Disclaimer

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Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

GRx+Biosims 2025
Nitrosamines, Nitrosamines, Nitrosamines…
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FDA Perspective of Nitrosamine Risk Assessment and Control

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Overview

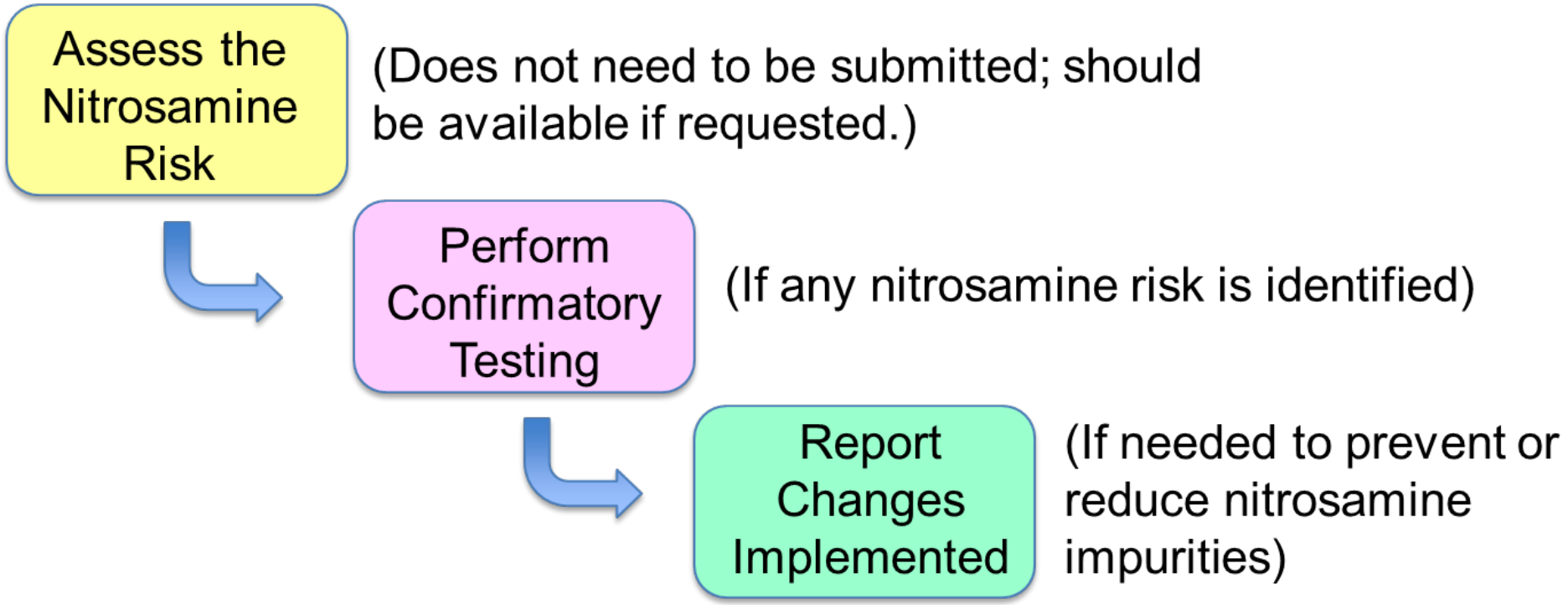
- Background on FDA publications
- Clarify FDA recommended approach
- Explain common pitfalls observed

FDA Publications on Nitrosamines

- Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August 2023) (RAIL Guidance)
- Control of Nitrosamine Impurities in Human Drugs (September 2024, Rev.2) (Nitrosamine Guidance)

CDER Nitrosamine Impurity Acceptable Intake Limits web page with updated information

Three-Step Nitrosamine Mitigation Strategy



- FDA Guidance for Industry: "Control of Nitrosamine Impurities in Human Drugs," September 2024.

Common Pitfalls to Avoid

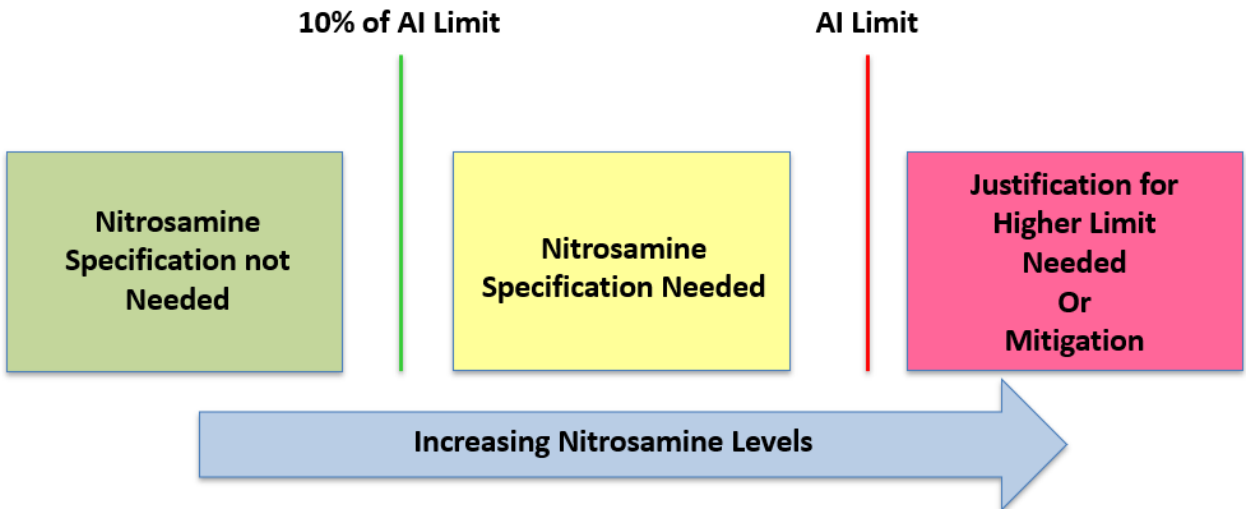
- Issues with reference standards
- Acceptable Intake (AI) limits not endorsed by FDA
- Misunderstanding interim limits
- Evolving landscape

Issues With Reference Standards

- Commercial reference standards may not be the correct structure
  - Importance of characterization
- Some secondary amines are difficult or impossible to nitrosate
  - *Hypothetical* NDSRIs are included on the CDER Nitrosamine Impurity Acceptable Intake Limits website
- Experimental evidence that a drug substance or impurity is chemically resistant to nitrosation can be an important part of the evaluation
  - May justify omission of confirmatory testing
  - Refer Nitrosamine Guidance (Section V)

AI Limits Not Available on FDA Web Page

- Acceptable Intake (AI) limits not listed on the CDER Nitrosamine Impurity Acceptable Intake Limits website need to be evaluated by FDA
  - Includes any AI limit for nitrosamines which are not listed on the website
  - Includes higher AI limits accepted by other regulatory agencies
  - Prior Approval Supplement vs Changes Being Effected Supplement



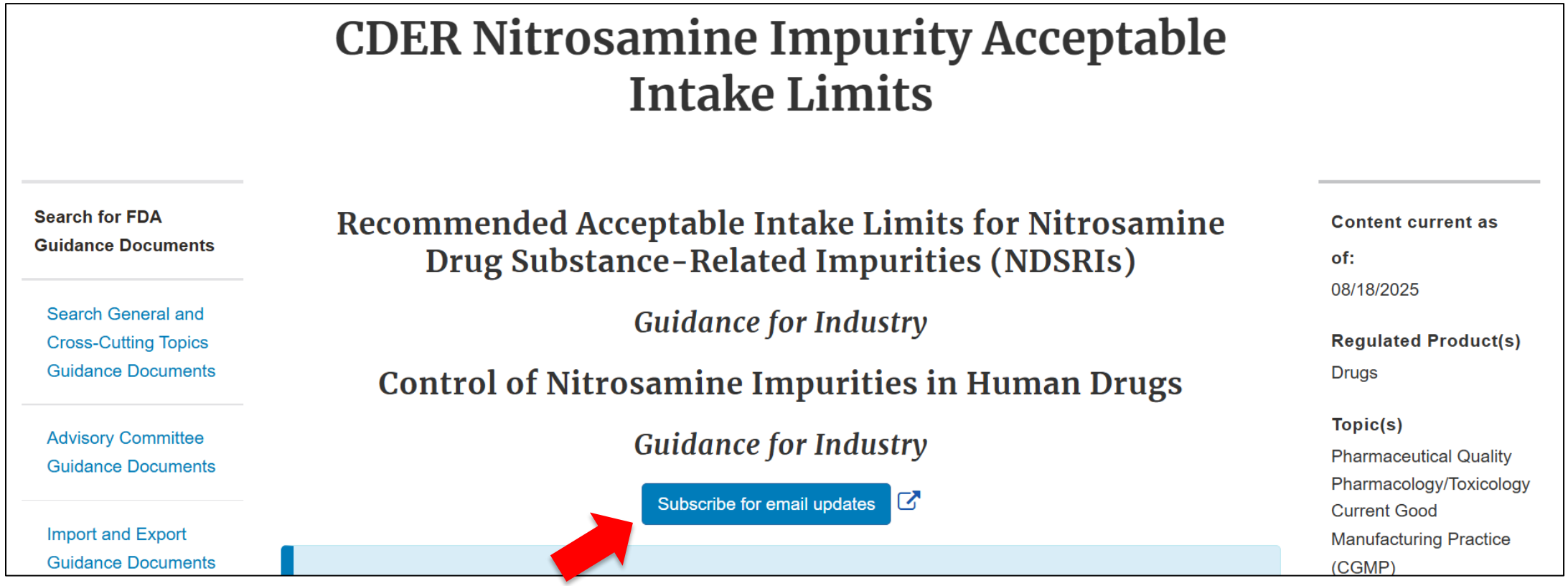
Misunderstanding Interim Limits

Recommended Interim AI Limits for Certain Nitrosamine Impurities

If drug product batches already in distribution contain nitrosamine impurities at levels above the FDA recommended AI limit, and manufacturing changes or recalls are likely to lead to a disruption in the drug supply, then manufacturers and applicants should immediately contact CDER's Drug Shortage Staff at drugshortages@fda.hhs.gov. When contacted about a potential disruption in the drug supply, FDA intends to evaluate each circumstance on a case-by-case basis. FDA may work directly with a specific manufacturer or applicant of the marketed drug and intends to consider whether it is appropriate to recommend an interim AI limit for a temporary period. If FDA recommends an interim AI limit, it generally does not intend to object, for example based on applicable underlying CGMP violations, to distribution of such drug product batches that contain nitrosamine impurity levels at or below the recommended interim AI limit during the specified period under certain circumstances which will be determined on a case-by-case basis. In certain cases where FDA does not intend to object to the distribution of drug products from multiple drug manufacturers that contain nitrosamine levels at or below the recommended interim AI limit, FDA intends to post such recommended interim AI limit on this website.

- Interim AI limits are not approved in a specification
- AI limits not listed on the CDER Nitrosamine Impurity Acceptable Intake Limits website need to be evaluated by FDA

Evolving Landscape



Subscribe to CDER Nitrosamine Impurity Acceptable Intake Limits Website to stay tuned to updates

Evolving Landscape

Scroll down to “Other Emerging Scientific and Technical Issues” section of the web page

Other Emerging Scientific and Technical Issues

As FDA becomes aware of new and emerging information on nitrosamine impurities, it may communicate new information on nitrosamine impurities and FDA’s understanding of the root cause of such impurities and their formations. It may also communicate recommendations for mitigation to address such nitrosamine impurities.

- August 18, 2025: Emerging Scientific and Technical Information on Leachable NDBA and Other Small-Molecule Nitrosamines in Infusion Bags
- October 28, 2024: Emerging Scientific and Technical Information on Ritonavir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