



# Prevalence and Sources of Artifacts in Trace Nitrosamines Analysis in Drug Products

GDSR Public Comment  
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June 23, 2021



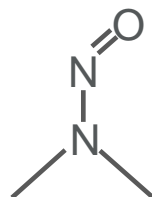
# The Issue



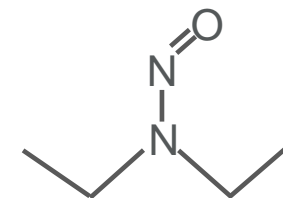
❖ **2018** – Valsartan/Irbesartan/Losartan- **2019**–Ranitidine- **2020**–Metformin/Nizatidine



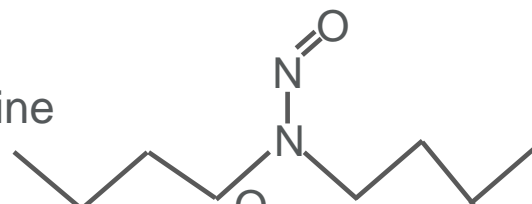
NDMA –  
nitrosodimethylamine



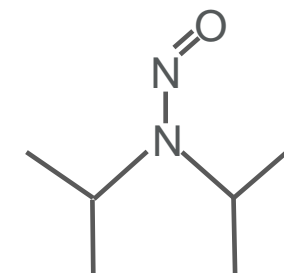
NDEA –  
nitrosodiethylamine



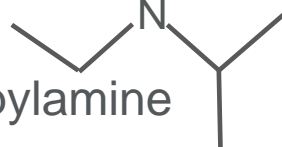
NDBA –  
nitrosodibutylamine



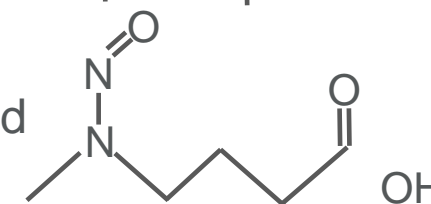
NDIPA –  
nitrosodiisopropylamine



NEIPA –  
nitrosoethylisopropylamine



NMBA –  
nitrosomethylbutanoic acid



❖ Very low Acceptable Intakes (AIs) → 100's to 10's ppb specifications

# The Proposal



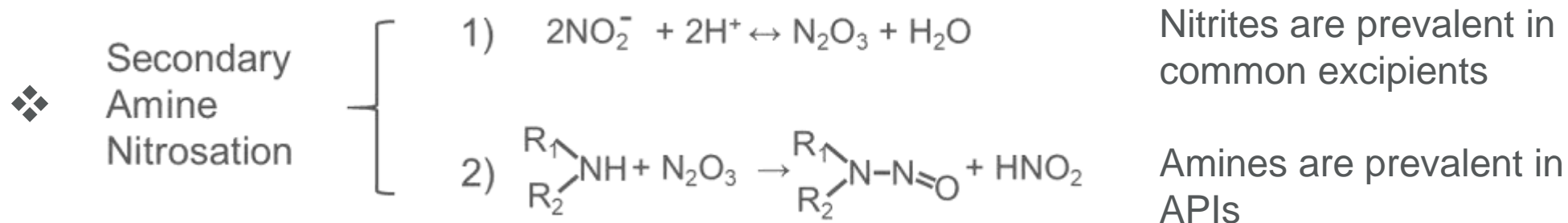
- ❖ **Prevalence and sources of artifacts in trace nitrosamines analytical methods for drug products**
- ❖ **Why does this matter?**  
*Ranitidine and metformin Valisure results*
- ❖ **Criticism –**  
*Poor method development on the part of one party is not a good reason to direct GDSR funds towards drug product research when there are many other worthy topics”*
- ❖ **Counterpoint - there is a case to be made.....**

# The Proposal:

## Nitrosamines are a Special Category of analyte in Drug Products



❖ AI's are very low – 96 ng/day for NDMA, 26.5 ng/day for NDEA



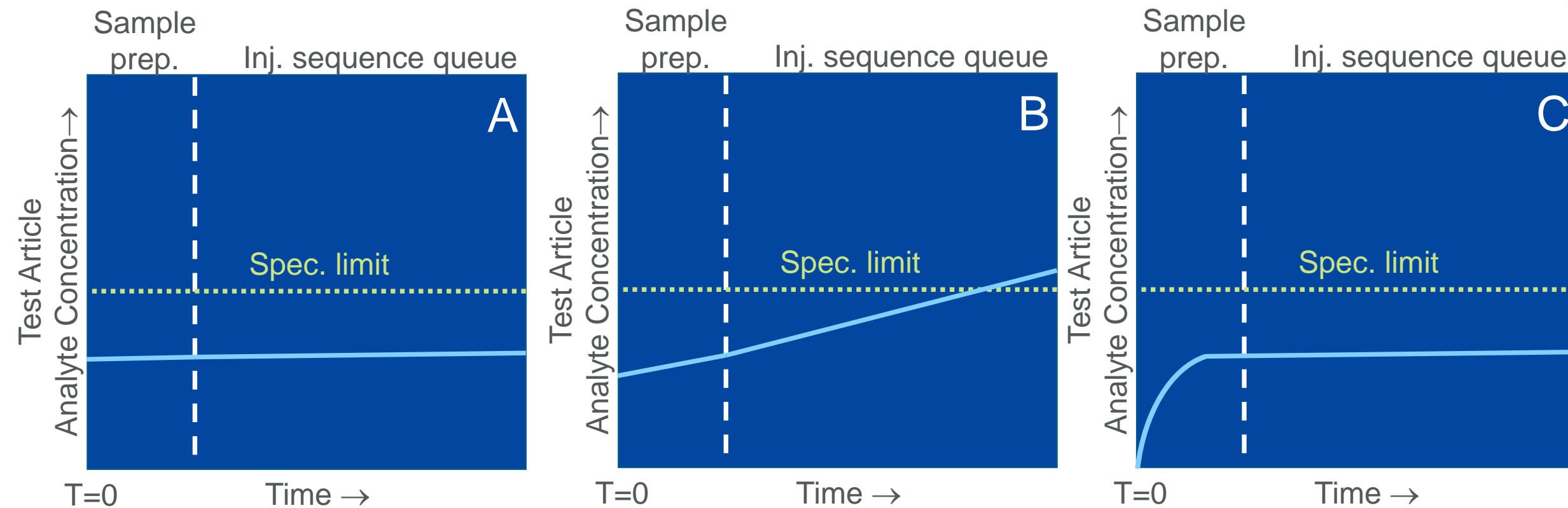
❖ Levels of amines and nitrites in drug product are often orders of magnitude higher than necessary to exceed AI's (with unknown reaction kinetics)

❖ Raw materials → Drug product mfg. → Release Testing → Stability Testing

# The Proposal: The question GDSR should address



❖ “The analyte pre-exists in the test article” – Is this always valid for nitrosamines?



❖ Sample prep extracts and combines both the nitrosamines and their precursors!



Thank you.

