Nitrosamine Mitigation Strategies: Insights from the FDA and Emerging Challenges

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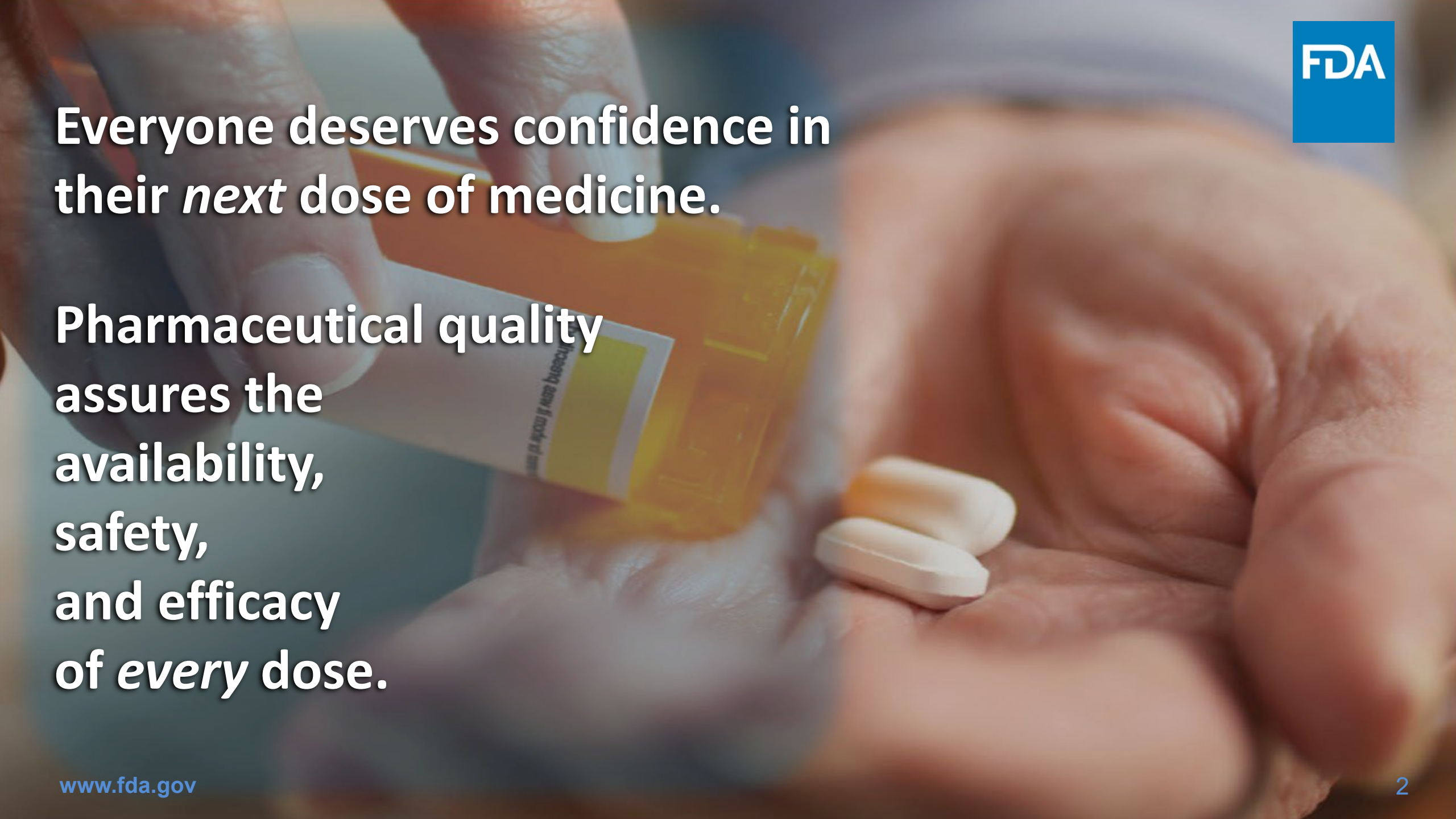


Everyone deserves confidence in their *next* dose of medicine.

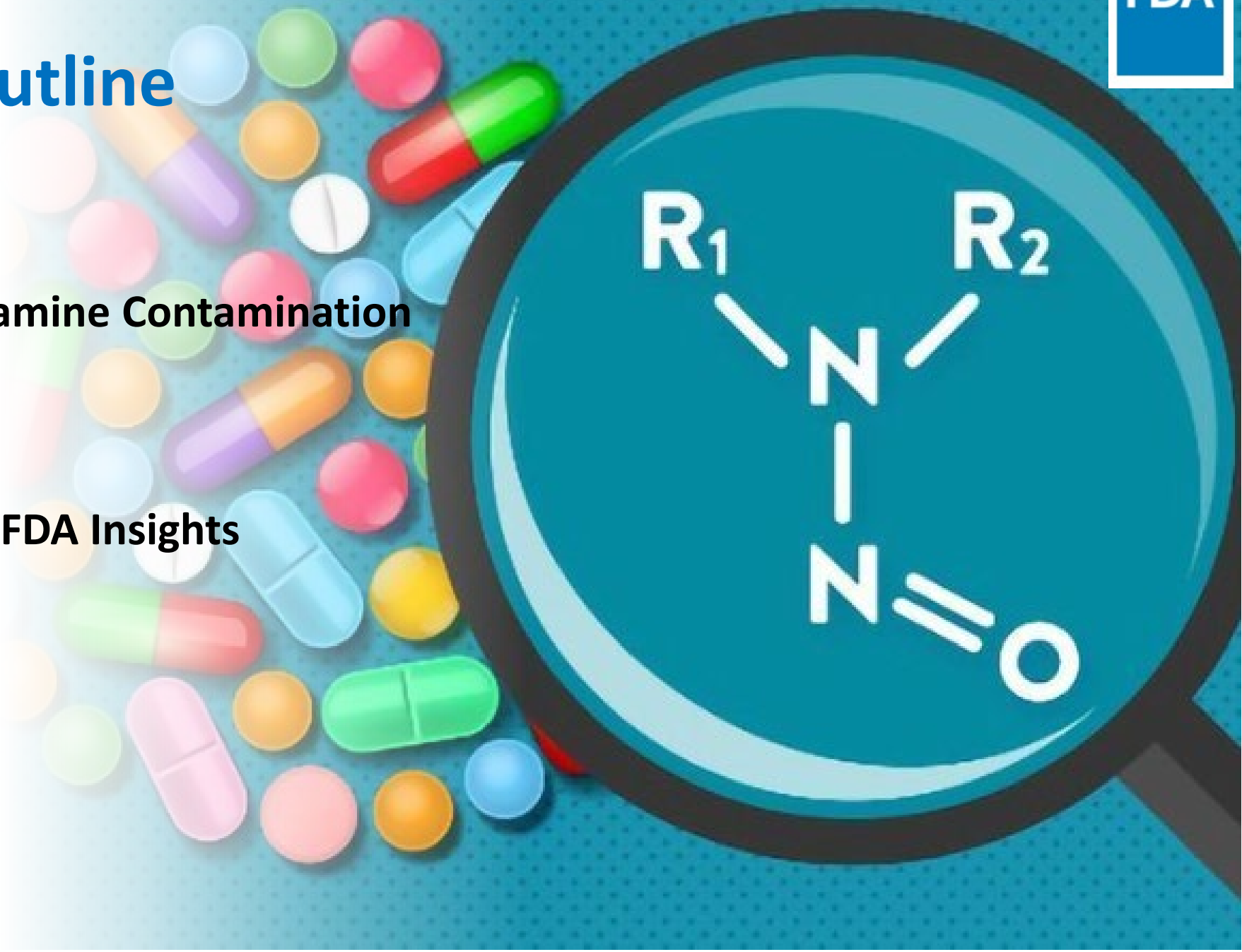
Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Disclaimer

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

Presentation Outline

- Root Causes of Nitrosamine Contamination
- Control Strategies
- Mitigation Strategies: FDA Insights
- Mitigation Challenges



Key Root Causes Across the Product Lifecycle

Manufacturing Process: Reactions, solvents, and processing conditions may create nitrosamines.

Raw Materials: APIs or excipients may contain impurities or precursors.

Storage & Degradation: Heat, moisture, and shelf life may promote formation over time.

Cross-Contamination: Shared equipment or inadequate cleaning may introduce contamination.

Process Changes: Supplier change, or scale-up changes can introduce new risks.

Key Takeaway: **Nitrosamine contamination can arise from multiple stages, requiring a systematic risk-based assessment.**

Control Strategies

API Manufacturing Controls & Nitrosamine Risk Mitigation

Supplier Qualification

Qualification program considering potential nitrite impurities across excipient suppliers and lots to reduce nitrosamine formation risk.

Antioxidants & pH Modifiers

Use of Vitamin C, Vitamin E, sodium carbonate, and related agents to minimize degradation and impurity formation.

Manufacturing Controls

Enhanced blending, drying, and process controls to maintain consistent product quality.

Packaging Controls

Protective packaging strategies to preserve product stability and minimize contamination risk.

Mitigation Strategies for Nitrosamine Formation

FDA Insights | OPQR Research Findings

Antioxidants

- Effective inhibitors for reducing nitrosamine impurities
- Top performers: Ascorbic acid, Caffeic acid, and Ferulic acid
- Intercept reactive species before they attack amine groups

pH Control

- Acidic conditions facilitate nitrosating reactions
- Neutral pH reduces the formation of reactive nitrosating agents
- Creates an unfavorable environment for nitrosamine formation

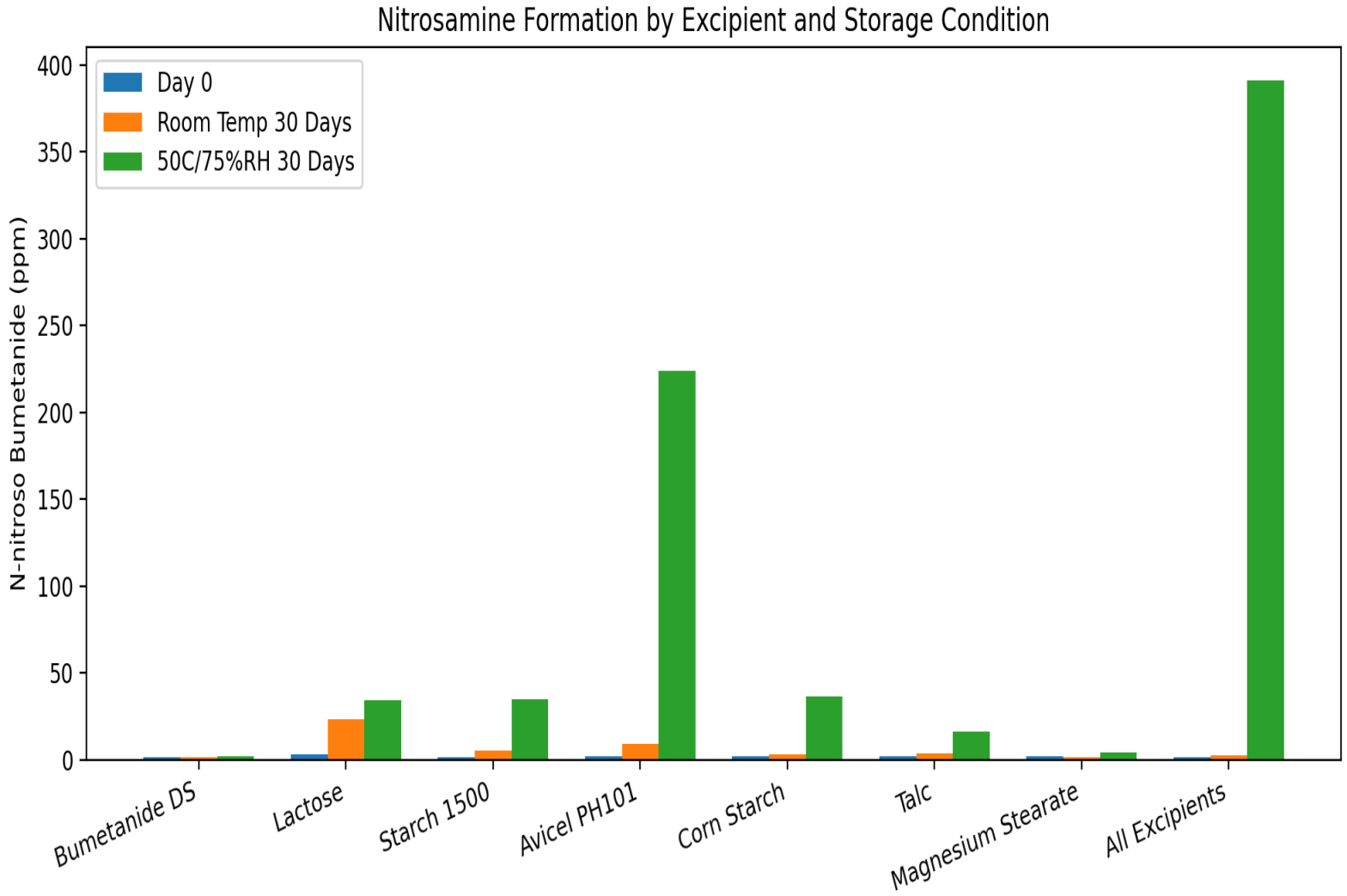
Heat & Moisture Control

- Elevated heat and moisture increase nitrosamine formation
- Wet granulation drying may create conversion hotspots
- Careful drying parameter control is critical

Experimental Workflow

1. A Marketed Drug product was selected
2. Drug and Excipients of selected products were analyzed for Nitroso-compounds and nitrite levels
3. In-house Preparation of several Drug formulations at different levels of antioxidants and different pH
4. Characterization of tablets
5. Analysis of samples at different levels of the manufacturing process for Nitroso-compound and nitrite
6. Manufactured tablets are placed under different stability conditions

Nitrosobumetanide Formation – Screening Study



- **Avicel PH101 and combined excipients** showed the highest nitrosamine formation under stress conditions.
- **Minimal increases** were observed with magnesium stearate.
- **Elevated temperature and humidity** significantly accelerated impurity formation.
- **Placebo and individual excipients alone** showed negligible nitrosamine content.

In-House Drug Formulations

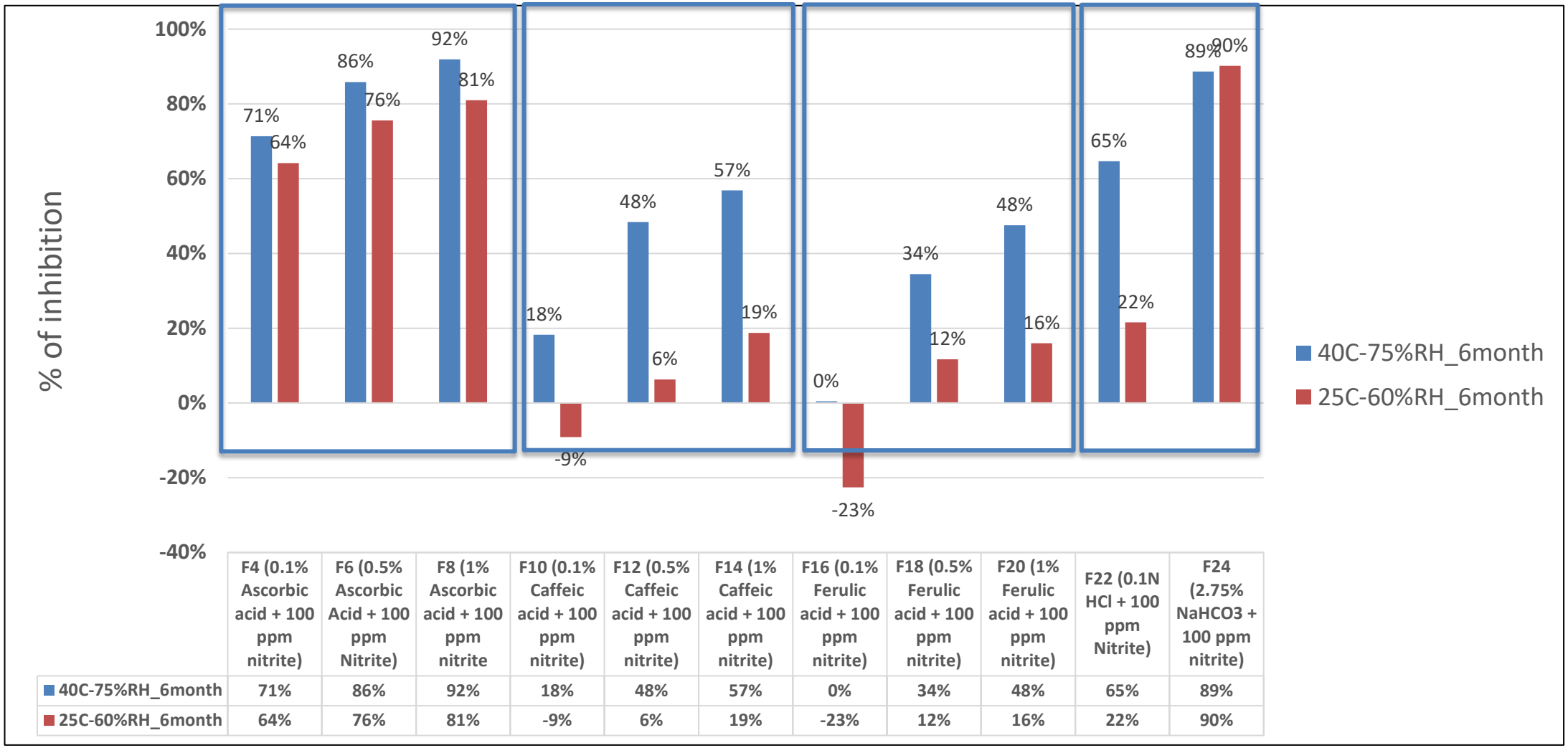
Basic Formulation	
Ingredient	(%)
Intra-granular	
Metformin	70.4
Antioxidant	0, 0.1, 0.5, 1
Granulation (binder)	
Povidone K-30	3.52
Water	10 (to the whole batch)
Nitrite/DMA	0, 100 ppm
Extra-granular	
Hypromellose	16.9
Crospovidone XL-10	4.22
Avicel PH-102	3.52
C. Silicon Dioxide	0.7
Magnesium Stearate	0.7
Total	100

Formulation #	Antioxidant	Percentage of Antioxidant (%)	Nitrite (100 ppm)	Formulation
1	---	---	---	Control
2	---	---	Spiked	Nitrite Spiked Control
3	---	---	Spiked	DMA Spiked Control
4	---	---	Spiked	Nitrite+DMA Spiked Control
5	Ascorbic Acid	0.1	N/A	Antioxidant effect on nitrite spiked and non-spiked formulations
6			Spiked	
7		0.5	N/A	
8			Spiked	
9		1	N/A	
10			Spiked	
11	Caffeic Acid	0.1	N/A	
12			Spiked	
13		0.5	N/A	
14			Spiked	
15		1	N/A	
16			Spiked	
17	Ferulic Acid	0.1	N/A	
18			Spiked	
19		0.5	N/A	
20			Spiked	
21		1	N/A	
22			Spiked	
23	None		N/A	Acidic pH Modifier (pH=3)
24			Spiked	
25			N/A	Basic pH Modifier (pH=8-9)
26			Spiked	
27			N/A	Original Fomulation without Povidone K-30 (Binder)
28			Spiked	Original Fomulation without Povidone K-30 (Binder); Nitrite/DMA spiked

EVALUATED FACTORS	
Antioxidant Type	Ascorbic Cid Caffeic Acid Ferulic Acid
Antioxidant Level	0.10% 0.50% 1.00%
Effect of spiking nitrite and DMA	Zero 100 ppm
Effect of pH	Acidic pH = 3.00 Basic pH = 8.00
Moisture and heat	60% water 60°C Heated air
Stability Conditions	50°C/75% RH 1 month 40°C/75% RH 1, 2, 3, 6 months 25°C/60% RH 1, 2, 3, 6 months

% of Inhibition Efficiency by The Antioxidants

(6-Month Stability of Bumetanide Tablets)



	F4 (0.1% Ascorbic acid + 100 ppm nitrite)	F6 (0.5% Ascorbic Acid + 100 ppm Nitrite)	F8 (1% Ascorbic acid + 100 ppm nitrite	F10 (0.1% Caffeic acid + 100 ppm nitrite)	F12 (0.5% Caffeic acid + 100 ppm nitrite)	F14 (1% Caffeic acid + 100 ppm nitrite)	F16 (0.1% Ferulic acid + 100 ppm nitrite)	F18 (0.5% Ferulic acid + 100 ppm nitrite)	F20 (1% Ferulic acid + 100 ppm nitrite)	F22 (0.1N HCl + 100 ppm Nitrite)	F24 (2.75% NaHCO3 + 100 ppm nitrite)
40C-75%RH_6month	71%	86%	92%	18%	48%	57%	0%	34%	48%	65%	89%
25C-60%RH_6month	64%	76%	81%	-9%	6%	19%	-23%	12%	16%	22%	90%

NDSRI Mitigation Challenges

Analytical Challenges

- Detection limits & sensitive instrumentation
- Matrix interference
- Lack of reference standards
- In-situ nitrosamine formation

NDSRI
Risk
Mitigation

Manufacturing & Process Challenges

- API stability
- Multiple formation pathways
- Antioxidant selection

Mitigation Workflow

Key strategies to reduce nitrosamine formation in pharmaceutical products

Antioxidant Optimization

Tailored antioxidants significantly reduced nitrosamine formation, highlighting the importance of formulation-specific mitigation strategies.

pH Management

Neutral pH conditions and sodium carbonate effectively minimized nitrosation reactions, demonstrating pH control as a critical preventive measure.

Process & Lifecycle Control

Robust raw material oversight, optimized manufacturing conditions, and continuous monitoring are essential to sustain nitrosamine risk mitigation.

Integrated formulation design, pH optimization, and manufacturing controls collectively provide the strongest defense against nitrosamine formation.

Acknowledgments

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