FDA Perspectives on Nitrosamine Risk Reduction in Manufacturing

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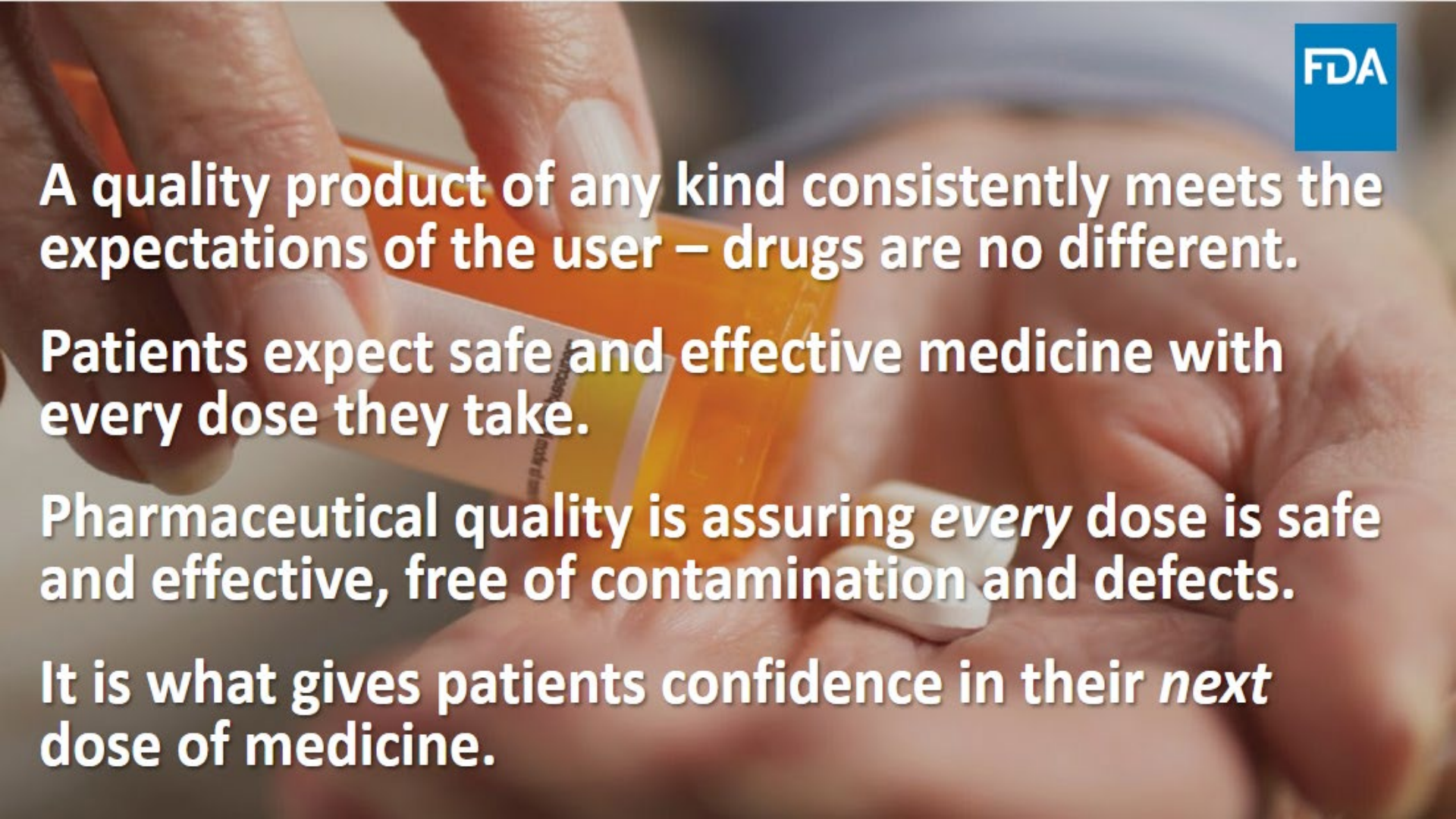

FDA
A quality product of any kind consistently meets the expectations of the user – drugs are no different.
Patients expect safe and effective medicine with every dose they take.
Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.
It is what gives patients confidence in their *next* dose of medicine.

Disclaimer

"This presentation is not intended to convey formal FDA policy"

Presentation Outline

- Identifying the risk factors and the control strategies
- Mitigation strategies
- Case study: Bumetanide & Metformin DP

Risk factors

- Risk Factors for nitrosamine formation:
  - **A susceptible nitrogen** containing compound (secondary or tertiary amines)
  - **A nitrosating agent** (e.g., introduced from nitrite present as impurities in excipients)
  - **pH conditions** to achieve the nitrosating reaction
  - **Manufacturing conditions** (Blending, Drying, granulation, etc.)
  - **Storage conditions & Packaging**

- **Study Objectives:** the primary objective of this work is to mitigate the risk of the formation of N-nitroso impurities by evaluating the role of different inhibitors in different formulations prepared by FDA formulation scientists using bumetanide & metformin as model drugs.

Control Strategies

- ***API manufacturing control***
- ***Supplier qualification program*** **that takes into account potential nitrite impurities across excipient suppliers and excipient lots to reduce the risk of nitrosamine formation in the drug product**
- ***Antioxidants*** **(Vitamin C, Vitamin E, etc.) and pH modifiers (Sodium carbonate, etc.)**
- ***Manufacturing control*** **(Blending control, Drying control, etc.)**
- **Packaging control (example: using inert, non-reactive materials)**

Mitigation strategies

- **Antioxidants:**
  - Have been shown to be effective inhibitors in reducing formation of nitrosamine impurities
  - **Ascorbic acid, Caffeic acid and Ferulic acid** were chosen for this study, and they each exhibited higher inhibition than other known antioxidants

- **pH Control**
  - Acidic conditions facilitate the nitrosating reaction to form the nitrosating agent
  - Maintaining neutral pH of the drug product will serve as a protection strategy against nitrosamine formation

- **Heat and Moisture Control**
  - **Elevated heat and moisture increase risk:** Nitrosamine formation is higher under high temperature and humidity conditions
  - **Potential formation during drying:** Nitrosamines or their precursors may be introduced or generated during the wet granulation drying process
  - **Role of precursors in wet mass:** Secondary amines or NOx present in the wet mass may convert into nitrosamine impurities during drying

Manufacturing Process (Tablet)

Sieving…

API and single excipients

Mixing…

API and antioxidants by geometric dilution

Intragranular blend

Homogenous and no aggregations

Granulation…

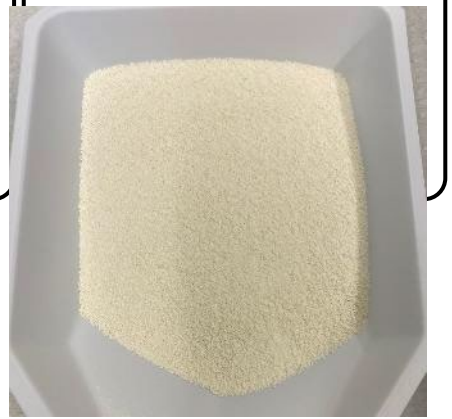
Binder 40% IPA in H_2O. (60% w/w to intragranular blend) Nitrite was spiked here

Manufacturing Process (Continued)

Semi-Drying…
Granules were sifted and placed in 60°C oven (45 mins.)

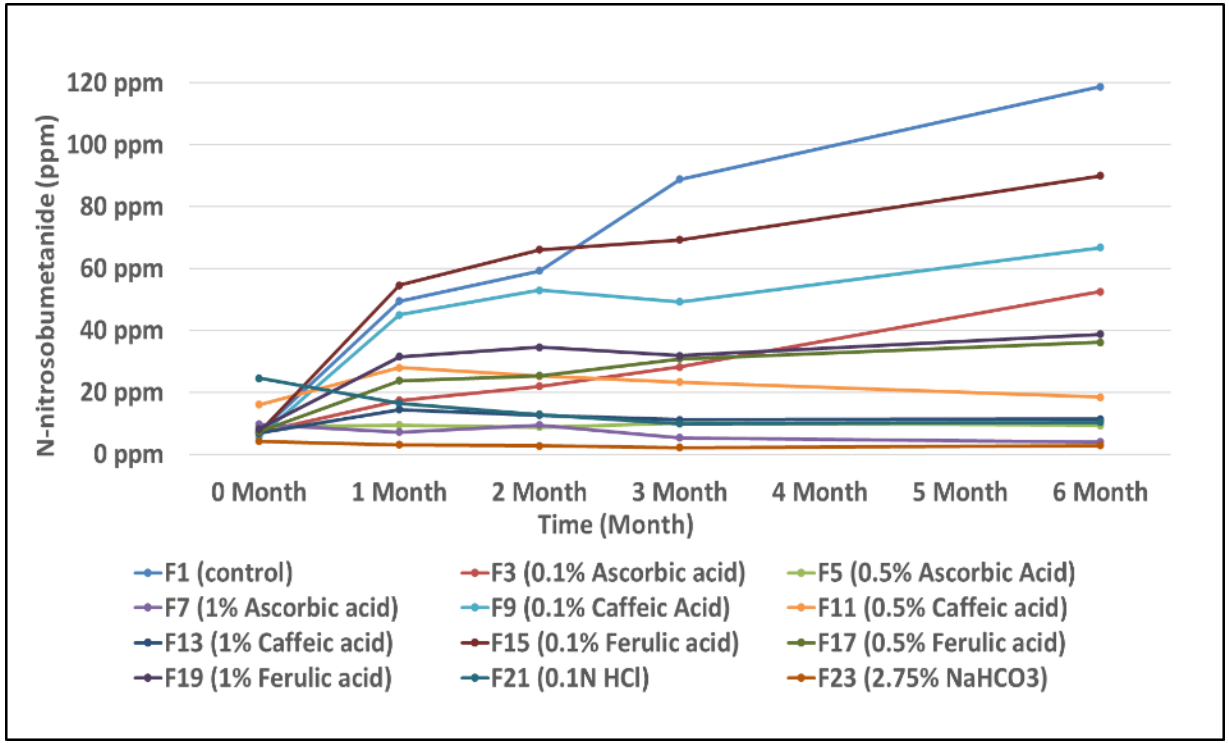
Drying…
Using a fluidized bed dryer. airflow: 20m^3/h temp : 60˚C

Granules…
Sifted thru #30 sieve.
Moisture (< 2%)



Tableting…
Granules were mixed with extra-granular mixture and ready for compression.

Comprehensive Profiles for N-Nitroso-BMT Mitigation in BMT Stability Tablets (25 ºC/60% RH)



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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Bumetanide as a Model NDSRI Substrate: *N*-nitrosobumetanide Impurity Formation and its Inhibition in Bumetanide Tablets

Diaa Shakleya, Bethel Asmelash, Alaadin Alayoubi, Nicolas Abrigo, Adil Mohammad, Jiang Wang, Jinhui Zhang, Jingyue Yang, Tim Andres Marzan, David Li, Maha Shaklah, Fahd M. Alsharif, Saaniya Desai, Patrick J. Faustino, Muhammad Ashraf, Thomas O'Connor, Matthew Vera, Andre Raw, Vilayat A. Sayeed, David Keire

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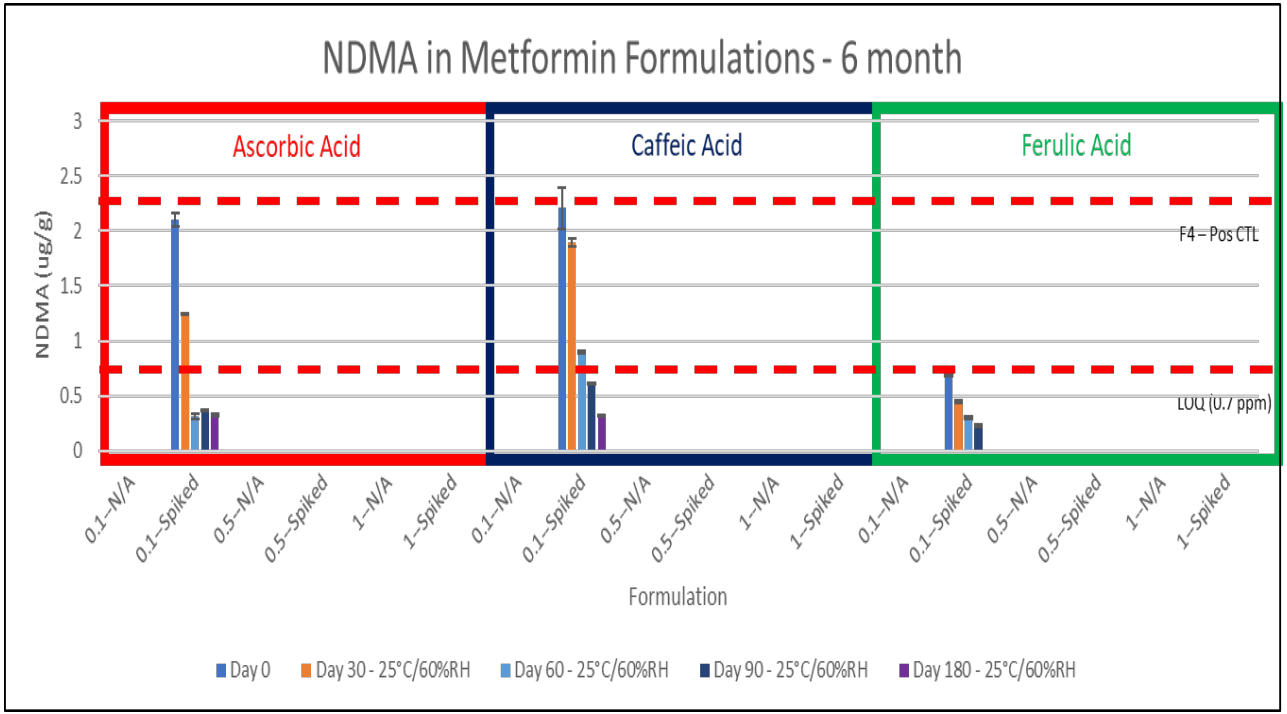
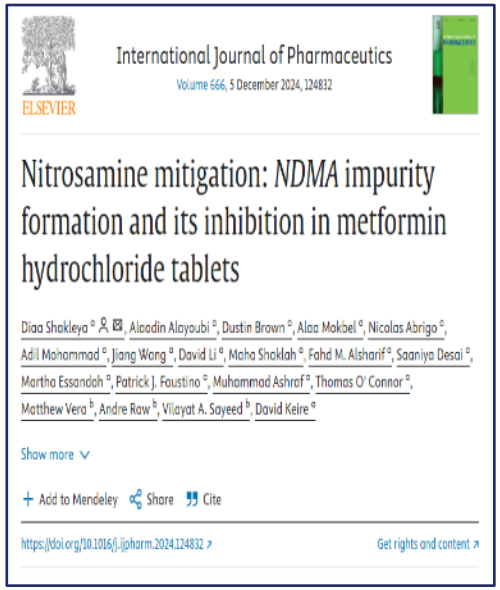
Comprehensive Profiles for NDMA Mitigation in Metformin Stability Tablets (25 ºC/60% RH)





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Nitrosamine mitigation: *NDMA* impurity formation and its inhibition in metformin hydrochloride tablets

Diaa Shakleya [a], Alaodin Alayoubi [a], Dustin Brown [c], Alaa Makbel [c], Nicolas Abrigo [c], Adil Mohammad [c], Jiang Wang [a], David Li [a], Maha Shaklah [c], Fahd M. Alsharif [a], Saaniya Desai [c], Martha Essandoh [a], Patrick J. Faustino [c], Muhammad Ashraf [a], Thomas O' Connor [a], Matthew Vera [b], Andre Raw [b], Vilayat A. Sayeed [b], David Keire [a]

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Summary & Conclusions

❑ Antioxidants

- Antioxidants need to be fit-for-purpose and their effectiveness depends on the drug substance, manufacturing process and the formulation
- Increase in antioxidant concentration improved NDMA and N-nitrosobumetanide mitigation in the metformin and bumetanide drug products, respectively

❑ pH Control

- Acidic conditions facilitated nitrosating reactions
- Maintaining neutral pH of the drug product served as a protective strategy against nitrosamine formation. An alkali modifier (sodium carbonate) had the most effective inhibition of nitrosamine formation for the tested metformin and bumetanide stability drug product

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