FDA Guidance for Industry

Control of Nitrosamine Impurities in Human Drugs

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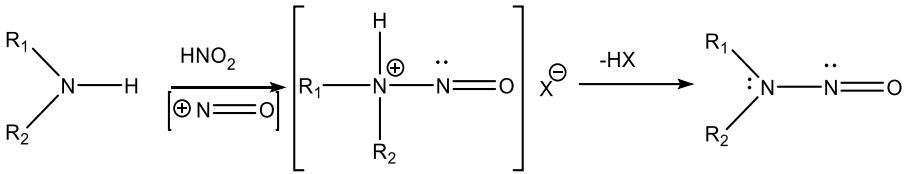
Outline

- Background
- Root Causes of Nitrosamines (NSA)
- FDA Recommendations to Manufacturers
- Recent NDSRI Issues and FDA Recommendations for Mitigation Strategies
- Reporting Changes to FDA

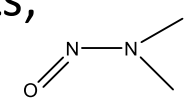
Background

- What are Nitrosamines (NSA)?

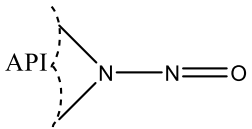


Secondary, tertiary, or quaternary amines

- Probable or possible human carcinogen; potent genotoxic agents; "cohort of concern" compounds in the ICH *M7(R1)*
  - Small molecule NSA (NDMA, NDEA..)
  - Nitrosamine drug substance-related impurity (NDSRI) found in drug products (DP) related to API (or API fragment)*

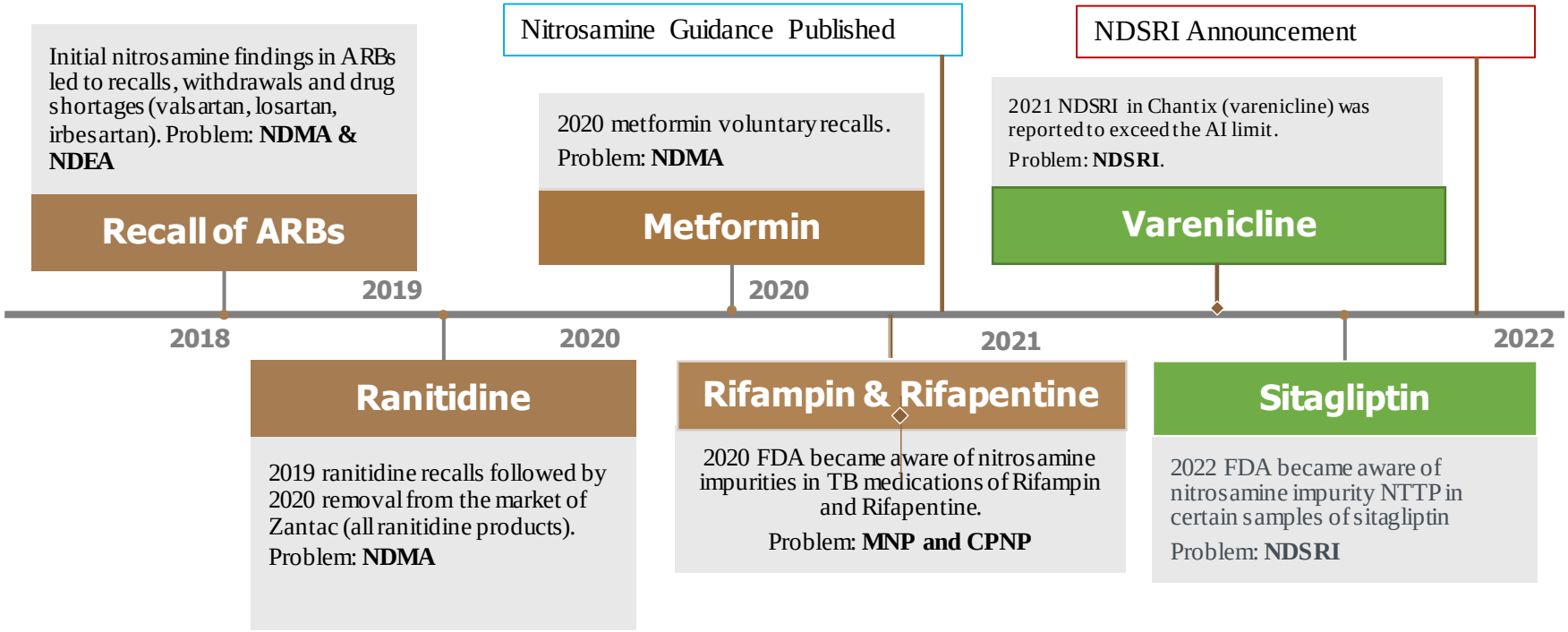


N-Nitrosodimethylamine (NDMA)



*See FDA's announcement on *Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products*

Brief History of Nitrosamine Issues



FDA's Efforts

- Information dissemination from FDA
  - Public webpage for announcements
  - Product-specific communications
  - Industry meetings
  - Workshops
- Various working groups within FDA and collaboration with international regulators
- Guidance
  - Guidance for immediate implementation because of importance of providing timely information to API and DP manufacturers
  - Revision 1- update on implementation dates (2/2021)

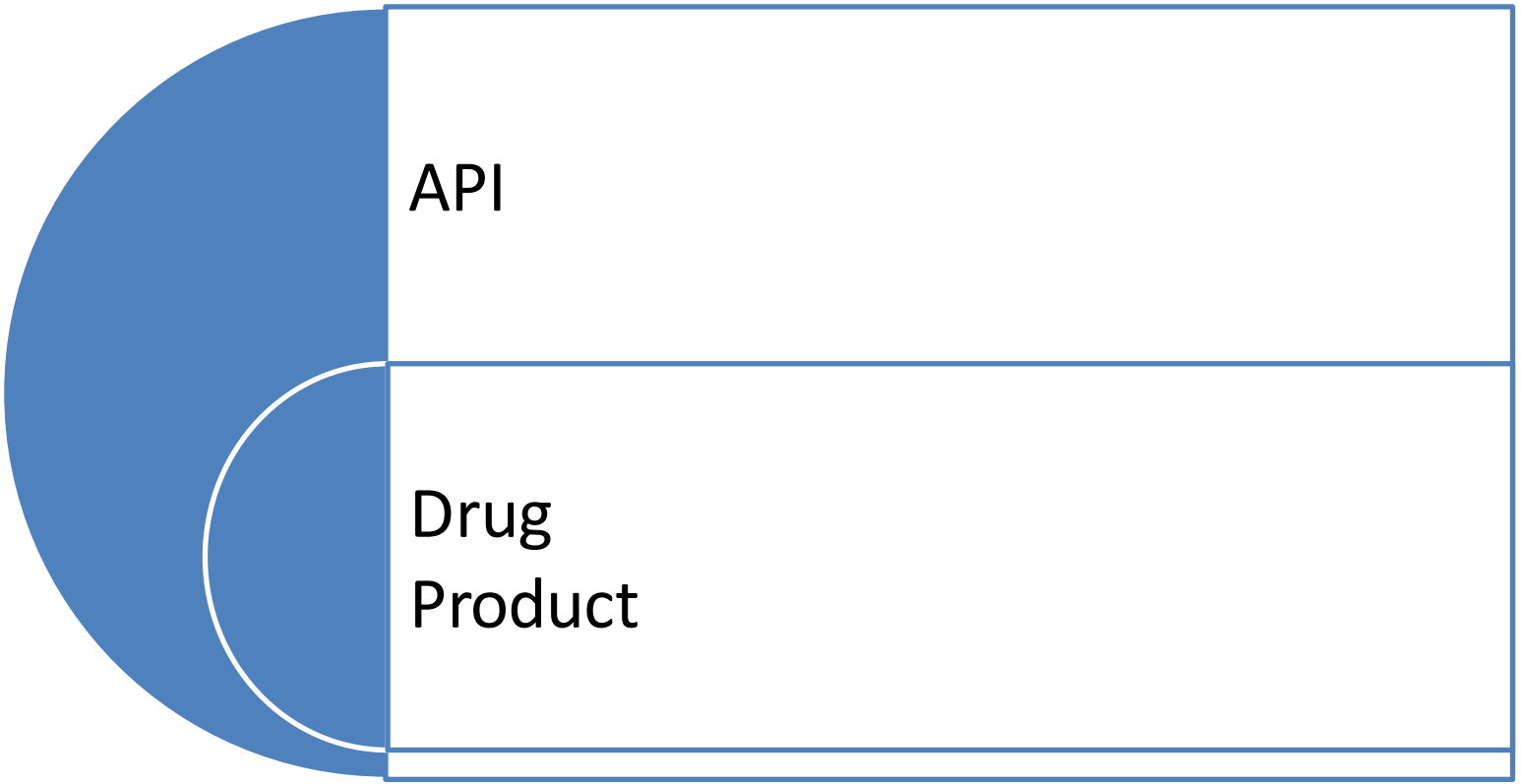
Contents of Guidance*

- Root causes
  - in APIs
  - in DP other than API sourced nitrosamines
- Recommendations
  - Acceptable Intake Limits
  - to API manufacturers
  - to DP manufacturers
- Reporting Changes

  Timeline for risk assessment, confirmatory testing and submission
  - Approved/marketed drug products
  - Pending applications

* Focused on small molecule nitrosamines

Root Causes



Recommendations

Acceptable Intake Limits (AI)

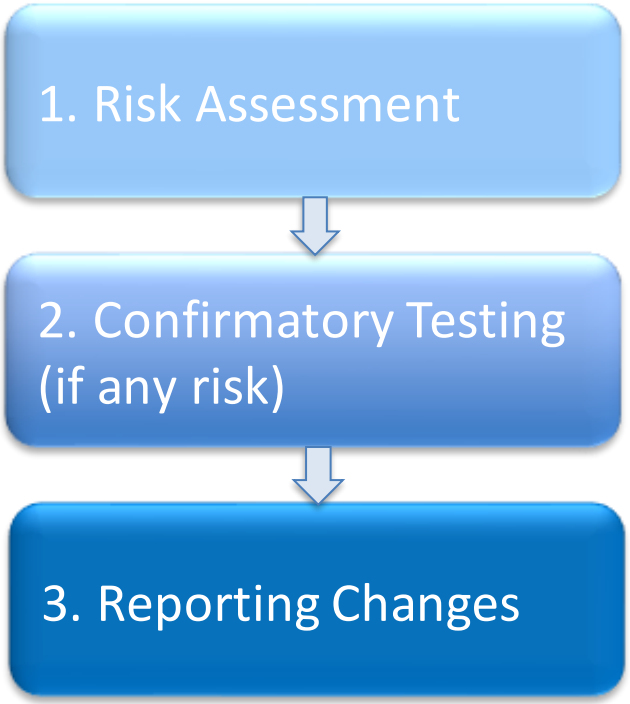
AI Limits for Some Nitrosamines in DPs

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

[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 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)).

* These AI are not included in the current guidance but were published in FDA public webpage

Three Steps for Mitigation Strategy



Recommendations to API Manufacturers

- API manufacturers: (corresponding to root causes)
  - Optimize design of process in ROS: condition, avoid amine bases/ solvent, control reaction sequence/ process conditions
  - Audit/monitor supply chain
  - Avoid cross-contamination
  - Reprocess/rework batches

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 DP Manufacturers

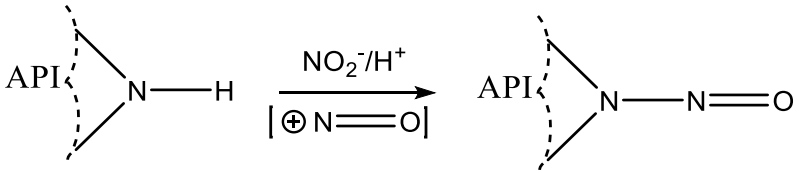
- DP manufacturers: (corresponding to root causes)
  - Collaborate with API manufacturers:
    - continuously test API lots until verified w/o unacceptable levels of nitrosamines (NSAs)
  - Evaluate all pathways (including degradation) during manufacture and storage
  - Remove precursor impurities (such as DMA) that may be carried-over from API synthesis which can form nitrosamine in drug products

Recommendations to DP Manufacturers

- Control of Nitrosamines in DPs
  - LOQ<NSA level ≤AI:
    - control strategy (specification);
    - necessary if risk is inherent from API or DP
  - NSA 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

Nitrosamine Drug Substance – Related Impurities (NDSRIs)

- Recently, NDSRIs were identified in certain products, e.g., Varenicline, Sitagliptin
- Sharing structural similarity to the API; unique to each API (containing API or API fragment)



- Root causes:
  - APIs (secondary or tertiary amines) are exposed to nitrosating compounds such as nitrite impurities in excipients
  - formed during drug product manufacture or shelf-life storage

NDSRI Mitigation Strategies

FDA public announcement 11/18/2021#

- Screen excipients for nitrite impurities
- Add Antioxidant
- Add pH modifier
- Other innovative strategies

https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

Reporting Changes to FDA

- Recommended timeline for three steps (risk assessment, confirmatory testing and submission of changes)
  - Approved/marketed DPs
    - Risk assessment: within 7 months from guidance's first publication (March 1st, 2021)
    - Confirmatory testing: start once risk identified; ASAP for high-risk products
    - Submission: last two steps within 3 years of guidance publication (October 1st, 2023); FDA is seeking comments on extension of recommended timeline.*
  - Pending applications
    - Pre-submission: risk assessment, confirmatory testing. Changes may be submitted in amendment if not included in original submission
    - Pending with FDA:
      - risk assessment, confirmatory testing if at risk
      - report to FDA if NSA>AI
      - If LOQ<NSA level ≤AI, amendment with control strategy

* See 88 FR 28557 https://www.federalregister.gov/documents/2023/05/04/2023-09526/identification-assessment-and-control-of-nitrosamine-drug-substance-related-impurities-in-human-drug (5/4/2023)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