Rethinking Nitrosamine Mitigation:

Leveraging Next-Gen Active Material Science Technologies to Achieve Regulatory Compliance and Avoid Reformulation

Aptar CSP Technologies

June 25, 2025

Speakers

Jean Daou, Ph.D.

R&D Manager EMEA

Aptar CSP Technologies

Amanda Murph

Lead Scientist Nitrosamines

Aptar CSP Technologies

Viky Verna

Regulatory Affairs

Aptar CSP Technologies

Aptar CSP Technologies

Aptar
CSP Technologies

3-Phase Activ-Polymer™ Platform Technology

3-Phase Activ-Polymer™ Material = Platform Material

Material Science: Adding Chemistry to Polymers

1 **Majority Polymer**

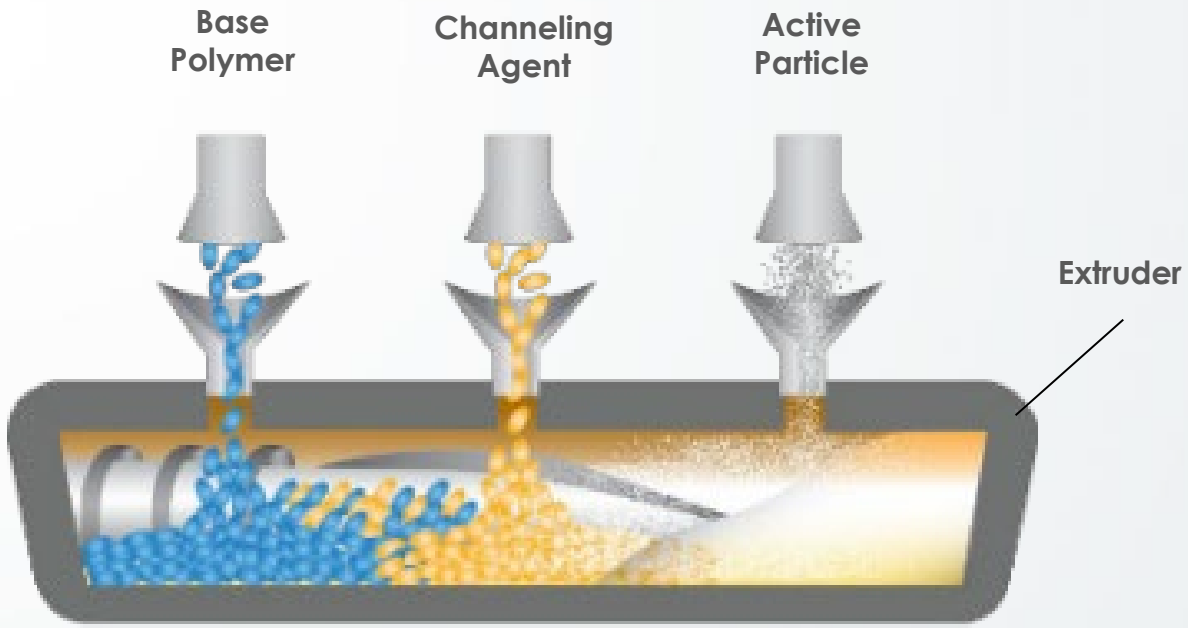
Base Structure Component

2 **Minority Polymer/ Channeling Agent**

Immiscible in majority polymer

3 **Particle(s)**

Adsorbing/Absorbing Buffering – Active Component

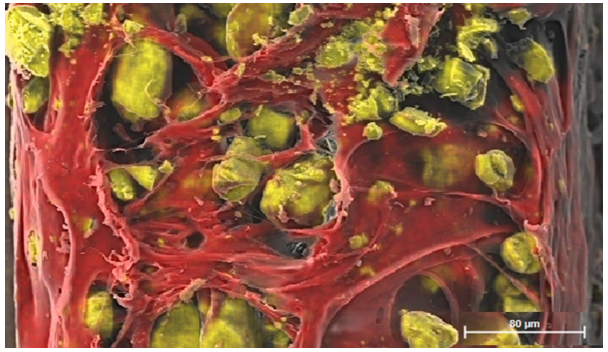


Aptar CSP Technologies

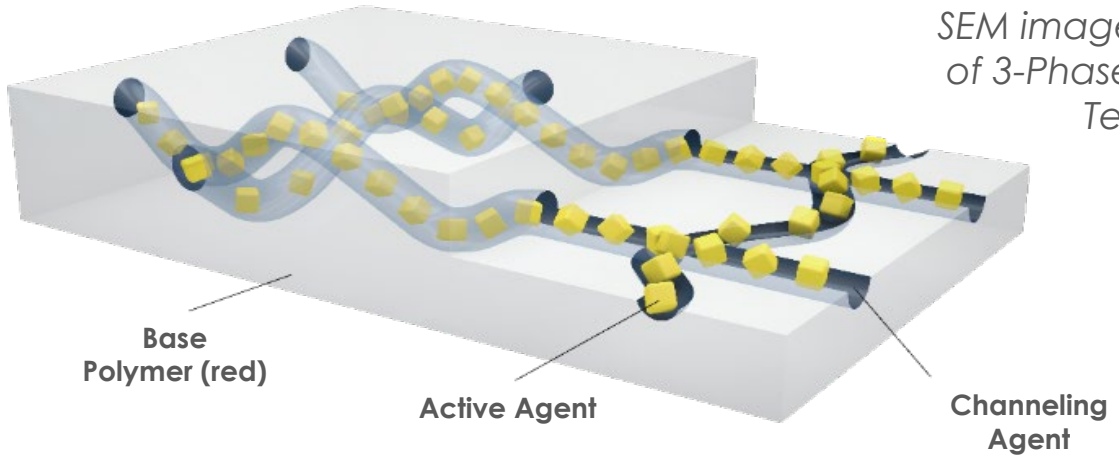
Material Science: Adding Chemistry to Polymers

HOW IT WORKS:

- Channels created within a polymer allow movement of gases
- "Active" particles are added to polymer to:
  - **Adsorb** or **Absorb**
  - **Scavenge**
  - **Release/Emit**
  - **Buffer**
  - **React**
- **Gas diffusion** is controlled through the channel composition

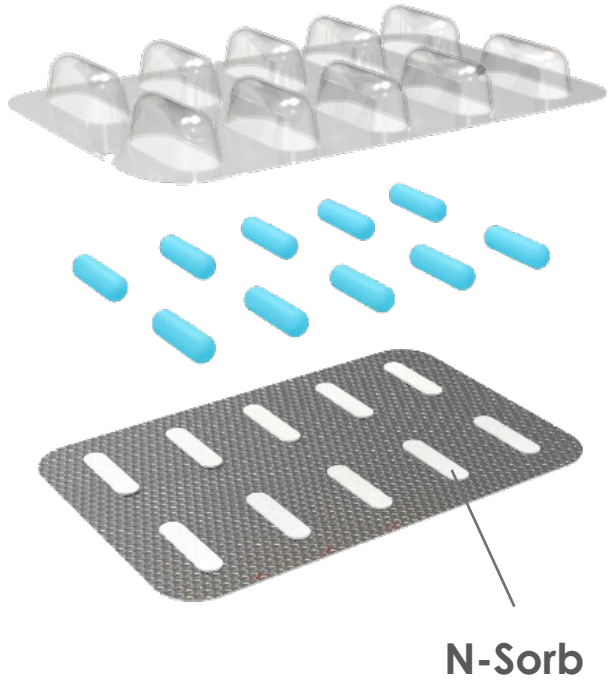


SEM image inside the matrix of 3-Phase Activ-Polymer™ Technology

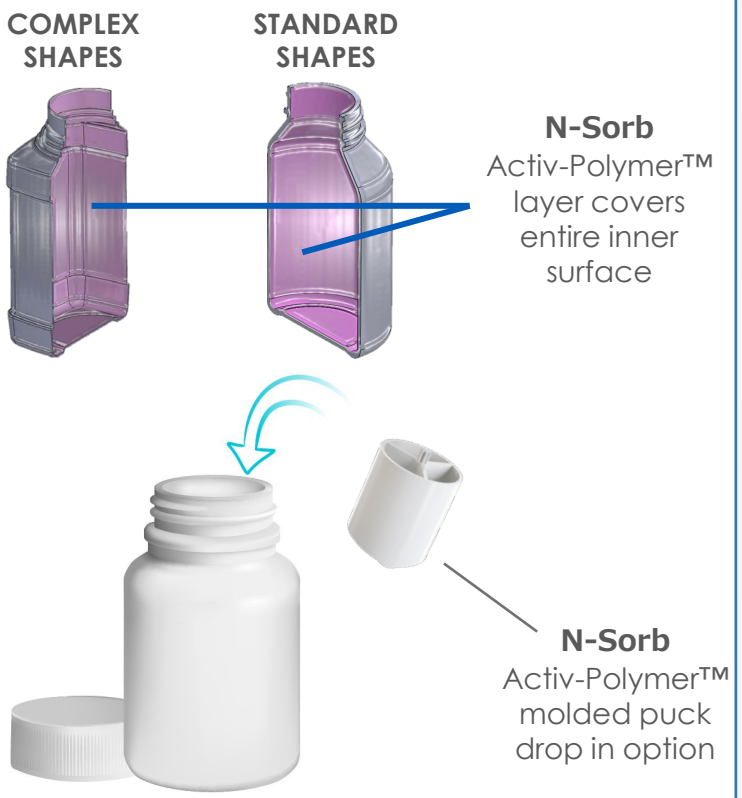


Activ-Polymer™ & N-Sorb Technology Deployment Methods

Activ-Blister™

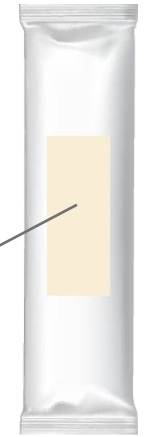


Activ-Polymer™ Multi-Layer Bottle



Fishbone

Stickpack



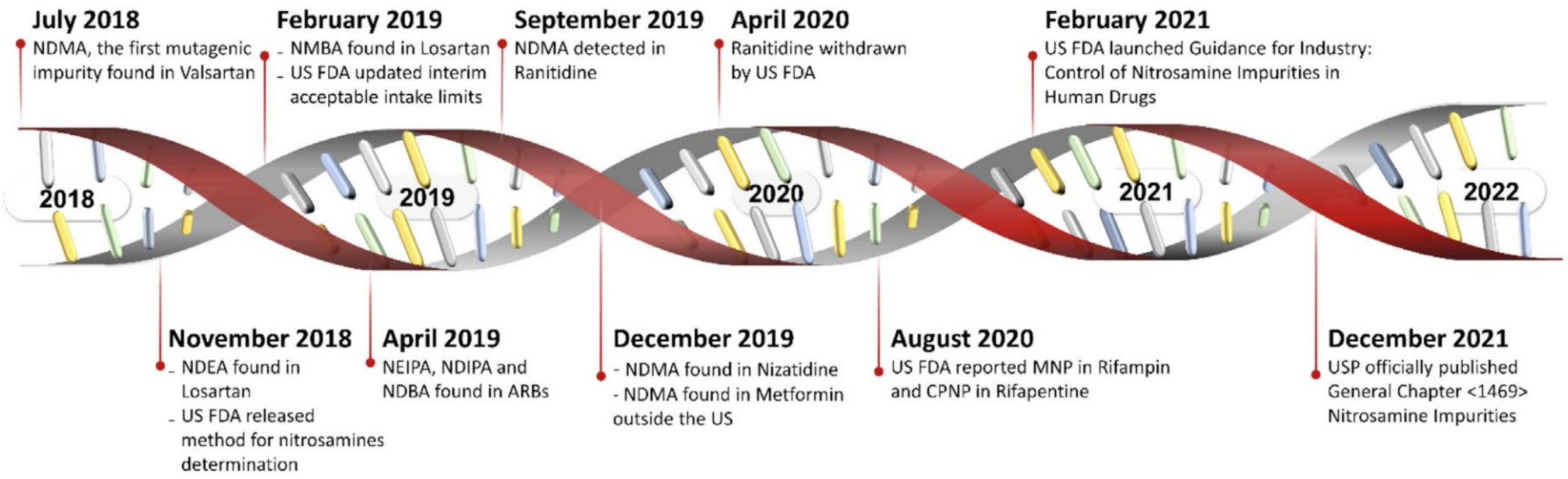
- No disruption to current drug manufacturing processes
- No impact on drug formulation

*Thermoform or Cold Form Alu /Alu

Aptar
CSP Technologies

Rethinking Nitrosamine Mitigation

Introduction



Evolution timeline of nitrosamine-contaminated pharmaceuticals.

N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA),N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitroso ethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA).*

* *W. Wichitnithad, S. Nantaphol, K. Noppakhunsomboon, P. Rojsitthisak, Saudi Pharmaceutical Journal,* ***2023****, 31, 295-311.*

Nitrosamine Formation

Environmental Factors

Amine (2^0 or 3^0)

Nitrosating Agent

Nitrosamine

Nitrosating Agents: What are they?

1. Can be used in the process during a reaction or work-up
2. Introduced as impurities
3. Generated during the process as an impurity

Commonly Known Agents:

Formaldehyde

H_2O_2

DMA

NO_x

Nitrite

Nitric oxide

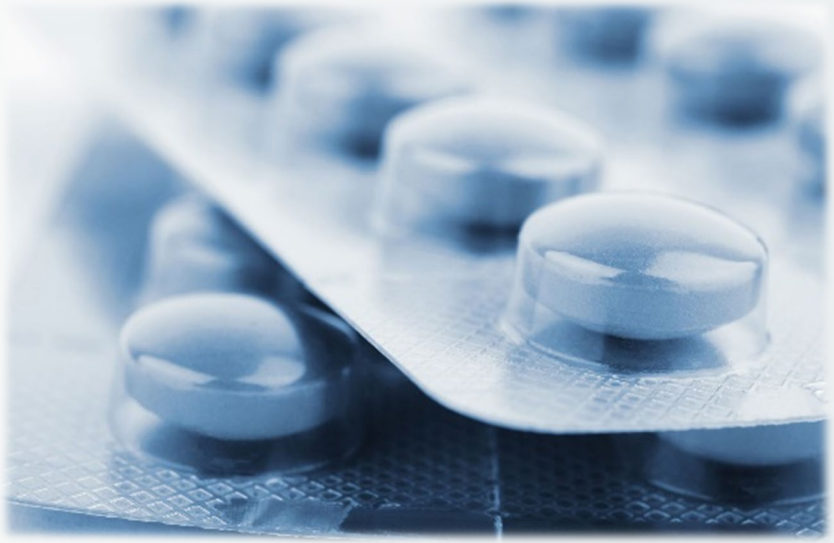
Solvents, Input materials, Recovered materials, Reagents/catalysis

CSP Technologies Packaging Mitigation Targets

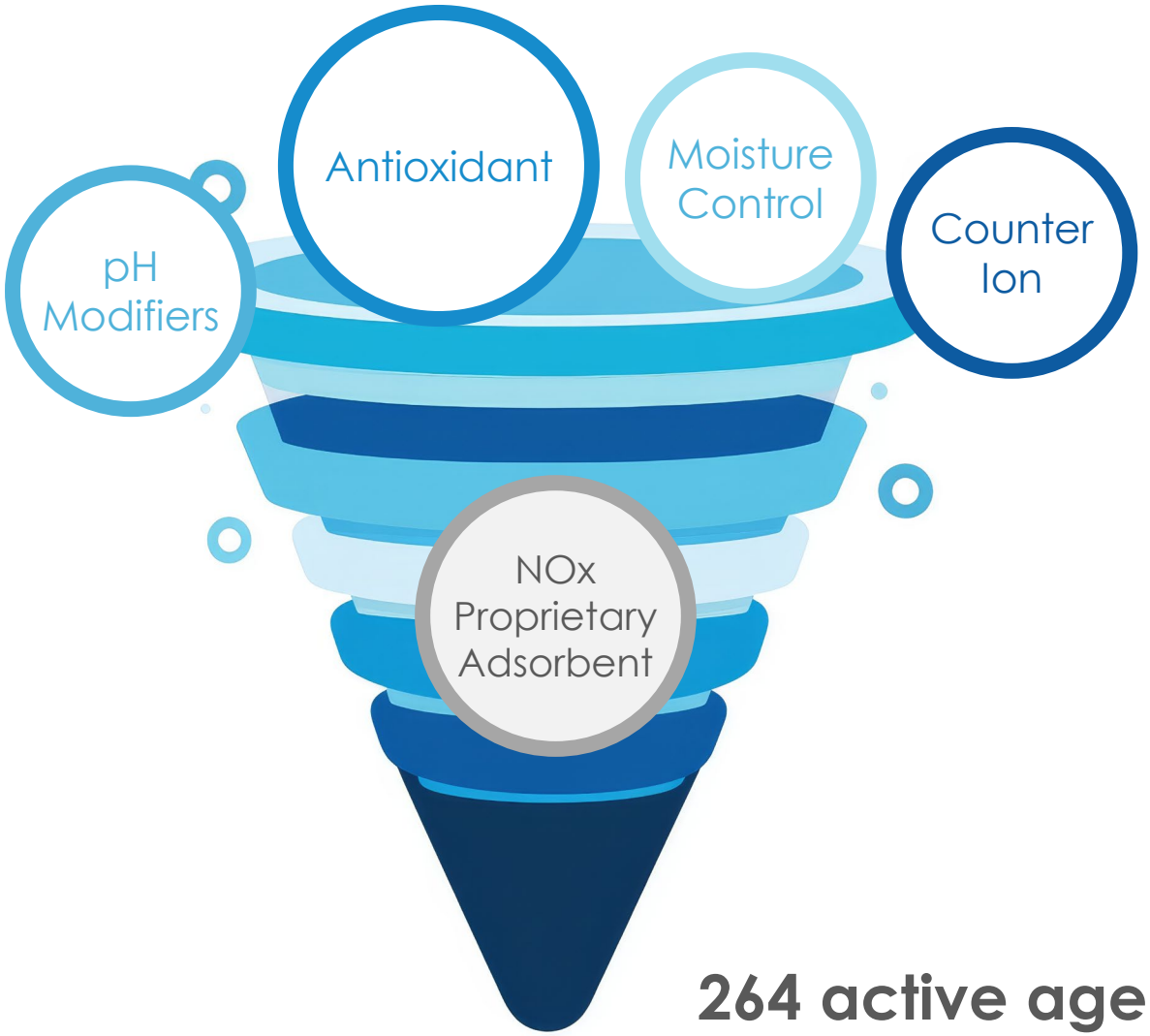
1 Nitrosating Agents in Excipients and Bulk Storage

Excipients | USP

2 Nitrosating Agents and Nitrosamines Post Formulation

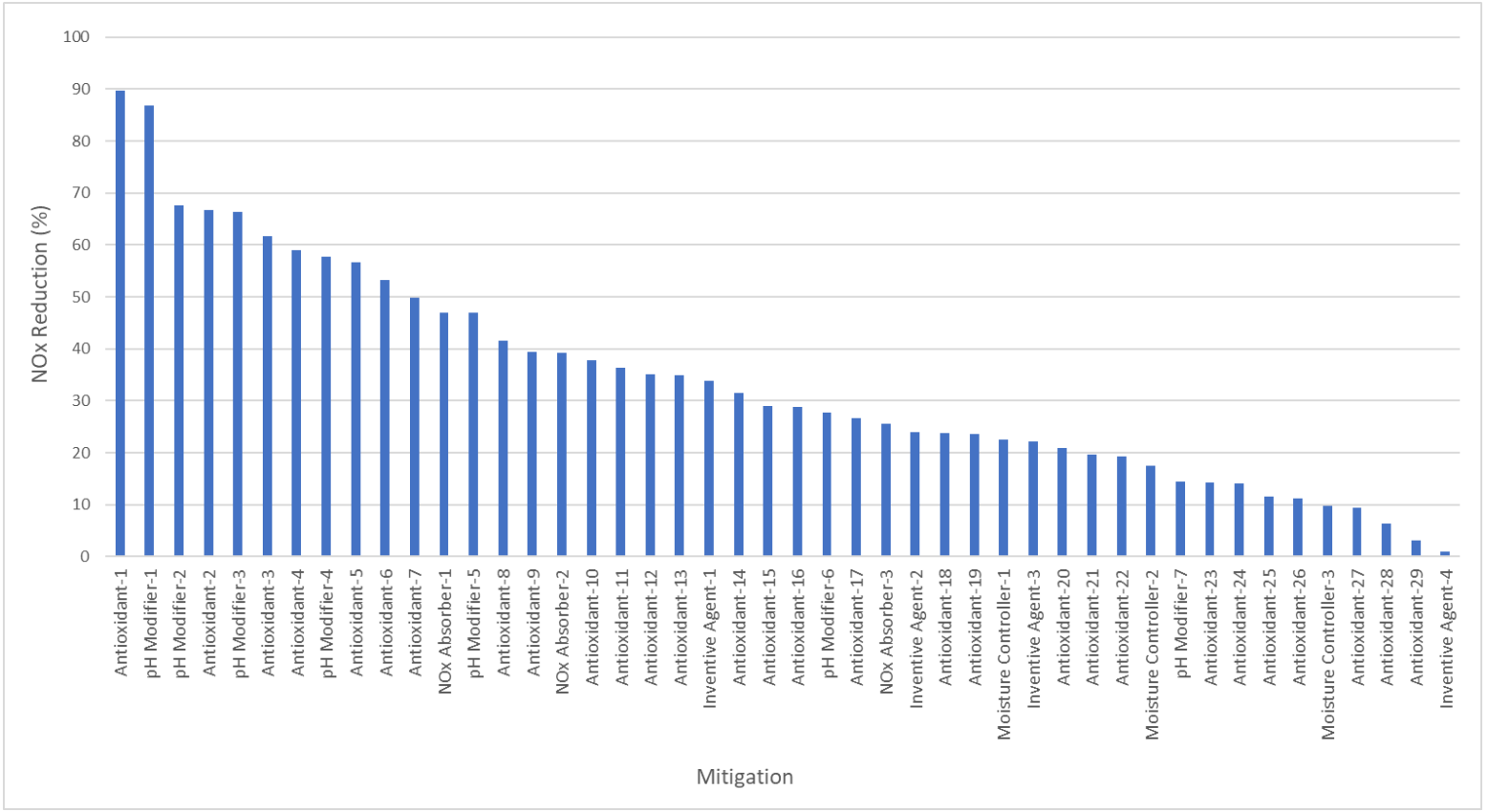


Mitigant/Active Material Screening



264 active agents evaluated to test

Top 50 Materials Screened



EXPERIMENTAL METHOD:

- 50 mg of active agent suspended
- 2 mL NOx providing solution
- Aged 24 hrs at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

50 active agents screened, ranging from 0-90% NOx reduction.

Aptar CSP Technologies

N-sorb Film Mitigation Solutions

Activ-Polymer™ Nitrosamine Mitigation Solutions	Activ-Film™ Platform	Proposed Mechanism of Action (MOA) Hypothesis
N-Sorb A	Engineered Oxygen Scavenger	Traps free radicals such as NO so that NO is not available to react with molecular oxygen and nitrogen to form NO_2 or N_2O_3 (nitrosating agents).[a]
N-Sorb B	Antioxidant	Reduces the nitrosating agent to non-nitrosating nitric oxide or via nitration reactions.[b]
		Yields dinitrosyl ascorbate.[c]
N-Sorb C	Alkaline Compound	Increases pH to create conditions less favorable to Nitrosamine formation [d]
		Reduces reactivity of nitrite ions
N-Sorb D, K	Porous materials	Removal of nitrosamine precursors (nitrosating agents or amines) and nitrosamines post formation
N-Sorb E	Ionic Compund	Impacts chemical equilibrium of nitrosation reactions by altering solubility [e]
N-Sorb F	Alkaline Buffer	Acts as a buffer to impact the pH
		Increases pH to create conditions less favorable to Nitrosamine formation [d]
N-Sorb G, J	Antioxidant	Scavenges reactive oxygen and nitrogen species including NO radicals [a]
		Neutralizes radicals to prevent chain reactions to form nitrosamines

[a] Rapid formation of N-nitrosamines from nitrogen oxides under neutral and alkaline conditions (B C Challis, A Edwards, R R Hunma, S A Kyrtopoulos, J R Outram)
[b] Free Radical Properties, Source and Targets, Antioxidant Consumption and Health (Martemucci, Giovanni, Ciro Costagliola, Michele Mariano, Luca D'andrea, Pasquale Napolitano, and Angela Gabriella D'Alessandro)
[c] Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study (Kausik K. Nandaa, Steven Tignorb, James Clancyc, Melanie J. Marotac, Leonardo R. Allainb, Suzanne M. D'Addioa)
[d] PRESERVATIVES | Permitted Preservatives – Nitrites and Nitrates (J.H. Subramanian, L.D. Kagliwal, R.S. Singhal)

Aptar CSP Technologies

Our Technology: Where Are We Effective?

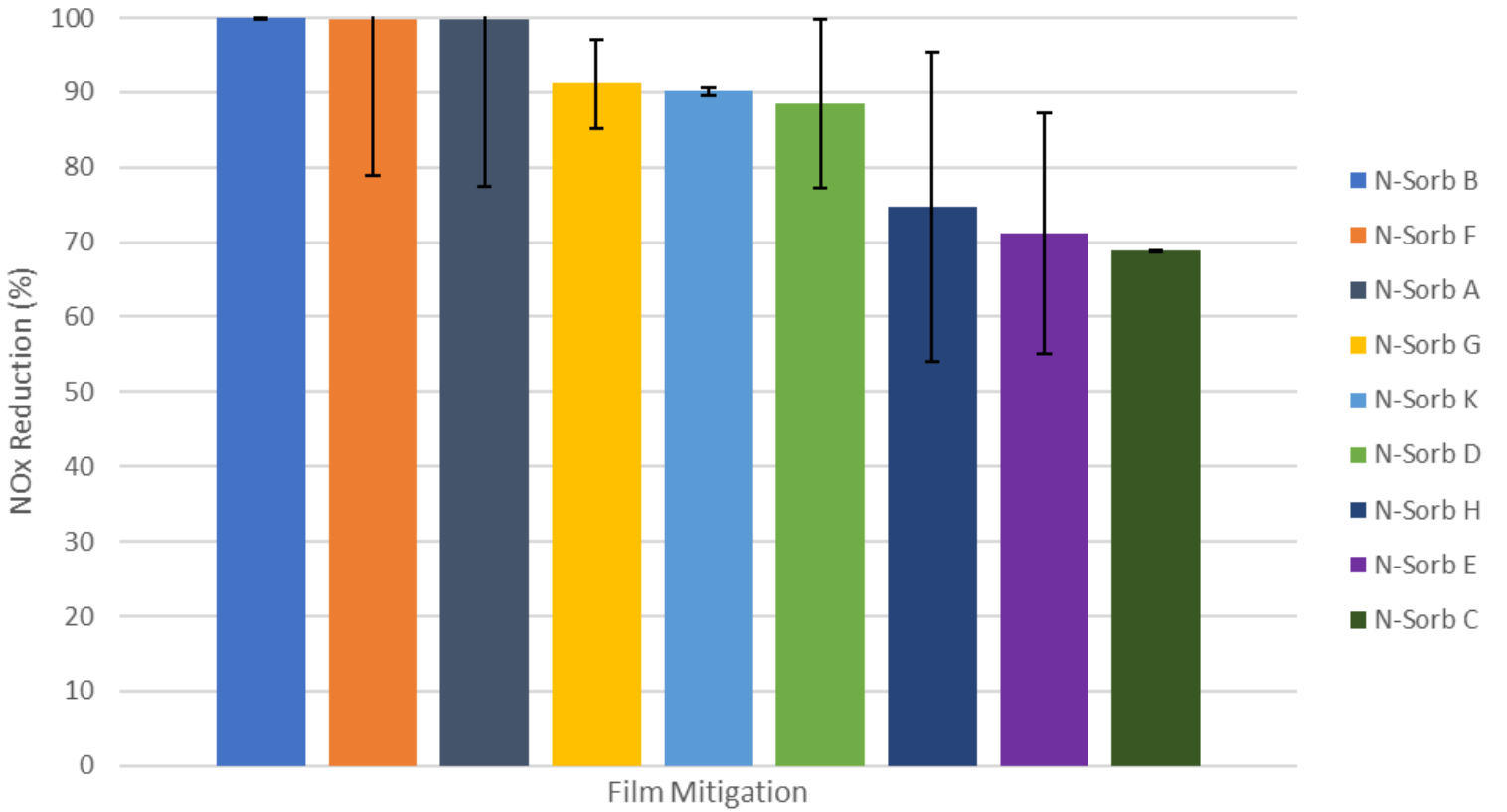
- Reduce Environmental Factors
- Reduce Nitrosating Agents
- Reduce Volatile Nitrosamines
- Prevent Further Nitrosamine Formation

We target nitrosamine precursors, primarily nitrosating agents.

Aptar
CSP Technologies

NO_x Data

Nitrite Mitigation – N-Sorb Film NO_x Testing



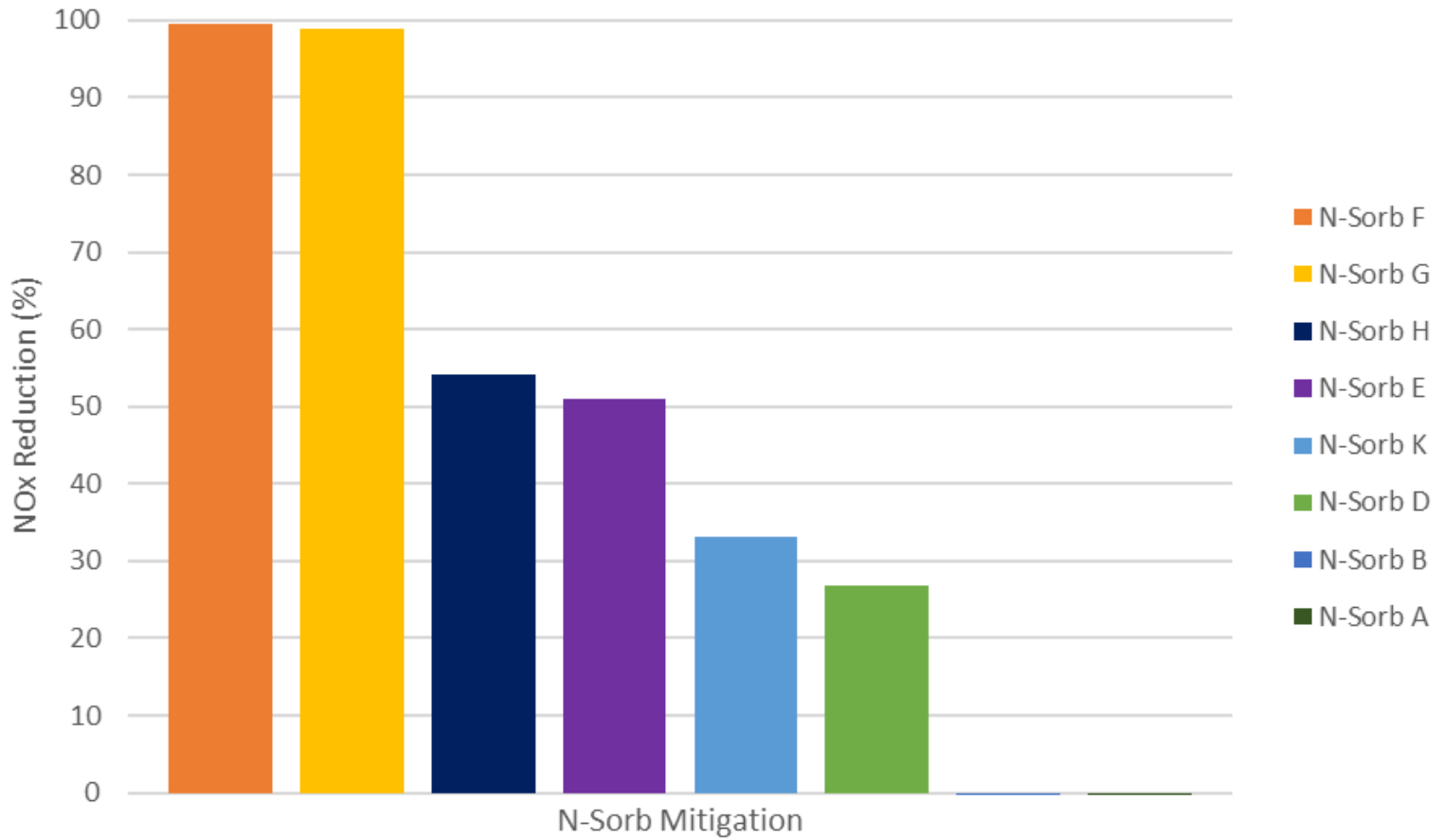
EXPERIMENTAL METHOD:

- 1cm^2 CSP N-Sorb Film
- Film suspended above 2mL NOx producing solution in sealed glass vial
- Aged 7 days at 60°C
- Characterization by GC-MS Headspace with derivative nitrite analysis

All N-Sorb films reduced NO_x by ≥70% compared to controls.

Aptar CSP Technologies

NO_x Mitigation – N-Sorb Blown Bottle POC Testing



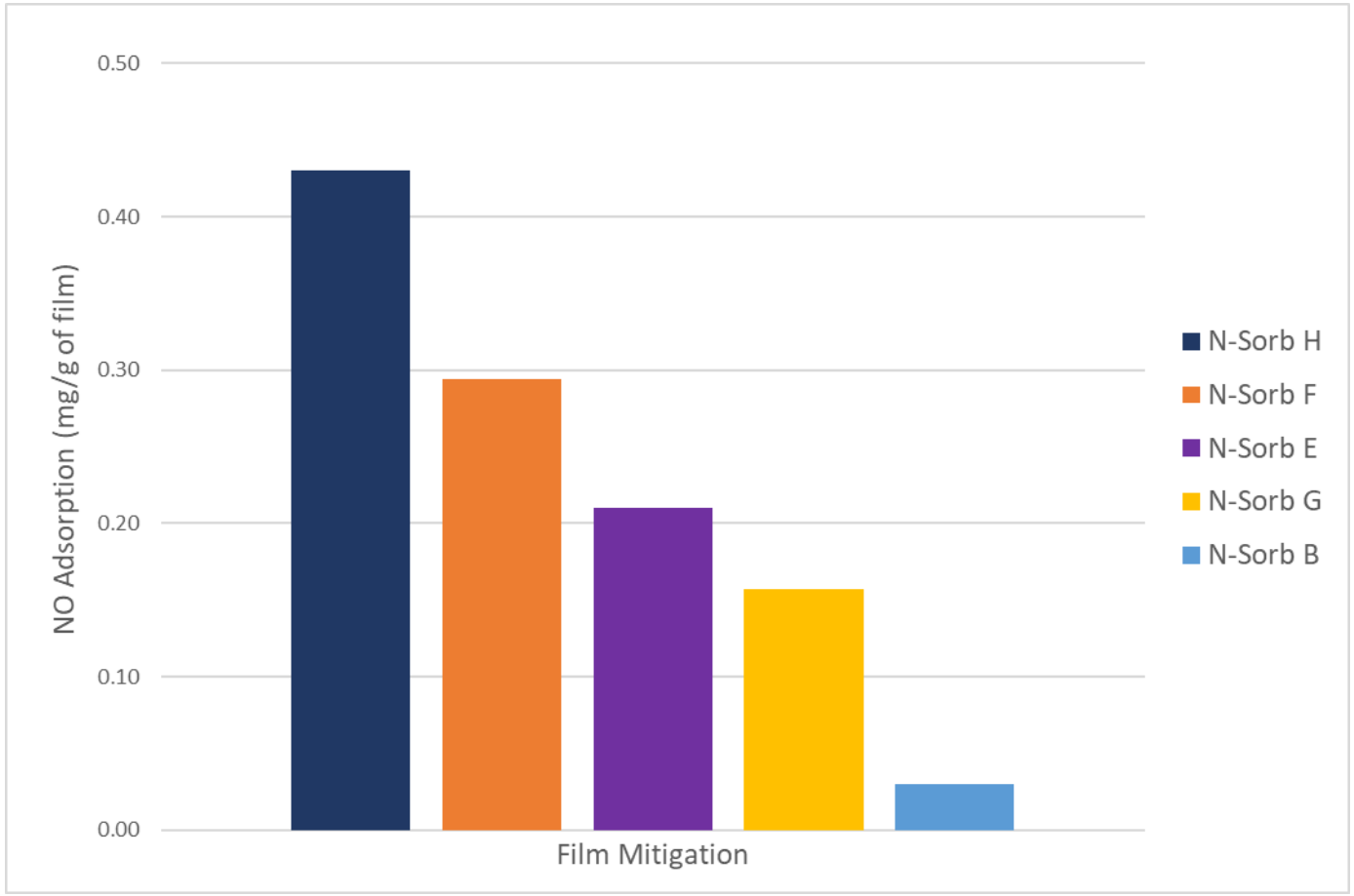
EXPERIMENTAL METHOD:

- 150mL CSP N-Sorb blown bottles
- 8.5mL NOx producing solution in glass vial within the bottle
- Aged 7 days at room temperature
- Characterization by GC-MS Headspace with derivative nitrite analysis

N-Sorb F and G reduced NO_x by ≥99% compared to controls.

Aptar CSP Technologies

Experimental Scavenging of NO Gas Probe Molecule

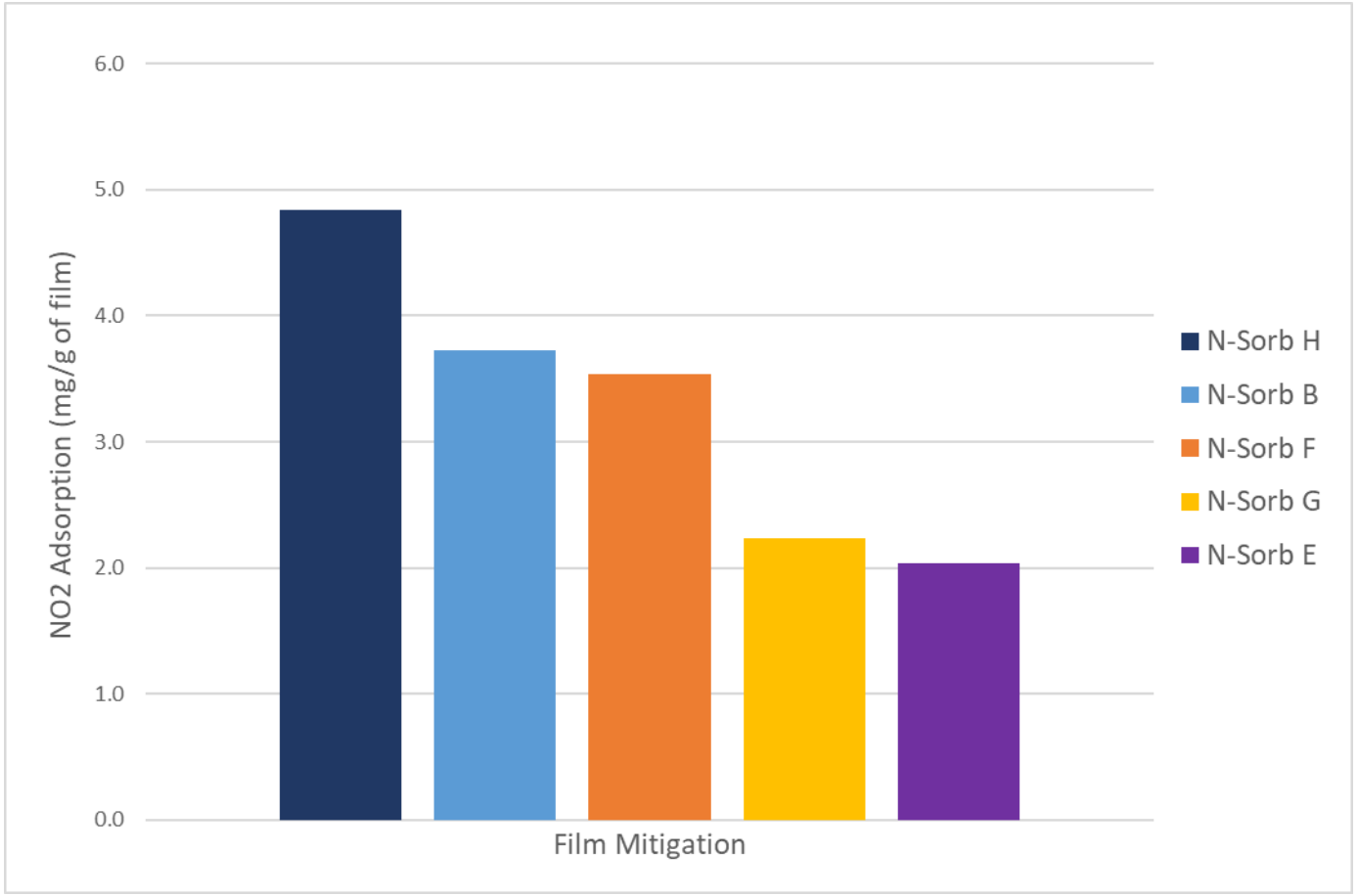


EXPERIMENTAL METHOD:

- 250 mg of film
- **22°C / 0% RH** reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO through the fixed bed column of the sample

All N-Sorb films show significant absorption capacities.

Experimental Scavenging of NO_2 Gas Probe Molecule



EXPERIMENTAL METHOD:

- 250 mg of film
- **22°C / 0% RH** reactor bed
- ROSEMOUNT NGA 2000 detector
- 505 ppm of NO_2 through the fixed bed column of the sample

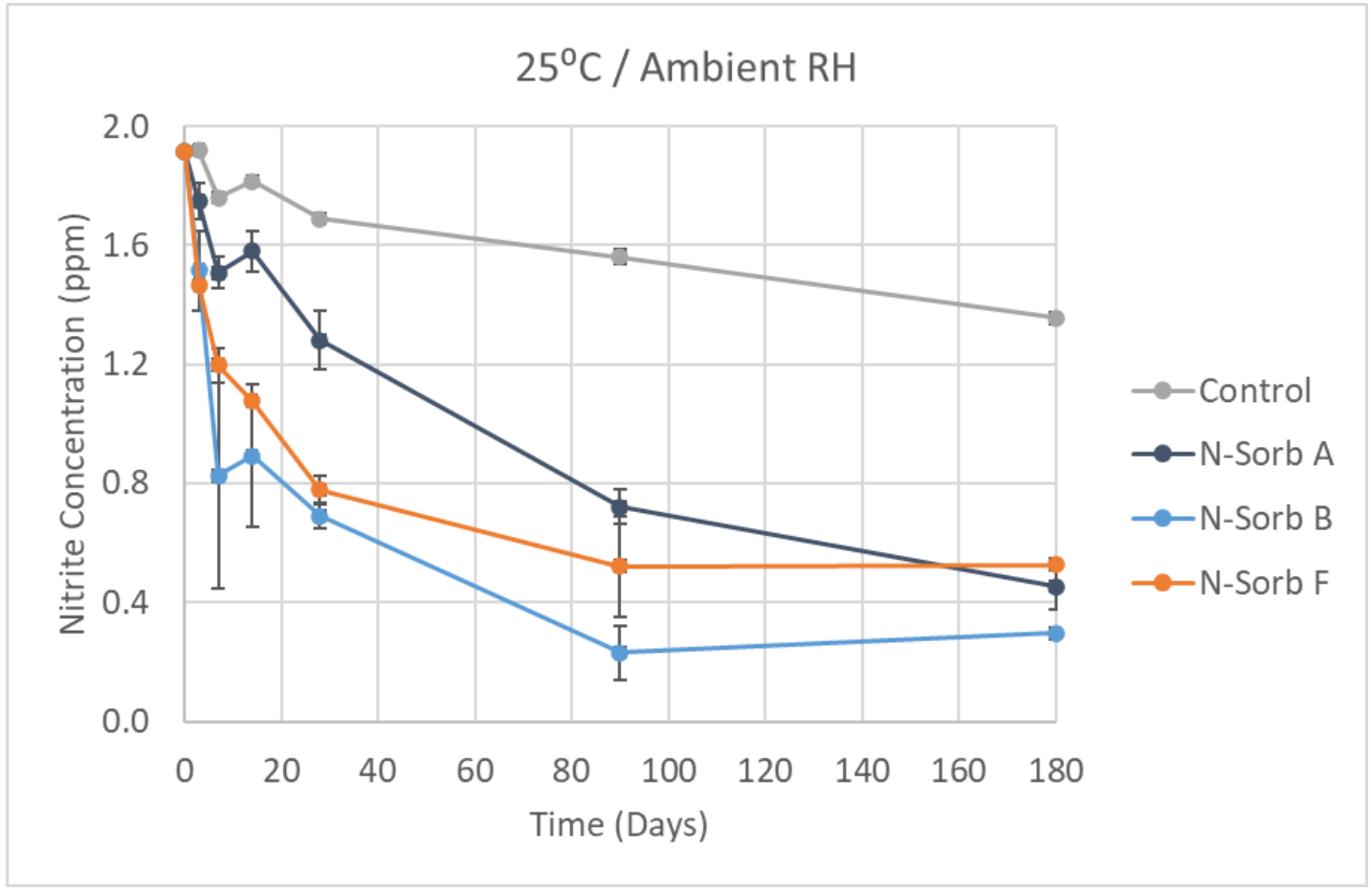
All N-Sorb films show significant absorption capacities.

Aptar CSP Technologies

Aptar
CSP Technologies

Nitrite Data

Nitrite Mitigation – Placebo Tablets



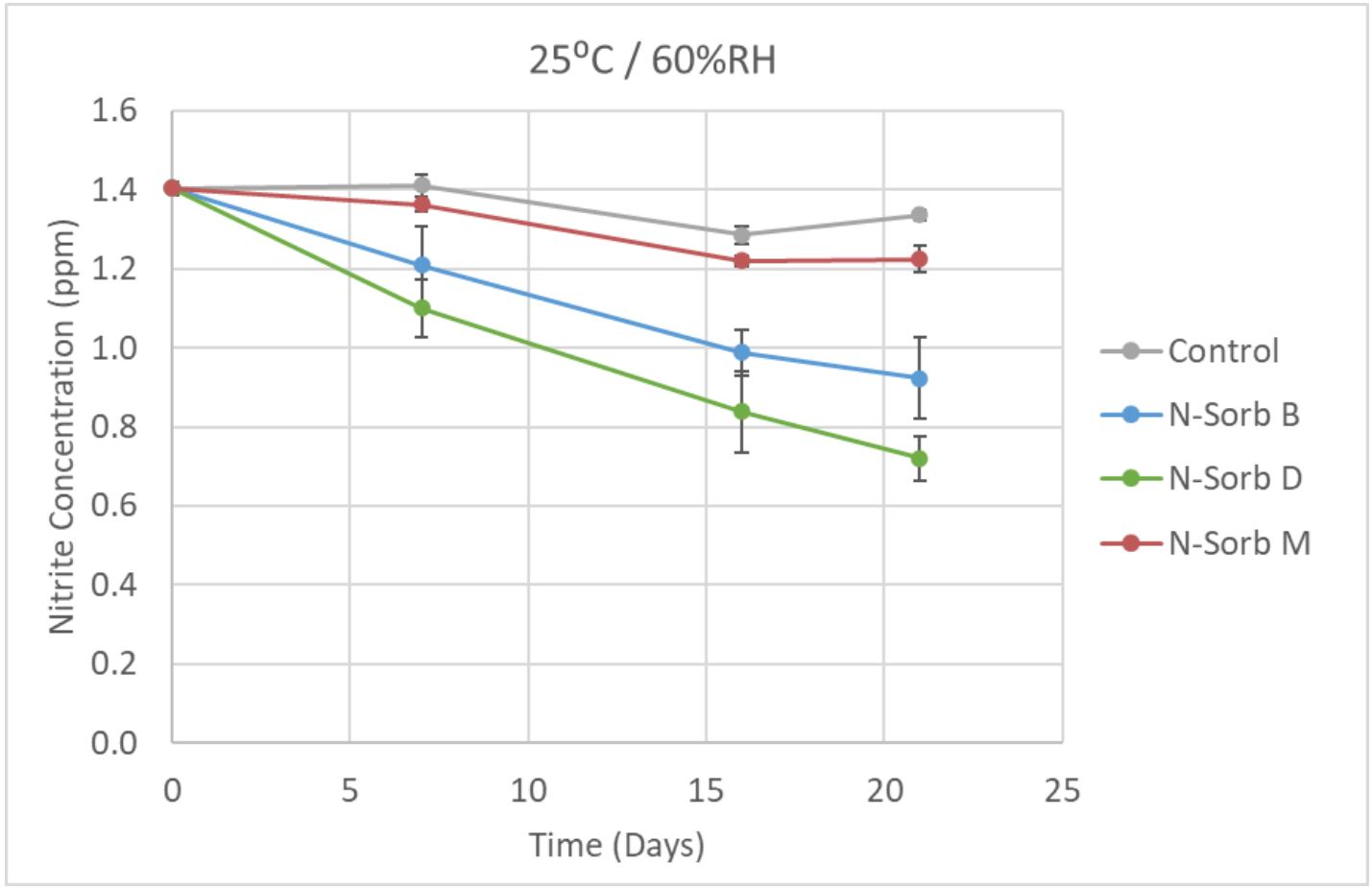
EXPERIMENTAL METHOD:

- 2 in^2 CSP N-Sorb Film
- Film and 11 tablets
  (66% MCC, 33% Lactose, 1% Mg St.)
- Sealed in foil bag
- Aged 180 days at **25°C**
- Characterization by Greiss reaction on LC-UV/VIS
  (LOQ = 0.1 ppm)

N-Sorb B reduced nitrite by >84% compared to controls.

Aptar CSP Technologies

Nitrite Mitigation – Bulk Excipient



EXPERIMENTAL METHOD:

- 300 g MCC
- Stored in HDPE pail lined with 2 poly bags
- 87 in^2 film total per pail
- Aged 21 days at **25°C/60%RH**
- Characterization by Greiss reaction on LC-UV/VIS (LOQ = 0.1 ppm)

N-Sorb D reduced nitrite by >49% compared to controls.

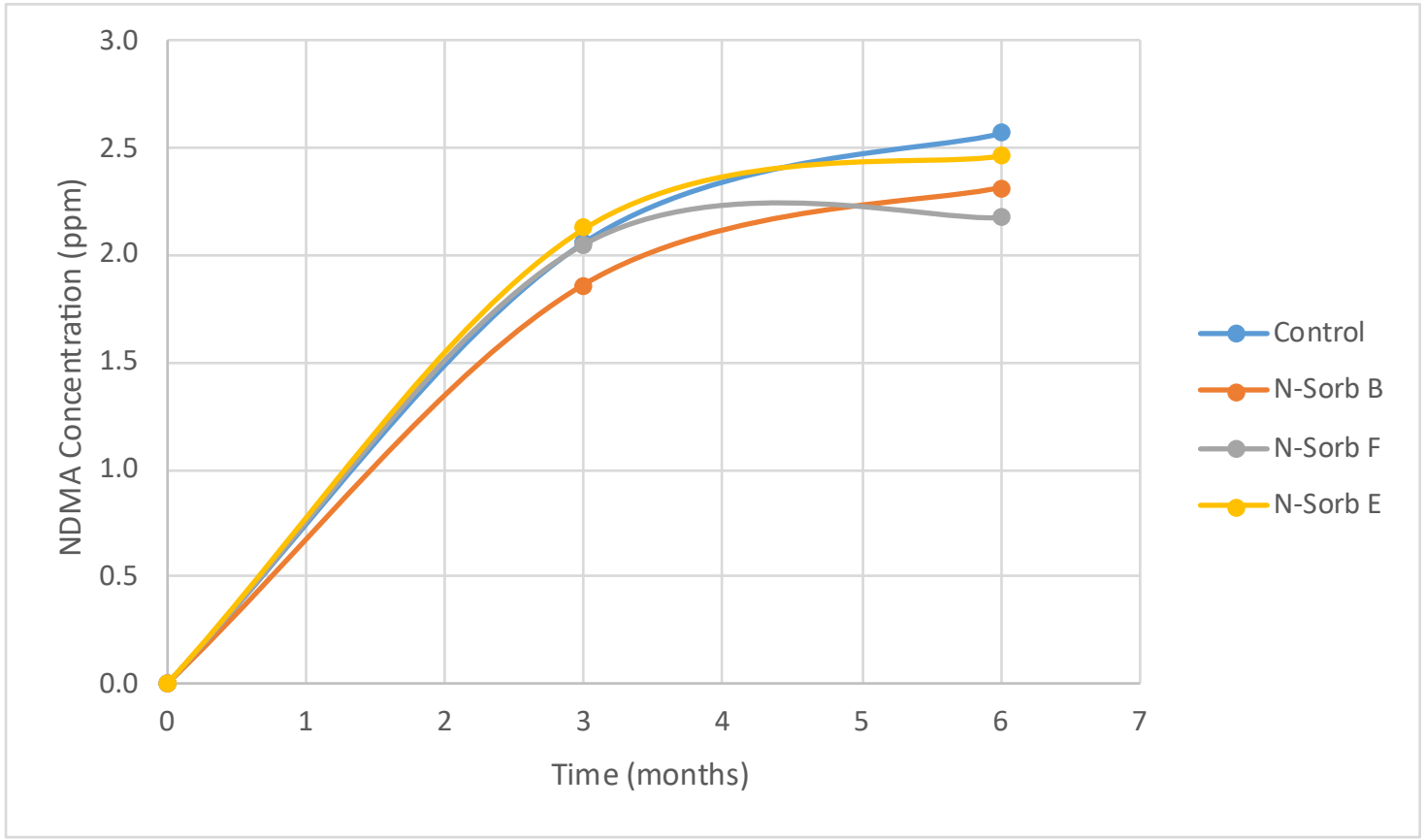
Aptar CSP Technologies

Aptar
CSP Technologies

Nitrosamine Data

NDMA Mitigation in Blister

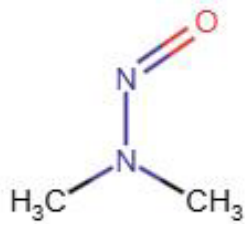
ICH 30°C / 65% RH – 6 months



EXPERIMENTAL METHOD:

- 1 cm^2 of film CSP N-Sorb Film
- Film and ranitidine with added nitrite capsule in blister
- Aged 6 months at **30°C/65% RH**
- Characterization by direct method on LC-QTOF

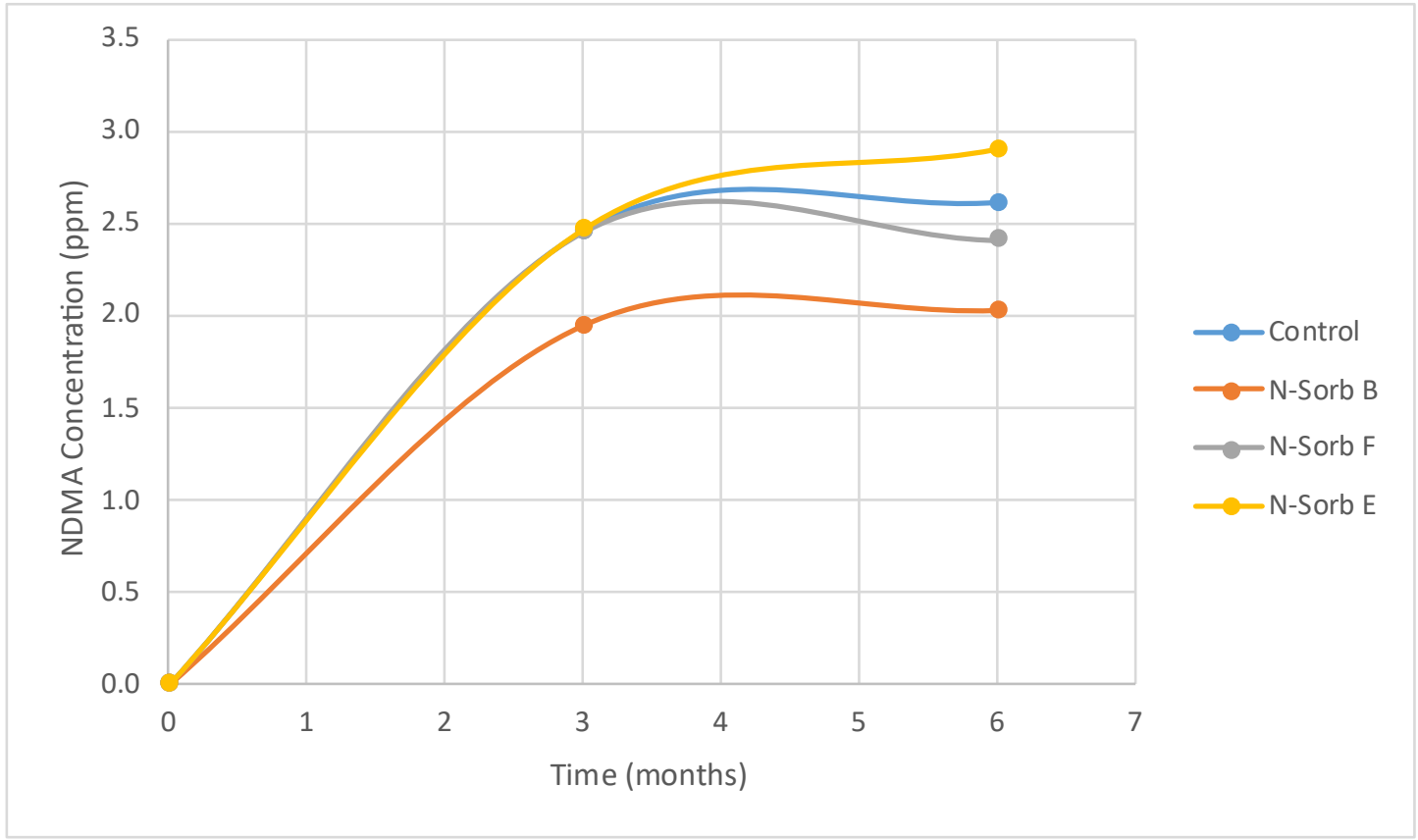
N-Sorb F reduced NDMA by 16% compared to controls.



Aptar CSP Technologies

NDMA Mitigation in Blister

ICH 40°C / 75% RH – 6 months



EXPERIMENTAL METHOD:

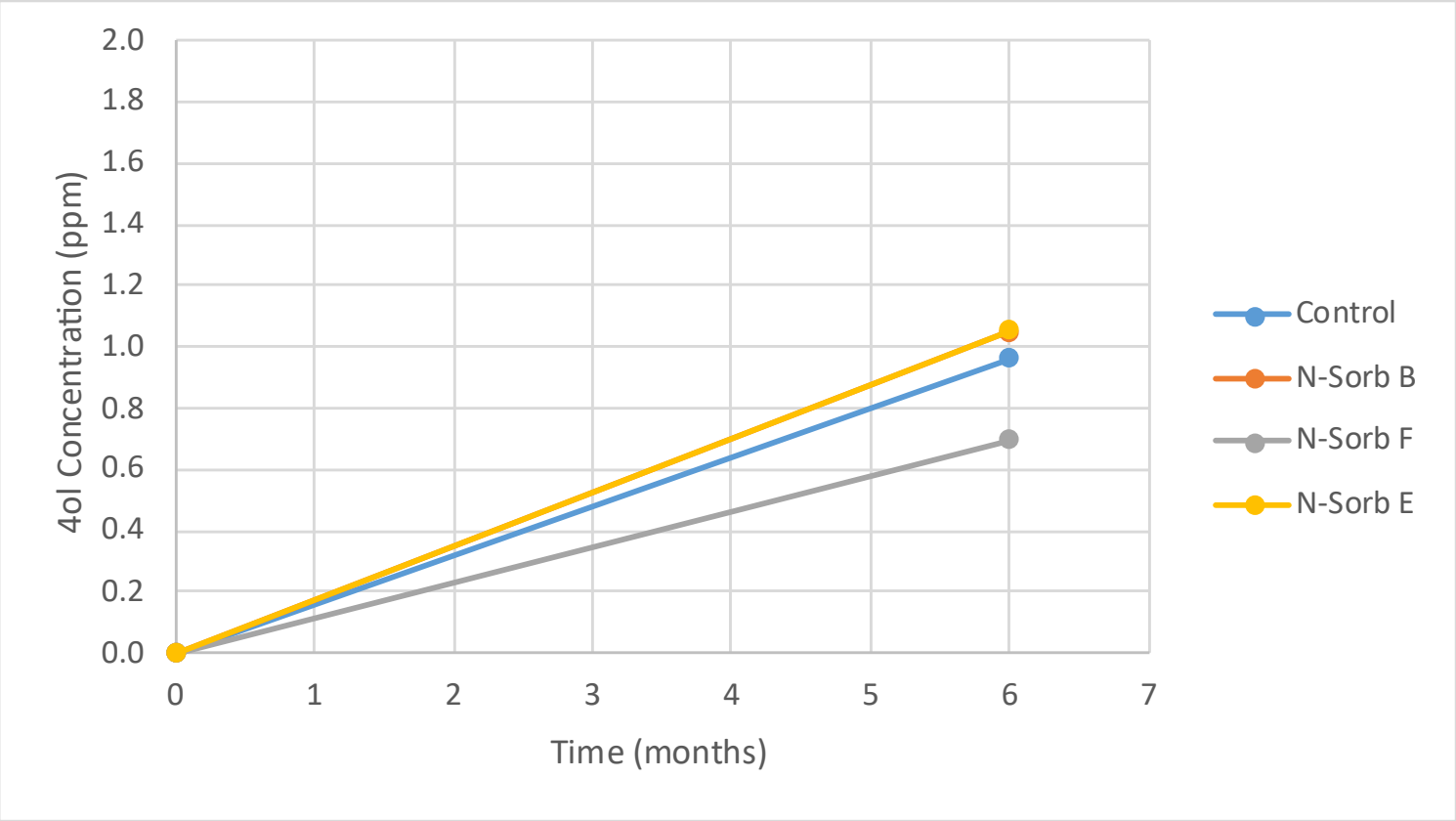
- 1 cm^2 of film CSP N-Sorb Film
- Film and ranitidine with added nitrite capsule in blister
- Aged 6 months at **40°C/75% RH**
- Characterization by direct method on LC-QTOF

N-Sorb B reduced NDMA by 22% compared to controls.

Aptar CSP Technologies

Model NDSRI Mitigation in Blister

ICH 30°C / 65% RH – 6 months

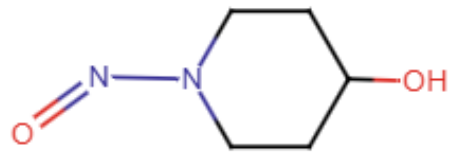


EXPERIMENTAL METHOD:

- 1 cm^2 of film CSP N-Sorb Film
- Film and 4-phenylpiperidin-4-ol HCl with added nitrite capsule in blister
- Aged 6 months at **30°C/65%RH**
- Characterization by direct method on LC-QTOF

N-Sorb F reduced 4ol by 27% compared to controls.

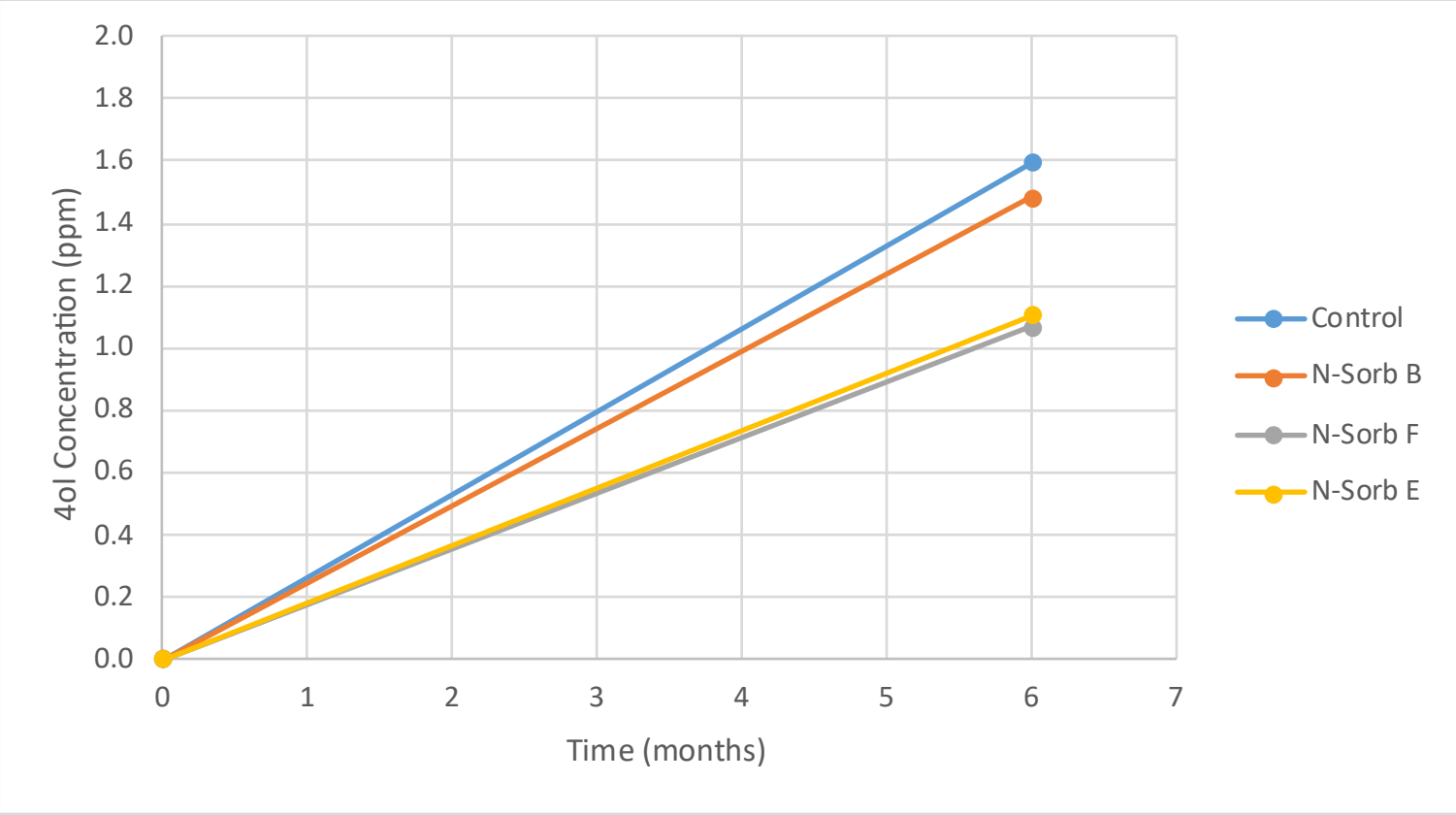
1-Nitrosopiperidin-4-ol (4ol) is a high molecular weight nitrosamine



Aptar CSP Technologies

Model NDSRI Mitigation in Blister

ICH 40°C / 75% RH – 6 months



EXPERIMENTAL METHOD:

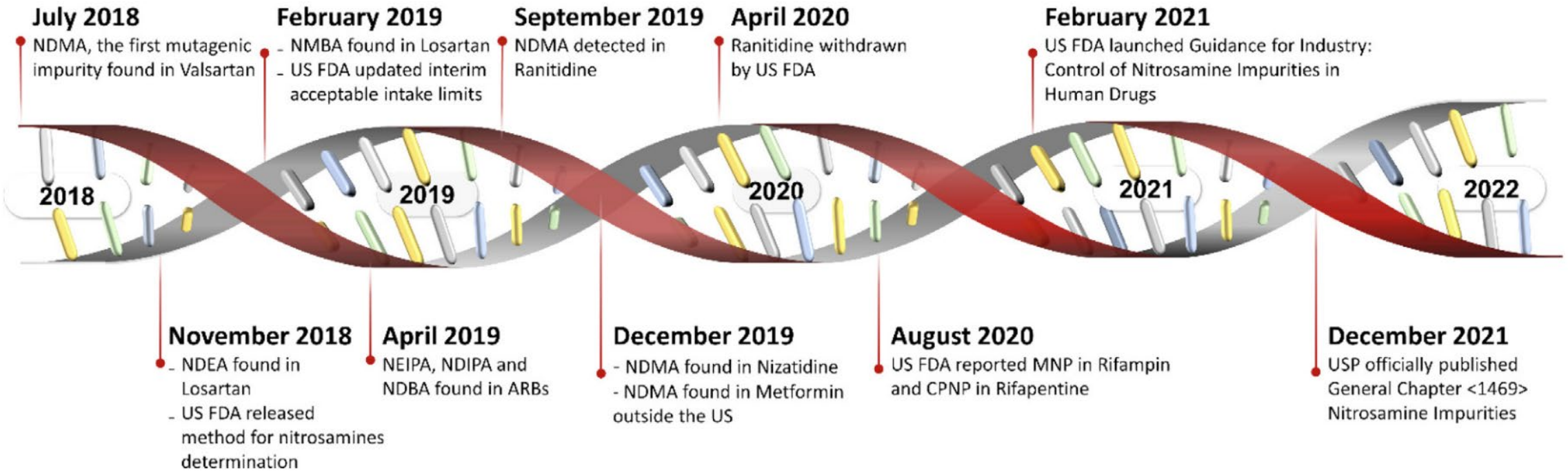
- 1 cm^2 of film CSP N-Sorb Film
- Film and 4-phenylpiperidin-4-ol HCl with added nitrite capsule in blister
- Aged 6 months at **40°C/75%RH**
- Characterization by direct method on LC-QTOF

N-Sorb E and F reduced 4ol by 30% compared to controls.

Aptar
CSP Technologies

Nitrosamine Regulatory Landscape

Introduction



What's the concern? Nitrosamines are Impurities / contaminations **- probable human carcinogens**

Evolution timeline of Regulatory Actions.

2018: EMA - Detected nitrosamine **(NDMA)** in **valsartan** → Product **recalls across EU**

2018 – 2019: FDA - Issued **recalls** of **valsartan, losartan, and ranitidine**

Aptar CSP Technologies

** W. Wichitnithad, S. Nantaphol, K. Noppakhunsomboon, P. Rojsitthisak, Saudi Pharmaceutical Journal, **2023**, 31, 295-311.*

Nitrosamine Control Regulatory History – Background

- Issuance of **Regulatory Guidance Documents**
  - 2020: FDA & EMA Issued guidance for nitrosamine **risk assessment, testing, and control implementation** requirements
  - 2021: WHO added nitrosamines to its **list of critical impurities**; issued **alerts on ranitidine and rifampin** – leading to **global alignment**.
  - 2023 - 2024: FDA Issued a updated revision of its Nitrosamine Guidance Document (Revision 2) to **include nitrosamine drug substance-related impurities (NDSRIs) category limits** and **updated timelines**

Nitrosamine Control Regulatory Landscape – Current Expectations

What should sponsors do?

Marketed Products

Complete **risk assessments** & **confirmatory testing**; report exceedances **by Aug 1 2025**

Products in Development

Integrate (or update with) **nitrosamine controls documentation** into Drug **Market Authorization Application** (MAA, IND, NDA, BLA, etc…) submissions

Pending Applications

Submit **amendments or responses addressing NDSRIs** and mitigation strategies

Aptar CSP Technologies

Review of Past Regulatory Enforcement Actions – 2018 to 2025

Pre-Market

- Clinical Trial Hold (at least 3 major cases)
- Complete Response Letters (at least 3 major cases)
  - Refuse To Accept

Reported Deficiencies

- Nitrosamine impurities **exceeding acceptable limits**.
  - additional testing including additional **stability data** and **repeat-dose studies on animals** especially for **reformulation**.
- Insufficient nitrosamine testing or risk assessments.
  - Risk assessments according to **ICH Q3D**, **M7(R2).**
- **CMC** (Chemistry, Manufacturing, and Controls) deficiencies.
  - Nitrosamines found **in production batches**.

Aptar CSP Technologies

Review of Past Regulatory Enforcement Actions – 2018 to 2025

Post-Market

- Form 483 Observations and Warning Letters (over 10 FDA 483, 7 WLs)
- Recalls and Market Withdrawals (over 40 recalls)
- Import Alert and Import Refusals

Deficiencies

- Gap in **risk assessments**, **control strategies**, or **documentation** of mitigation efforts
- **Releasing** products **without demonstrating** that nitrosamine **levels** were within acceptable intake **(AI) limits**
- **Failure to** adequately **investigate the root causes** of unexpected nitrosamine findings

Aptar
CSP Technologies

FDA Emerging Technology Program & Guidance Update

FDA Emerging Technology Program

- Promotes and facilitates adoption of innovative approaches to pharma product design and manufacturing.
- **CSP accepted 8/2024**
- **Ongoing meetings with FDA to help facilitate adoption of N-Sorb technology for nitrosamine mitigation**

Recommended Implementation Timelines

FDA recommends different implementation timelines depending on the regulatory status of the drug product and the type of nitrosamine impurity at issue. When recommending implementation timelines, FDA may consider factors such as the potential risk to the public health, the state of scientific knowledge, the scope of the problem, the feasibility and complexity of implementing effective prevention or mitigation strategies, and the risk of drug shortages. For example, to address a new nitrosamine impurity, the most effective mitigation may be reformulation, which could require substantial time to complete, and thus FDA may recommend a longer implementation timeline. A different nitrosamine impurity may be best addressed through replacement of packaging, for which FDA may recommend a shorter implementation timeline. If the need for the change is urgent due to a significant public health concern posed by the nitrosamine impurity, immediate implementation may be recommended. In some cases, FDA may also consider international harmonization in establishing implementation timelines.

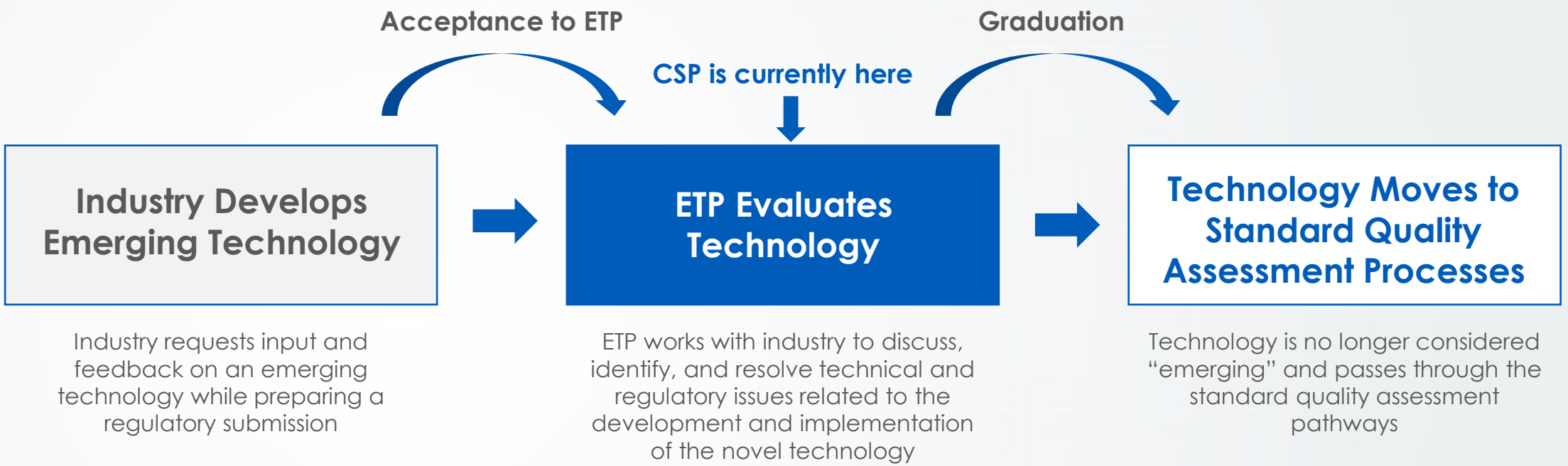
Table 4: Recommended Implementation Timelines

(Updated: 9/4/2024)

Nitrosamine Impurity	Performing Risk Assessment	Confirmatory Testing	Submission of Required Changes
Small Molecule Nitrosamines	March 31, 2021	When a risk is identified	October 1, 2023
NDSRIs	November 1, 2023	When a risk is identified	August 1, 2025

Aptar CSP Technologies

FDA Emerging Technology Program Overview



CSP has held **2 successful meetings** with the Emerging Technology Team (ETT).

CSP will be holding a **third meeting** with the FDA in **July 2025**.

Aptar CSP Technologies

ETP Meeting Outcomes – Key Takeaways – Ongoing Discussions

DMF Strategy – Alignment on DMF Content

- No initial concerns with material of constructions (N-sorb formulations)
- Safety data – Compliance to USP 661 expected
- Testing Method Validation approach for product release (CoC/CoA)
- Production Validation strategy

Presented R&D **Performance Data** generated so far

- Recommendations on study designs taking in considerations different factors temperature, humidity, tablet forms, formulations, etc…
- Results prove the potential to reduce Nitrite, NOx, and Nitrosamines – Product specific data to be generated to confirm for each application.

Final Drug Product Stability Study according to ICH expectations

- Post-approval Change Supplement – PAS (now) → CBE 30 (future)

Aptar CSP Technologies

Reformulation Vs Packaging Mitigation – Regulatory Considerations

Regulatory Consideration	Reformulation	Packaging Update with N-Sorb
FDA Submission Type	PAS (Prior Approval Supplement) or 505(b)(2)	PAS or potentially CBE-30 after experience gained
Regulatory Review Timeline	~10-12 months	~ 4-6 months (case dependent)
Risk of Impact on Bioequivalence	High - formulation changes can affect PK profile	Low - packaging change does not affect API PK
Stability Study Requirements	Full real-time & accelerated stability studies required	3-month accelerated + supporting long-term data may suffice
Need for Clinical Bridging Studies	Likely required for many drugs	Not typically required
Impact on Product Labeling	Label updates typically required	Minimal or no change
Manufacturing Process Changes	Significant - may involve new process validation	Moderate - packaging component qualification required
Time to Market Impact	Longer timeline - often >1 year	Shorter timeline - may be <6 months
Regulatory Burden	High	Moderate to Low

Aptar CSP Technologies

Acknowledgments

Ivy Comer

Aptar CSP Technologies

Jason Pratt

Aptar CSP Technologies

Questions & Answers

Thank You for Your Attention!

cspinfo@aptar.com
csptechnologies.com

Aptar CSP Technologies