Begin with the end in mind

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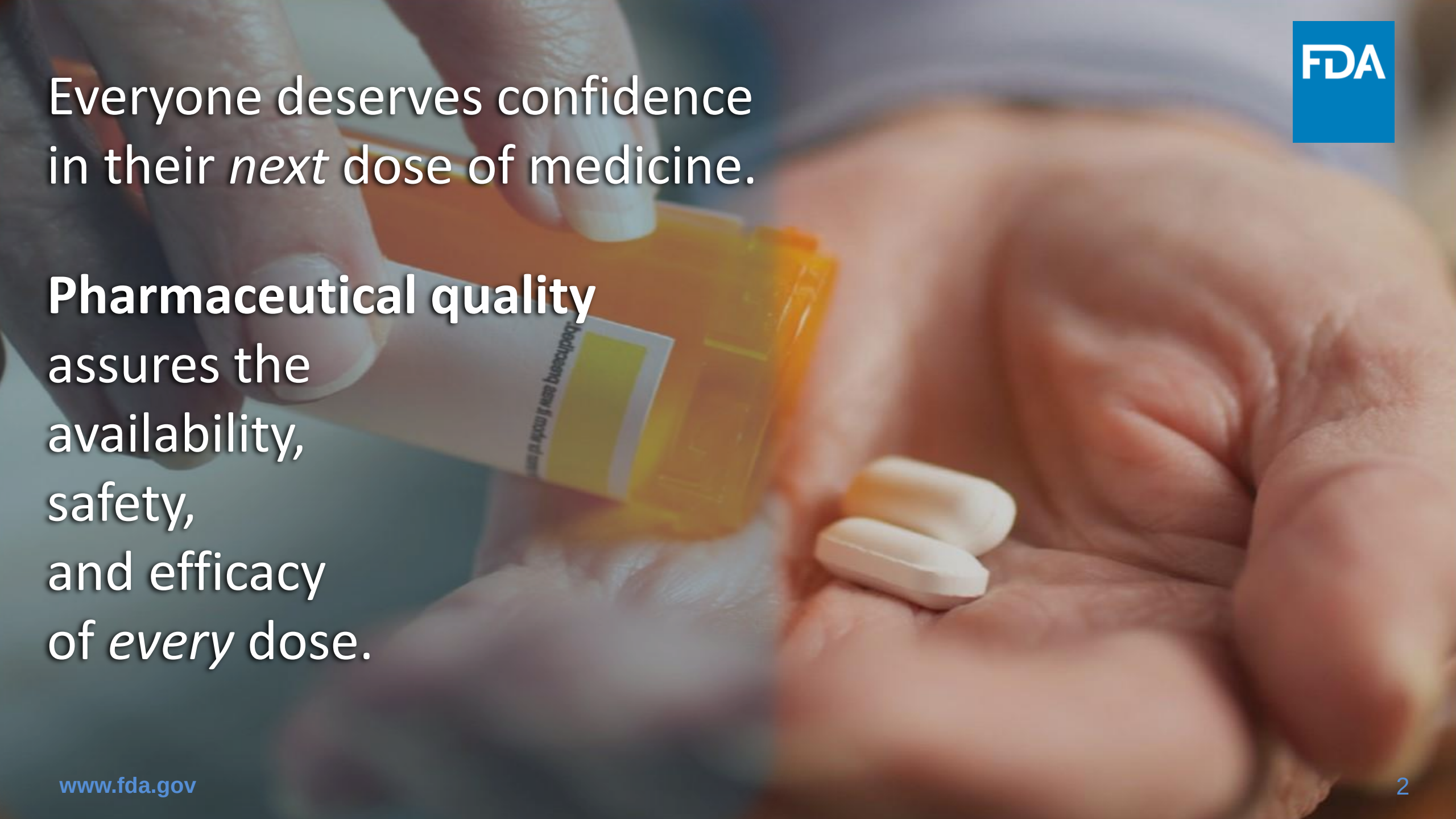
Thursday, November 7, 2024

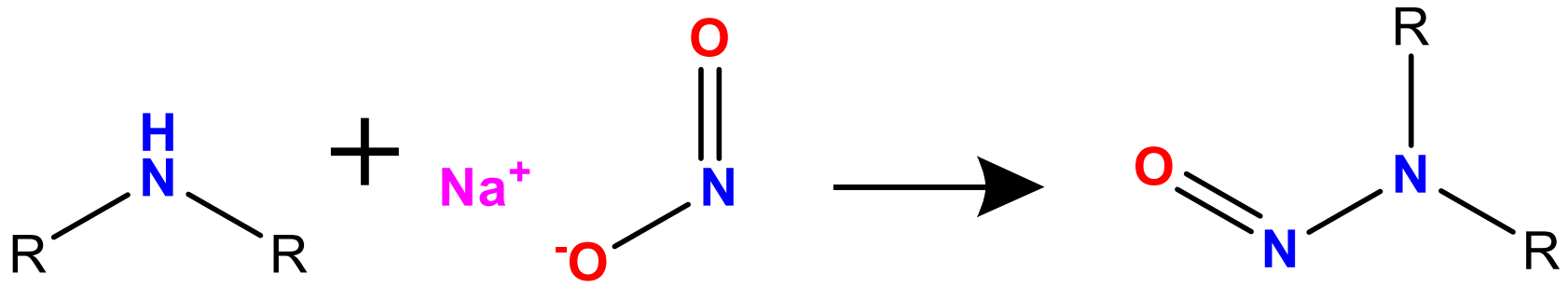


Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Nitrosamines are everywhere.

- NDMA and other nitrosamines are common contaminants in low amounts (ppm) in foods, beverages, cosmetics, water, tobacco products and consumer goods (1-4). But still not acceptable.



1. Gushgari AJ, Halden RU. Critical review of major sources of human exposure to N-nitrosamines. Chemosphere. 2018;210:1124-36.
2. Kocak D, Ozel MZ, Gogus F, Hamilton JF, Lewis AC. Determination of volatile nitrosamines in grilled lamb and vegetables using comprehensive gas chromatography - nitrogen chemiluminescence detection. Food Chem. 2012;135(4):2215-20.
3. Park JE, Seo JE, Lee JY, Kwon H. Distribution of Seven N-Nitrosamines in Food. Toxicol Res. 2015;31(3):279-88.
4. Lim DS, Roh TH, Kim MK, Kwon YC, Choi SM, Kwack SJ, et al. Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics. J Toxicol Environ Health A. 2018;81(12):465-80.

NDSRIs in Drug Products

- *In silico* analysis found that ~40% of APIs are potential precursors for formation of NDSRIs[1]
- NDSRIs have a broad impact on generic drugs
  - Need to maintain supply for essential medicines until NDSRIs can be eliminated or reduced to acceptable levels.
  - Collaborations with international regulators have been helpful as nitrosamines are a global issue.

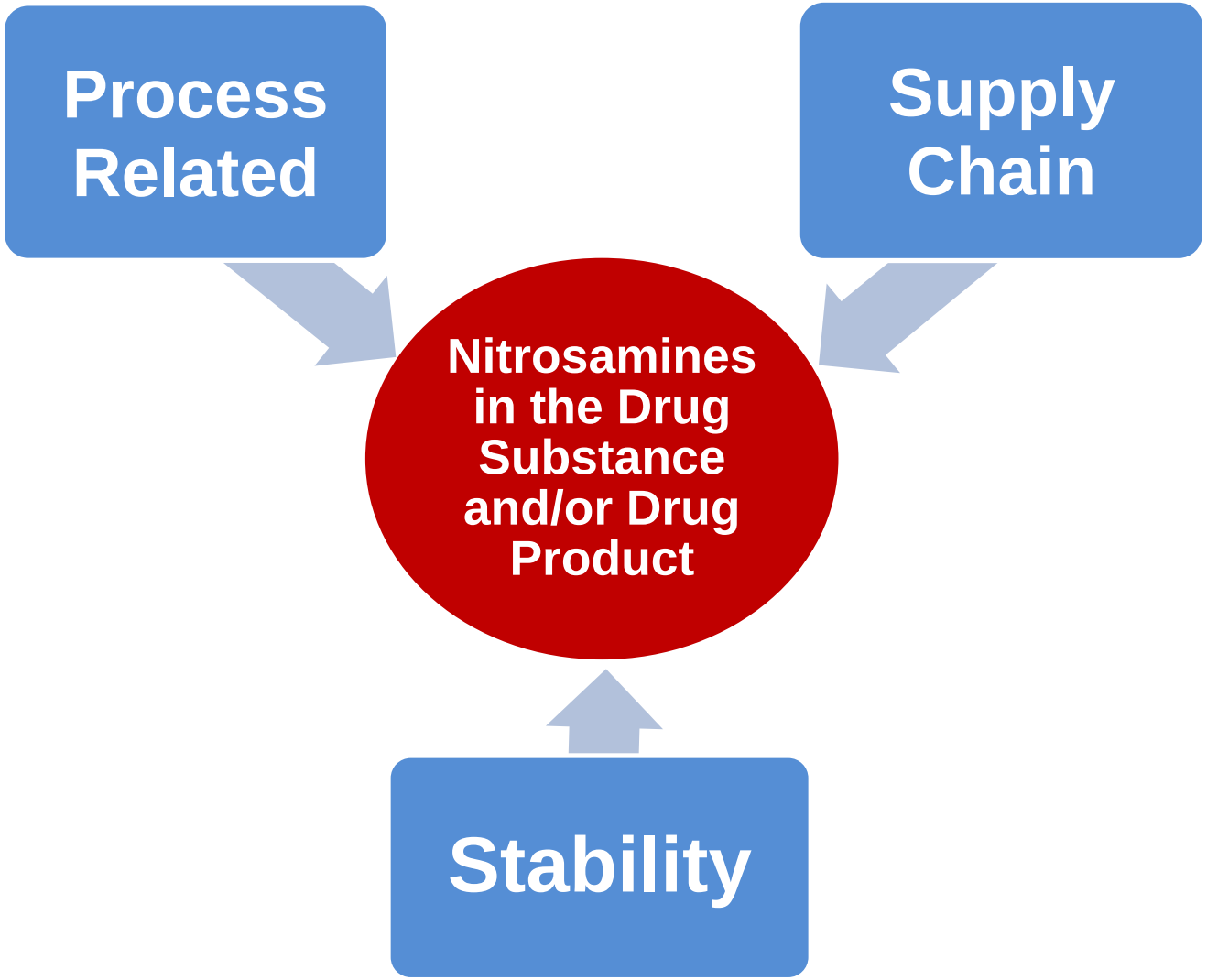
[1] Schlingemann J. et al., The Landscape of Potential Small and Drug Substance Related Nitrosamines in Pharmaceuticals, J. Pharm. Sci., 2023, 112: 1287-1304

Impacts

- Drug Shortages
- Withdrawals (e.g., ranitidine)
- Many information requests to and from regulated industry
- Delays in drug approvals

Over the past 6 years industry and regulators have learned a lot about what *factors* lead to the risk of nitrosamine impurities in pharmaceuticals

Root Causes of Nitrosamine Contamination



Nitrosamine Lens

Regulatory Toxicology and Pharmacology 150 (2024) 105640

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Determining recommended acceptable intake limits for *N*-nitrosamine impurities in pharmaceuticals: Development and application of the Carcinogenic Potency Categorization Approach (CPCA)

Information is out there.
This meeting!

NISG
NITWG-Safety
NITWG-Quality

Regulators are sharing knowledge.

Other Sources of Information:
https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

https://nitrosamines.usp.org/

Journal of Pharmaceutical Sciences 112 (2023) 1166–1182

Contents lists available at ScienceDirect

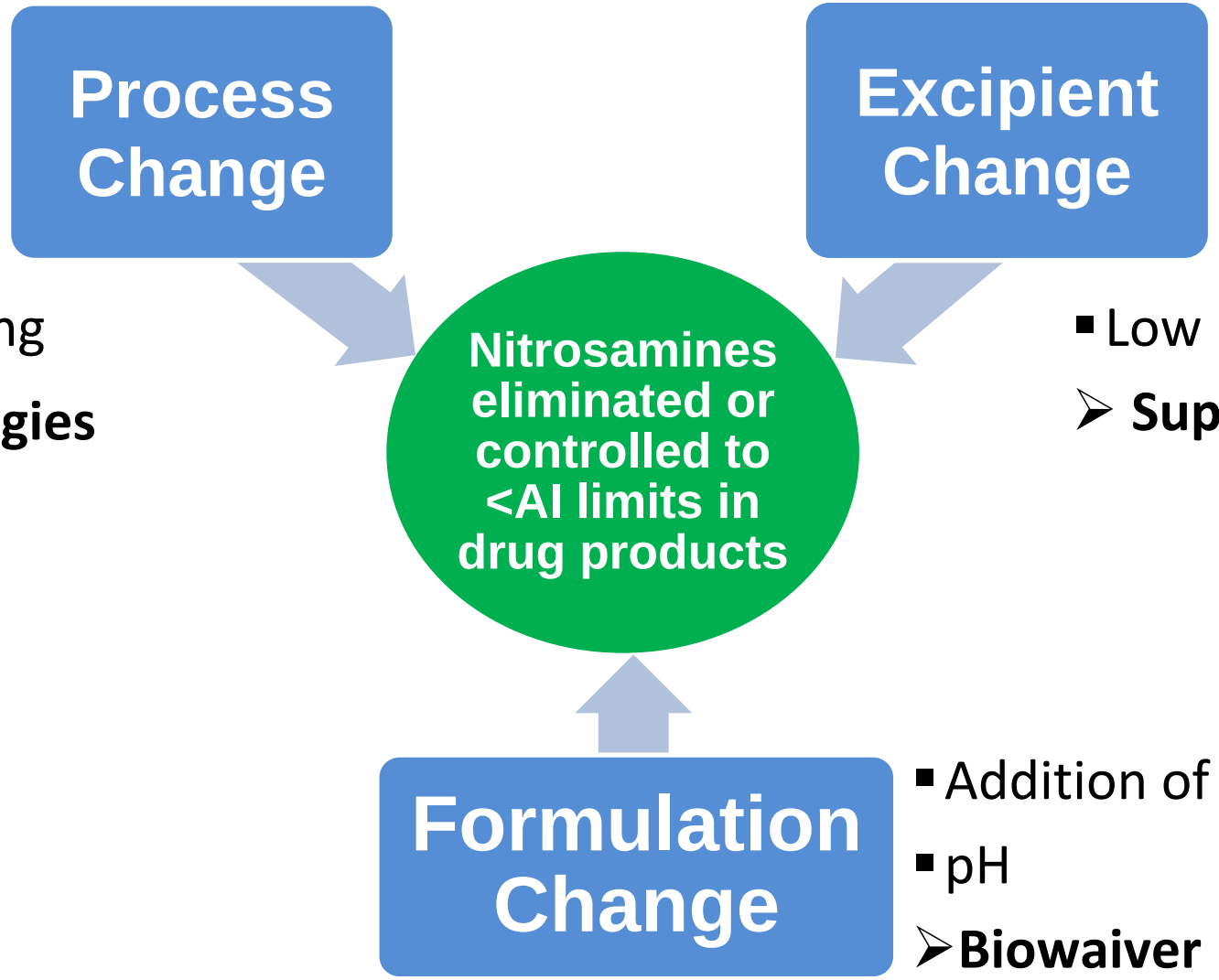
Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Special Topic Commentary

Regulatory Experiences with Root Causes and Risk Factors for Nitrosamine Impurities in Pharmaceuticals

The End in Mind



- Fluid bed drying
- ➢ **Control Strategies**

- Low Nitrite excipients
- ➢ **Supply chain monitoring**

- Addition of antioxidants
- pH
- ➢ **Biowaiver**
- ➢ **Control Strategies**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