

Mitigation studies for nitrosamines in pharmaceutical formulations

David Keire

Office Director

CDER/OPQ/Office of Testing and Research
US Food and Drug Administration

SBIA

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A close-up photograph of a person's hand holding an orange pill bottle, pouring three white, oval-shaped pills into their palm. The background is blurred, showing the person's arm and clothing.

**Patients expect safe and effective
medicine with every dose they take.**

The background image shows a close-up of two hands. One hand is holding an orange plastic pill bottle, tilted to pour three white, oval-shaped pills into the palm of the other hand. The text is overlaid on this image.

Pharmaceutical quality is
assuring *every* dose is safe and
effective, free of contamination
and defects.



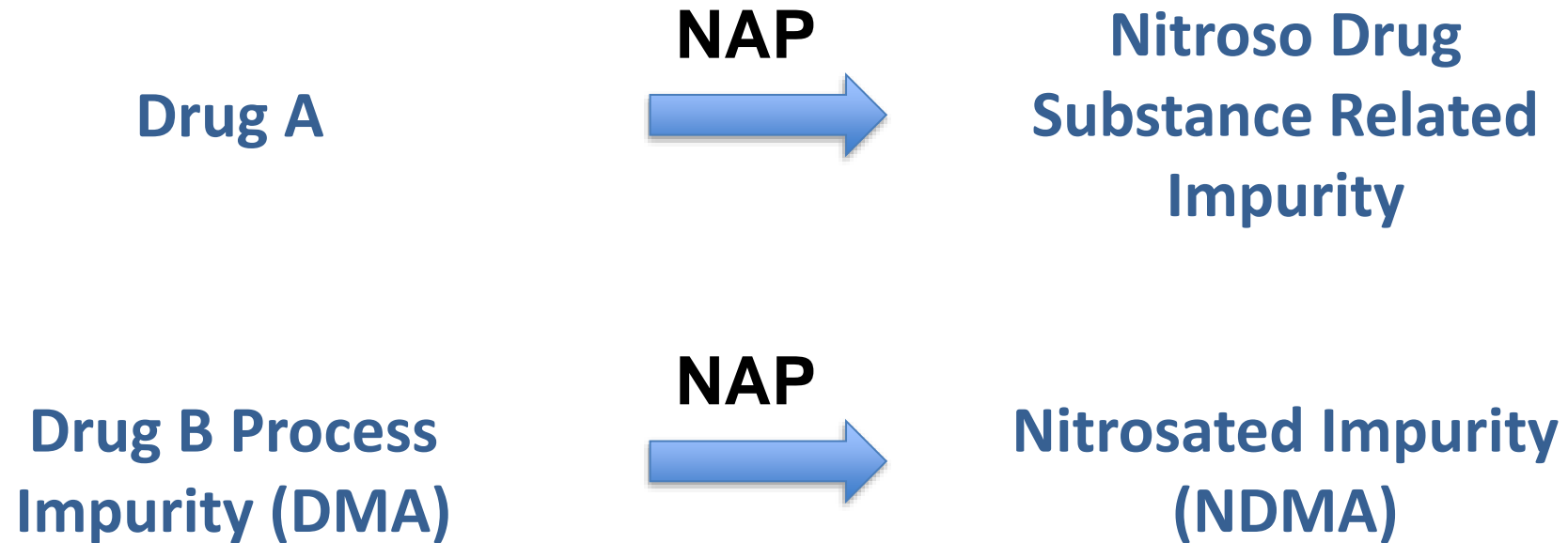
It is what gives patients confidence
in their *next* dose of medicine.

NAP



- In 1978, a WHO Expert Group suggested the nitrosation assay procedure (NAP test) as a general *in vitro* test system under standard conditions (10 mmol/L drug, 40 mmol/L nitrite, 37°C, pH 3-4, with reaction times 1-4h) to study the nitrosation ability of drug substances

Drug A and Drug B



NAP conditions are favorable for nitrosamine formation. Drugs containing reactive amines may never experience these conditions.

Lhasa Database Report

Research Article

A Nitrite Excipient Database: A Useful Tool to Support N-Nitrosamine Risk Assessments for Drug Products

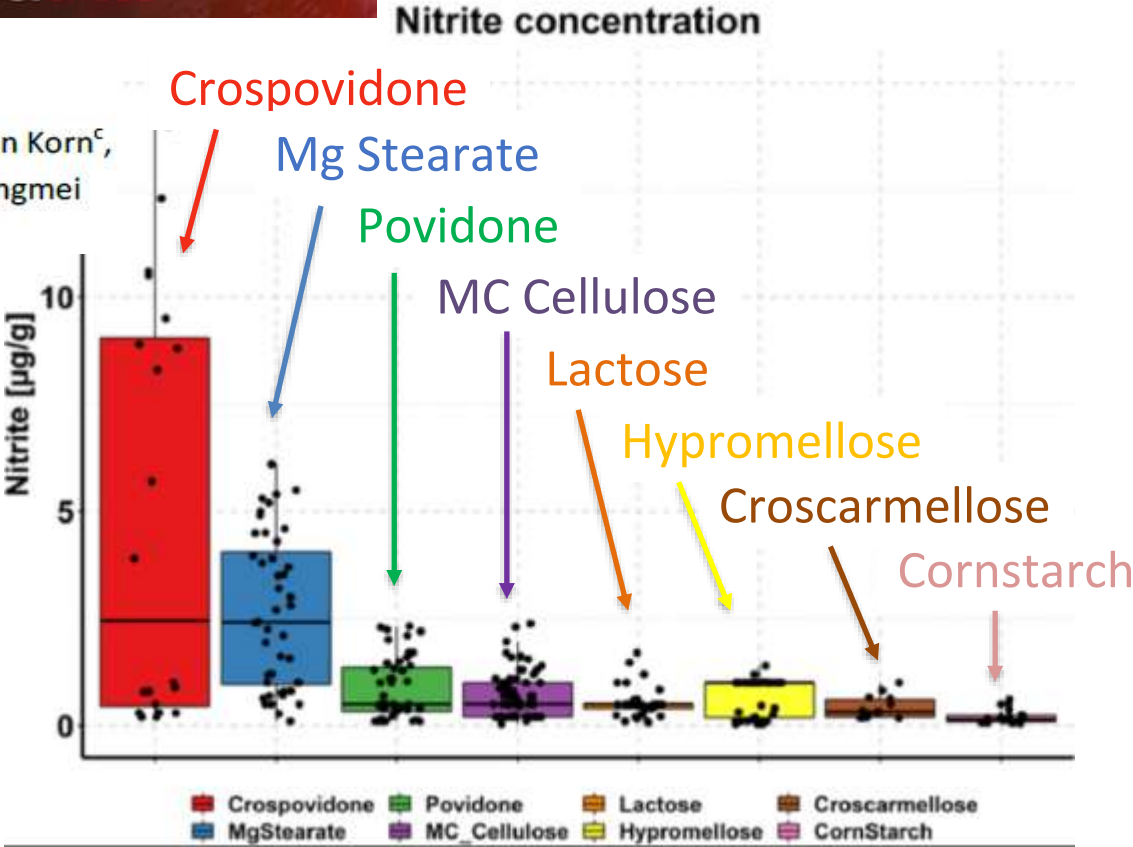
Ruth Boetzel^{a,*,#} ruth.boetzel@pfizer.com, Joerg Schlingemann^{b,*}, Sebastian Hickert^b, Christian Korn^c, Grace Kocks^d, Bert Luck^e, Giorgio Blom^f, Mark Harrison^f, Marc François^g, Leonardo Allain^h, Yongmei Wuⁱ, Youssi Bousraf^g,

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Nitrite concentration in selected excipients

- In a typical formulation: an average value of **1 µg/g (1 ppm)** nitrite



Nitrosamine Mitigation by Formulation (Drug A and Drug B)



Problem:

- Nitrosamines identified in marketed drug products dependent on the formulation.

Approaches:

- Evaluation of the effect of antioxidant & pH on mitigation of nitrosamine levels in drug products.
- <https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities>

Deliverables:

- Widely share results and findings via available pathways.
- Provide examples of potential strategies to mitigate nitrosamine formation in products

Drug Product Manufacturing Steps

Spiked nitrite

Heat

Humidity

**In House
Manufactured Tablets**

Antioxidants

pH

OTR Manufacturing process



Sieving:
Drug (active ingredient) and single excipients (sieve #30)



Mixing:
Drug and antioxidants by geometric dilution (to ensure homogeneity)



Granulation:
Binder Povidone K-30 in H₂O. (intragranular blend)/Nitrite and DMA was spiked here/



Semi-Drying & Drying:
Using a fluidized bed dryer. airflow: 20m³/h temp.



Granules:
Moisture content (< 2%)



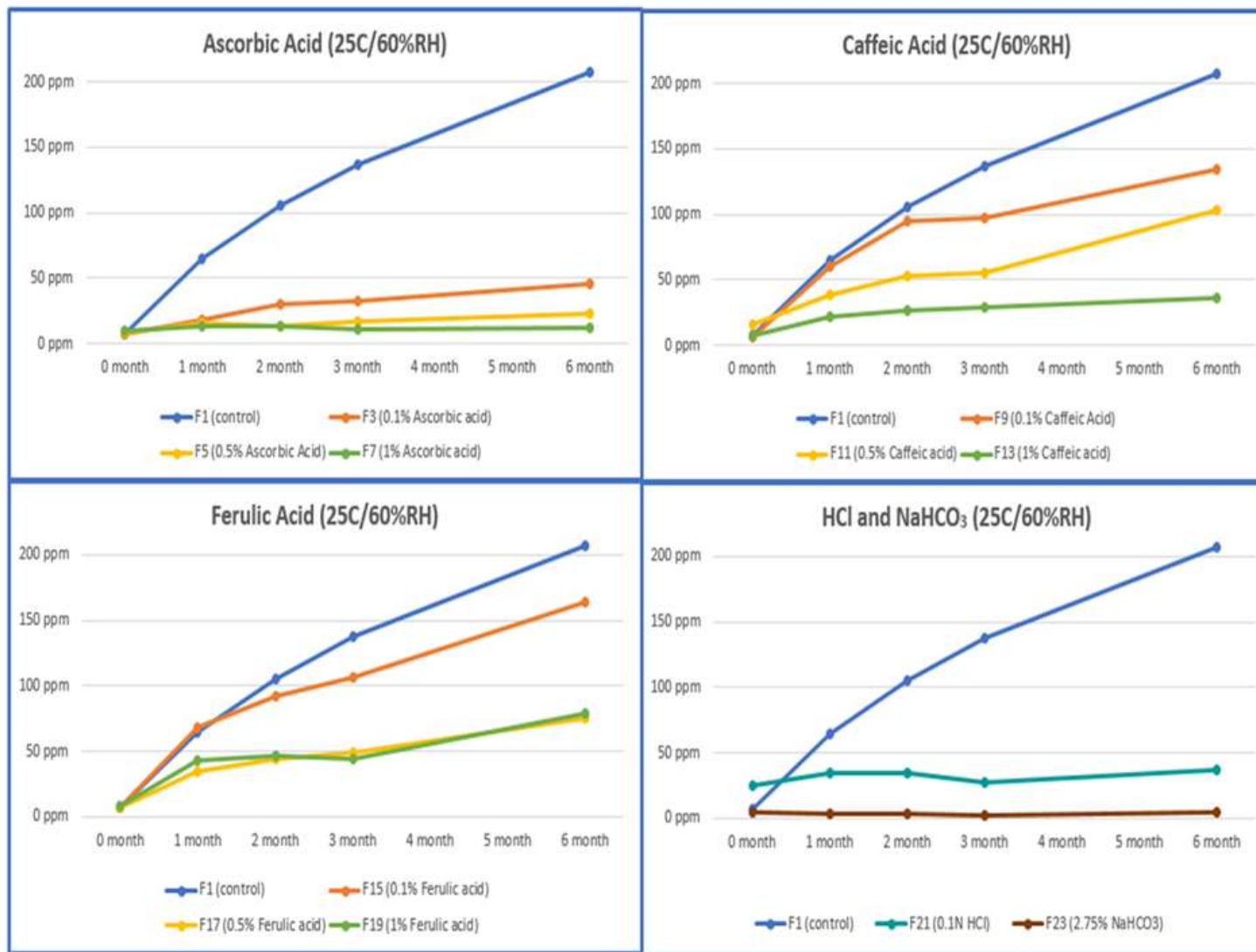
Tableting:
Granules mixed with EG mixture, And ready for compression.



N-Nitroso-Drug A (NDSRI) in Stability Samples – With Antioxidant OR pH Modifier;

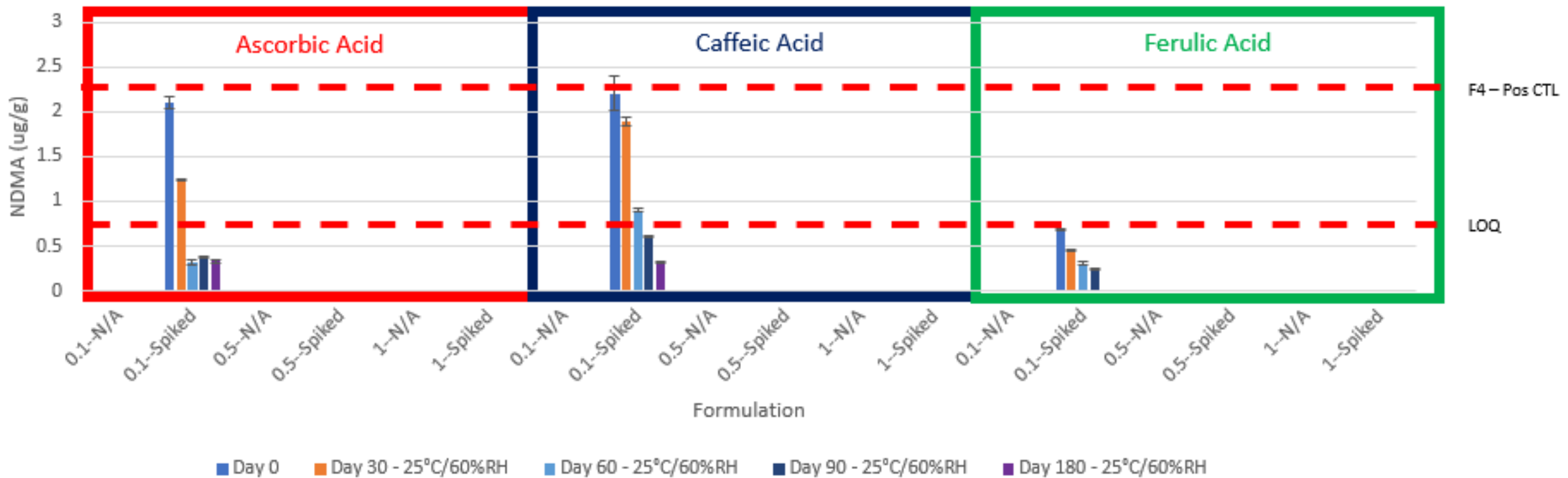
25°C/60% RH

**NDSRI Amounts
formed**



Stability: NDMA in Drug B

6 months 25°C/60%RH



Preliminary Observations (1)

➤ Antioxidants:

- For the first drug substance the highest inhibition of NDSRI formation among the antioxidants was observed as ascorbic acid > caffeic acid > ferulic acid.
- For the second drug substance tested the rank order potency was reversed: ferulic > caffeic = ascorbic.
- Antioxidants need to be fit-for-purpose and their effectiveness depends on the drug substance, manufacturing and formulation
- **An increase in antioxidant concentration improved the NDSRI mitigation.**

Preliminary Observations (2)



➤ pH manipulation

- Acidic conditions facilitated nitrosating reactions.
- Maintaining neutral pH of the drug product served as a protective strategy against nitrosamine formation. An alkali modifier (sodium bicarbonate) had the most effective inhibition of NDSRI formation for the two drug substances tested.

Preliminary Observations (3)



➤ Heat and Moisture Control

- The data suggested that formation of nitrosamines was greater under conditions of elevated heat and moisture.
- Nitrosamines or the main progenitors were introduced or formed during the drying step of wet granulation.
- This might be due to the presence of a secondary amine and NO_x (Oxides of nitrogen) in the wet mass which was then converted into a nitrosamine impurity during drying.

General Observations

- Antioxidants and pH mitigate formation of nitrosamines in Drug A and Drug B formulations.
- The effectiveness of the mitigation strategy was product dependent.

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