Nitrosamines: Where are we now?

Deborah Johnson, PhD

Branch Chief

CDER/ONDP/DLAPI/Branch 1

SBIA-DMF Drug substance workshop

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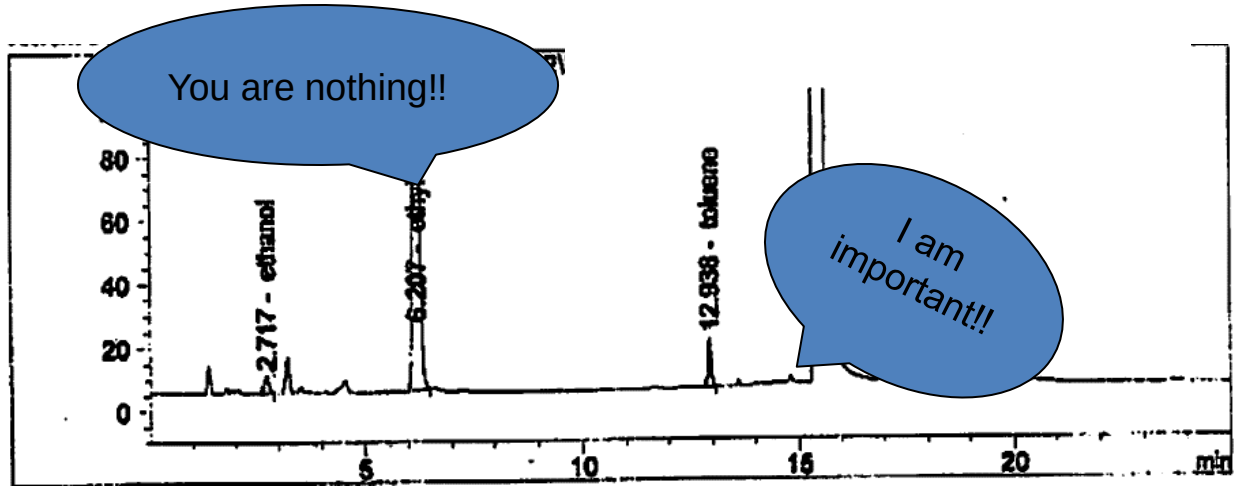
Learning Objectives

- Discuss lessons learned
- Provide suggestions for future considerations
- Briefly discuss the Agency's nitrosamine guidance

Do not judge a peak by its size:

In early 2018 a "tiny" peak was detected in a GC chromatogram. The impurity was eventually identified as NDMA.

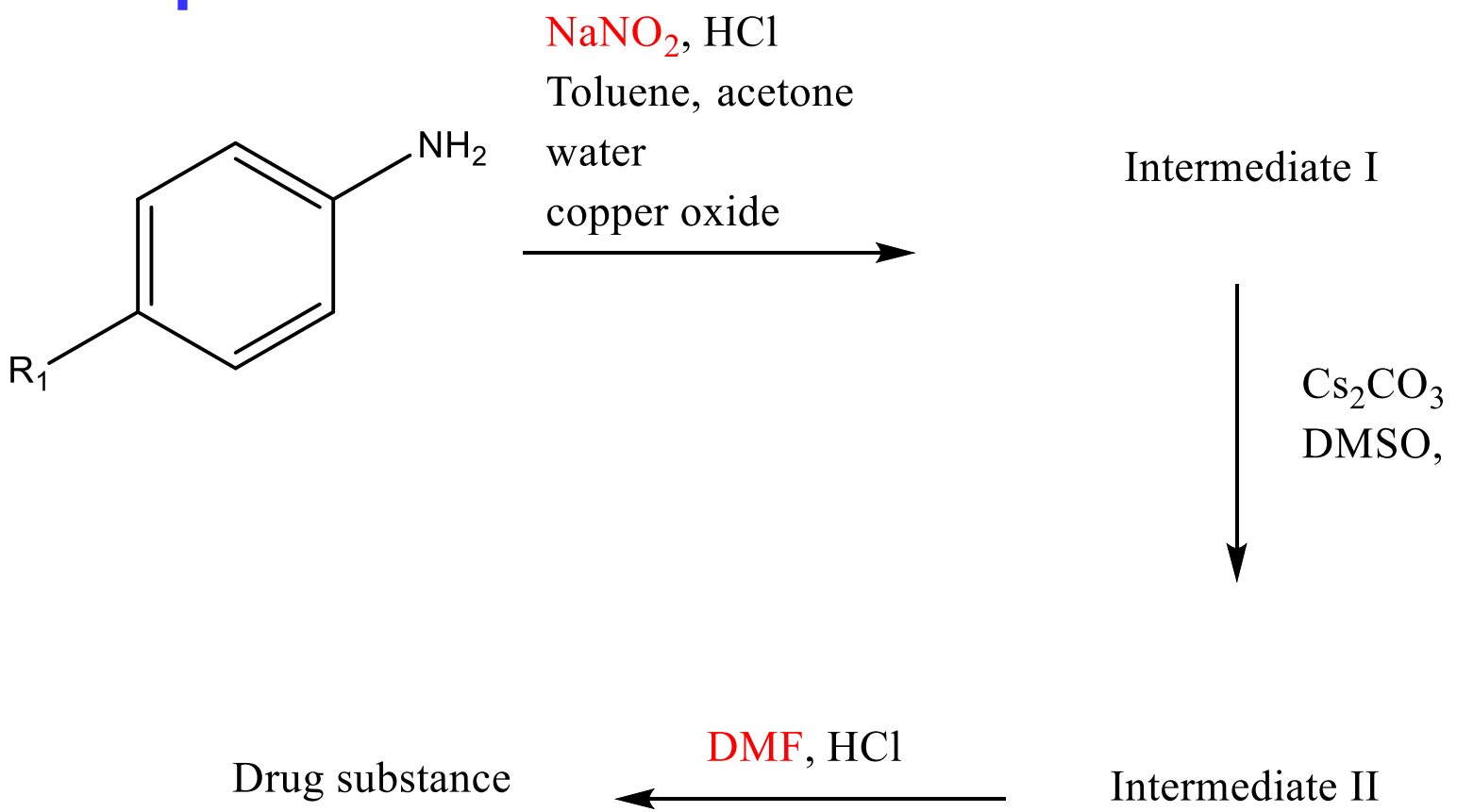


Detection of this peak has resulted in an investigation which has been ongoing for over 24+ mo and has expanded to multiple APIs and drug products!

Lessons Learned: API

- **Process understanding should be holistic:**
  - **Carryover of reagents/impurities.**
  - **Understand how all components could react.**
- **Comparability of pre- and post-change material:**
  - **Original specification may not be sufficient.**
  - **Current analytical methods may not be sufficient.**
- **Draft Post-approval Changes Guidance for Drug Substance (2018) (https://www.fda.gov/media/109615/download):**
  - ✓ **Watch the number, RRT and levels of unknown impurities.**
  - ✓ **Know what PGIs might form.**
    - ❑ **Will current methods detect them.**
    - ❑ **Small unknown peaks can hide big problems.**

Example:



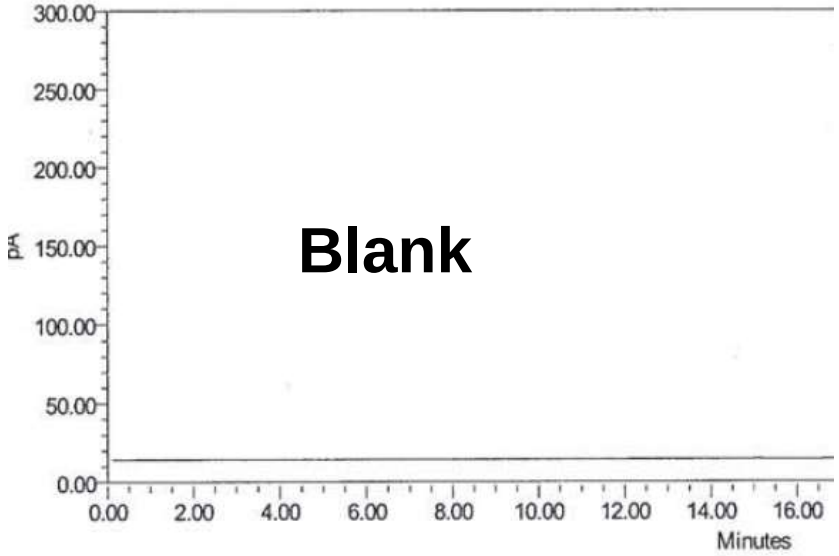
DS is contaminated with NDMA. How???

Nitrite in Intermediate I and DMA in last step reacted.

Lessons learned: Recovered Solvents

- **Process understanding should extend to recovered solvents.**
- **New unknown peaks-ESPECIALLY after a process change:**
  - **No limit for "any unknown impurity" in ICH Q3C.**
  - **Which peaks belong to impurities controlled under other tests?**
  - **Which peaks belong to process solvents and by-products?**
  - **Which peaks belong to the mobile phase and diluent?**
    - ✓**Use solvents of appropriate grade.**
- **Don't assume fresh solvents are "clean".**
  - **Exercise due diligence when choosing vendors**
  - **Is vendor recycling solvents?**
  - **How are tankers cleaned?**

Lessons learned: Recovered Solvents



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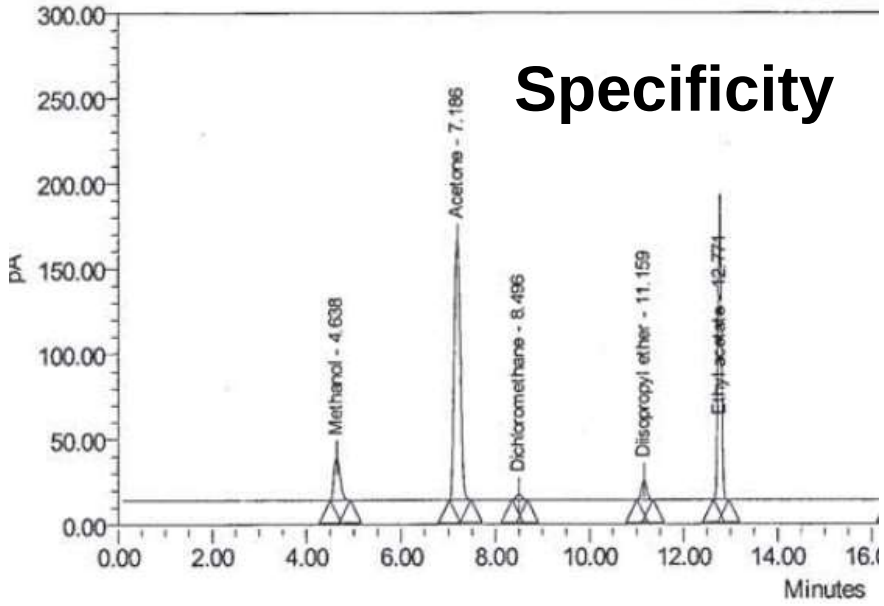
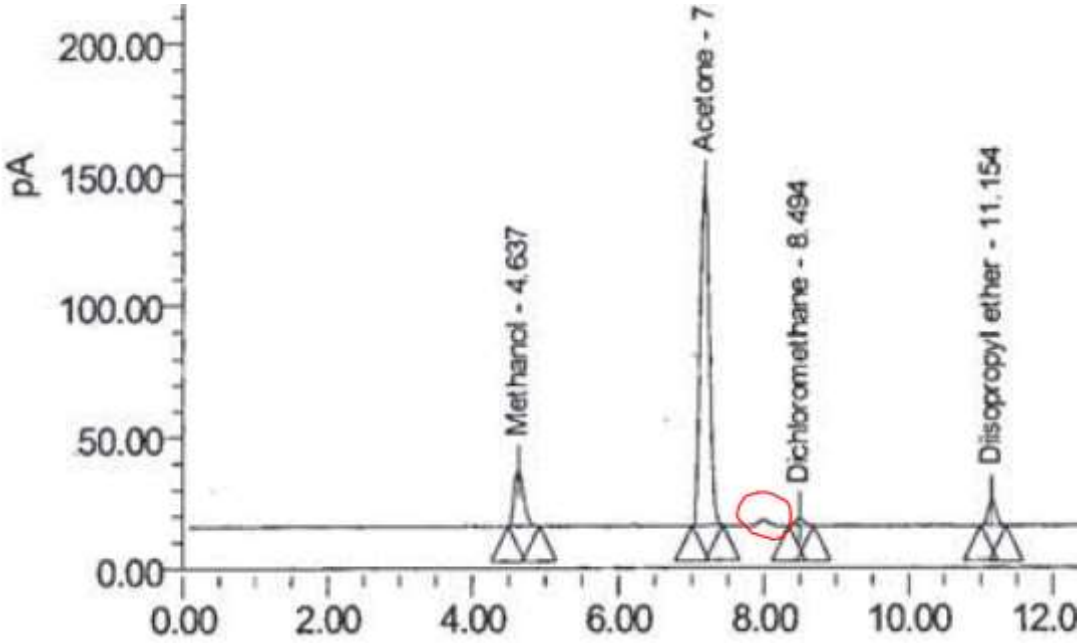


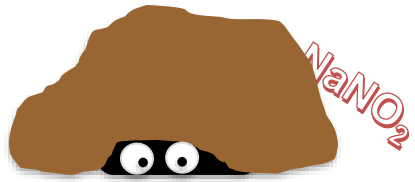
Specificity



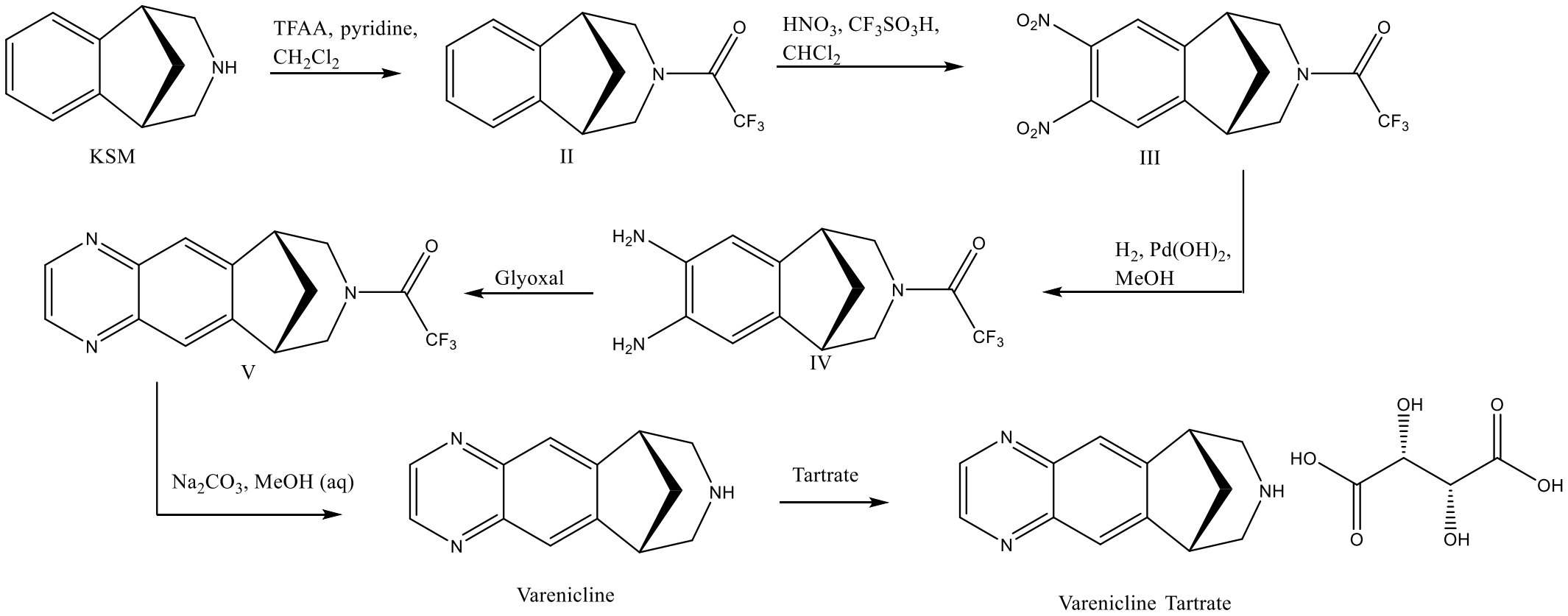
Precision

Lessons learned: Hidden sources of precursors

- **Substantial quantity of sodium nitrite in sodium azide.**
- **Contaminating amines in amine bases/catalysts.**
- **Degradation of amide solvents generates secondary amines.**
- **Amine contaminants present in starting materials or intermediates.**
- **Secondary and tertiary amine functional groups on intermediates and API molecules.**



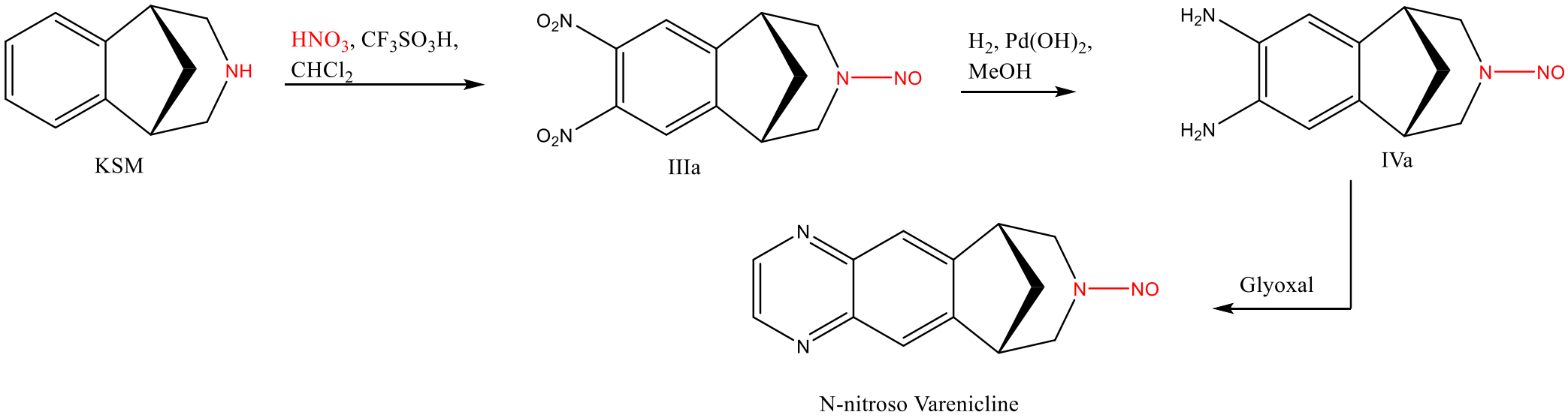
Example: Varenicline Tartrate



Y. Lu et al. / Journal of Pharmaceutical and Biomedical Analysis 155 (2018) 306–313

Is this synthetic route at risk for nitrosamine formation???

Example: Varenicline Tartrate



Is this synthetic route at risk for nitrosamine formation???

YES!!

- **Nitric acid contains traces of nitrous acid.**
- **KSM present during the nitration reaction could form IIIa.**
- **IIIa may carry through the reaction and result in a DS nitrosamine impurity.**

Lessons learned: Faulty assumptions

- **Missteps in assessing risk or process capability:**
  - **When nitrosamines are by-products**
    - ✓ **Amount formed from batch to batch is unknown.**
    - ✓ **Makes spike/purge or process capability assessment difficult.**
  - **Purging capacity appears to be MUCH lower than is predicted:**
    - ✓ **NDMA is water miscible and soluble in organic solvents.**
      - ❑ **Aqueous wash of organic layer may not be effective.**
      - ❑ **Theoretical purge calculations may overestimate purging factor of process.**
    - ✓ **Reactivity of nitrosamines may be overestimated.**

FDA's "Control of Nitrosamine Impurities in Human Drugs Guidance for Industry"

- **Published Sep 1, 2020.**
- **Contains acceptable intakes (AI) for six nitrosamines:**
  - **Follow ICH M7 for nitrosamines without published AIs.**
  - **TTC does not apply to nitrosamines.**
- **Establishes limit for total nitrosamine at 26.5 ng/day based on the MDD of the DP.**
  - **Applicable when the number of nitrosamines in the specification is >1.**
- **Control strategy should be focused on nitrosamines which are possible.**

FDA's "Control of Nitrosamine Impurities in Human Drugs Guidance for Industry"

- **Analytical methods should have LOQ NMT 0.03 ppm.**
  - **LOQ <0.03 ppm for high dose DP or multiple nitrosamines present.**
- **If nitrosamines are detected root cause should be investigated.**
- **If confirmatory testing shows nitrosamines are ≥LOQ then release testing is recommended.**
  - **Control strategies based on ICH M7 Options 2-4 should be supported by sufficient data.**
  - **Amount of data to support impurity control strategy  with the proximity to the final API.**
    - ✓ **Impurities formed or introduced in final step need testing data.**

Acknowledgements

- David Skanchy, Division Director, DLAPI
- CTEC Nitrosamine Task Force
- OPQ Nitrosamine Task Force

Thank You!

- **Please refer to the following presentation for additional information: Safety Evaluation of Drug Substance Impurities in Generics by Chanchal Gupta.**

- **Please remember to type any questions into the Q&A box so that the questions can be answered during the live Q&A following this session.**

- **To submit questions on this presentation for inclusion in the Follow-on webinar on April 9th, send them by March 19th to: DMFWorkshop2021@fda.hhs.gov**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