ppm
2. Q2(R1) Validation of Analytical Procedures: Text and Methodology (November 2005)

Implementation of Control Strategies – Assessing Test Results

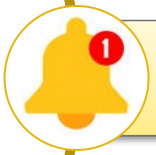


Additional Reporting Considerations

- Timely reporting of confirmed nitrosamine findings above AI limits via Field Alert Reports (FARs) for marketed products
- Action likely to lead to a disruption in drug supply, Notify FDA's Drug Shortage Staff

Timelines and Updates

FDA recommend conclusion of NDSRI confirmatory testing of drug products and submission of changes by August 1, 2025.



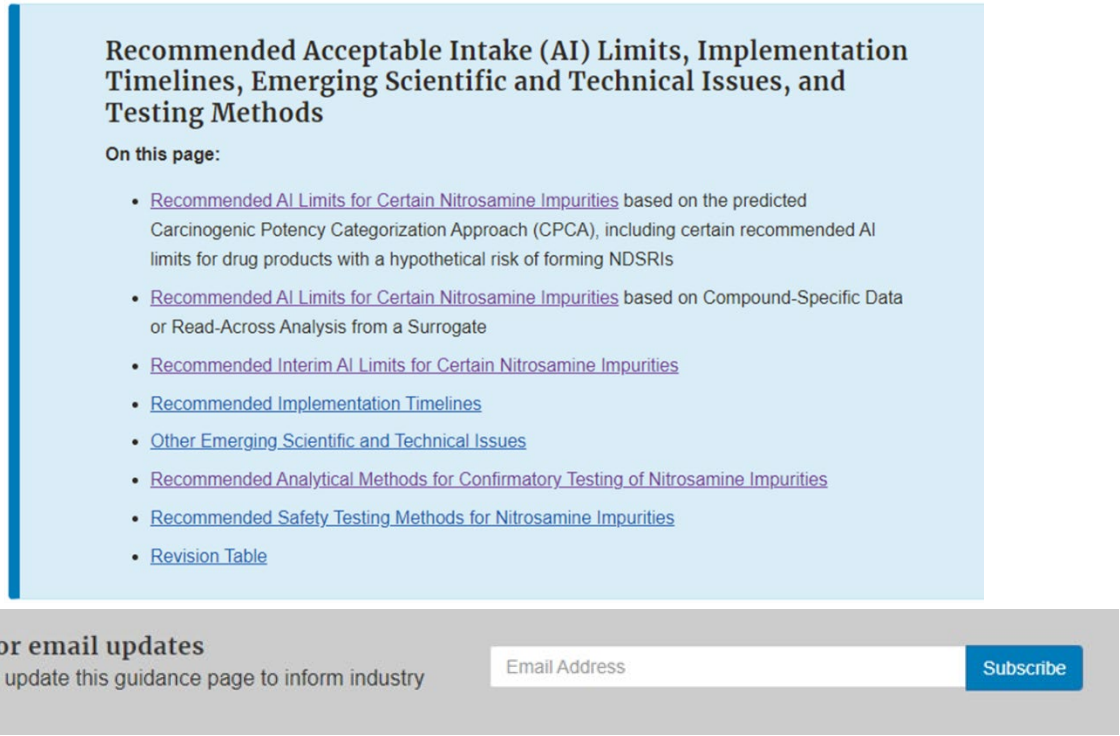
As FDA becomes aware of new and emerging information on nitrosamine impurities, it may communicate information on the identification of new nitrosamine impurities and FDA's understanding of the root cause of such impurities and their formations.

FDA may communicate new recommended AI limits, recommendations for prevention or mitigation to address such nitrosamine impurities, and recommended timelines for implementing the mitigation recommendations.

Check the CDER Nitrosamine Impurity Acceptable Intake Limits webpage for updates.

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits

CDER Nitrosamine Impurity Acceptable Intake Limits – Webpage



Recommended Acceptable Intake (AI) Limits, Implementation Timelines, Emerging Scientific and Technical Issues, and Testing Methods

On this page:

- Recommended AI Limits for Certain Nitrosamine Impurities based on the predicted Carcinogenic Potency Categorization Approach (CPCA), including certain recommended AI limits for drug products with a hypothetical risk of forming NDSRIs
- Recommended AI Limits for Certain Nitrosamine Impurities based on Compound-Specific Data or Read-Across Analysis from a Surrogate
- Recommended Interim AI Limits for Certain Nitrosamine Impurities
- Recommended Implementation Timelines
- Other Emerging Scientific and Technical Issues
- Recommended Analytical Methods for Confirmatory Testing of Nitrosamine Impurities
- Recommended Safety Testing Methods for Nitrosamine Impurities
- Revision Table

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https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits

NDSRI Mitigation Strategies

- Recommendations to mitigate nitrosamine formation in drug products
  - Screen excipients for nitrite impurities
  - Add antioxidant
  - Add pH modifier
  - Other innovative strategies

Stability Data to Support Reformulated Products

- Three batches
- 3 mo. data at submission
  - accelerated time points 0, 1, 2, and 3 mo.)
  - long-term (0 and 3 mo.)
- For OTC monograph products, manufacturers should retain similar supporting information at the facility
- FDA may request 6 mo. accelerated stability data with potential upward trend.
- Long-term stability data of first three production batches, through shelf life, submitted to annual report.

Alternative Bioequivalence (BE) Approaches

- Challenges
  - Such reformulation may need an in vivo BE study to support changes
- Alternative BE approaches
  - Regulation:
    - 21 CFR 320.24(b)(6): any other approach deemed adequate by FDA
  - Science: three research projects
    - Addition of antioxidants to formulations could significantly inhibit nitrosamine formation[1]
    - Small amounts of four antioxidants (ascorbic acid, α-tocopherol, propyl gallate, or cysteine) do not affect permeability of BCS III model drugs[2]
    - Small amounts of antioxidants do not affect intestinal transporter activities[3]

1. Shakleya, et al. Journal of Pharmaceutical Sciences, 2023, 112 (12): 3075-87
2. Lu, et al. Journal of Pharmaceutical Sciences, 2024, 113 (9): 2708-14
3. Kulkarni et al. Pharmaceutics, 2024, 16: 647

Challenge Question #2

Which of the following statements is NOT true?

A. FDA recommends that applicants perform confirmatory testing if a Risk Assessment indicates an impurity is at a low risk of formation.

B. FDA recommends that applicants routinely control a nitrosamine if testing results indicate that nitrosamine is found <10% of the Acceptable Intake Limit.

C. FDA recommends that applicants routinely control a nitrosamine if testing results indicate that nitrosamine is found >10% and ≤ the Acceptable Intake Limit.

D. FDA recommends that if applicants find nitrosamine impurities in their product exceeding recommended AI limits, they mitigate and report changes as a Prior Approval Supplement (PAS). Alternatively, they may provide justification for a different limit via PAS.

Future Considerations

- Research into novel nitrosamine compounds and formation pathways
- Development of advanced analytical technologies for improved detection
- Ongoing evaluation of long-term health impacts

Industry Responsibilities

- Proactive risk assessment of product portfolio
- Implementation of robust control strategies across facilities
- Timely communication with regulators on findings and engagement on mitigation efforts
- Investment in research and technology for nitrosamine control

FDA's Expectations

- Observe current and future nitrosamine guidance recommendations
- Transparency in reporting and addressing nitrosamine issues
- Commitment to patient safety through rigorous quality control
- Collaboration with FDA on improving nitrosamine control measures

Take-Away Messages

- Defined Nitrosamines and described their two structural classes
- Described evolution of FDA Guidance on Nitrosamine Impurities
- Added new recommendations for nitrosamine impurity controls
- Provided the webpage for nitrosamine acceptable intake limits
- Encouraged ongoing vigilance required from industry and regulators
- Highlighted importance of proactive risk assessment and mitigation
- Emphasized a collaborative approach remains essential for protecting public health

Acknowledgements

- Colleagues
  - Office of Pharmaceutical Quality
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Questions?

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