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BIOTECH 2.0: RETHINKING NITROSAMINES – MOVING BEYOND COMPLIANCE

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NITROSAMINES – REGULATORY SPOTLIGHT
"NITROSAMINES: WHY THEY MATTER?"

FDA's Key Focus:

The detection of nitrosamines became a priority after contamination in drugs like sartans, ranitidine, and metformin led to recalls starting in 2018.Nitrosamines are classified as probable human carcinogens (Group 2A) by the IARC. High-profile recalls have triggered global scrutiny, leading to enhanced guidelines by the FDA, EMA, and other agencies.

Key Facts:

The presence of NDMA in valsartan was linked to a manufacturing change involving dimethylamine (DMA) and sodium nitrite under acidic conditions.NDMA, NDEA, and other nitrosamines often form when nitrites react with secondary or tertiary amines.

Call to Action:

Understanding nitrosamine formation and implementing controls is now an essential compliance metric for pharma companies globally.

Reference: FDA Guidance on Nitrosamines, 2024 Update

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"GUIDANCE IN ACTION: WHAT'S IMPLEMENTED?"

Risk Assessments:

Manufacturers must conduct nitrosamine risk assessments for all products, including existing and pipeline drugs.

Areas assessed include:

a. API Synthesis: Check for nitrosating agents or amines in the process.
b. Formulation: Evaluate excipients and interactions during manufacturing.
c. Packaging and Storage: Ensure materials do not promote impurity formation.

NDSRIs (Nitrosamine Drug Substance-Related Impurities):

- These impurities are specific to APIs and demand tailored control strategies.Risk assessments must include toxicity data for structurally unique nitrosamines.

Implementation Deadlines:

- 2021: Initial risk assessments.
- 2024: Full control strategy implementation for products already in the market.

Reference: FDA Nitrosamine Guidance Document, 2024

Pros and Cons of the Current Approach

Pros:

Enhanced Patient Safety: Standardized limits for nitrosamines ensure products are safer for patients.

Process Transparency: Encourages manufacturers to adopt rigorous quality-by-design (QbD) principles.

Encourages Innovation: Drives the adoption of advanced detection technologies such as LC-MS/MS and High-Resolution MS.

Cons:

Resource Heavy: Small and medium-sized companies may need help with the cost of additional testing, validation, and process modifications.

Regulatory Complexity: Navigating varying international requirements (FDA vs. EMA) adds operational challenges.

Reactive Nature: Much of the guidance responds to existing contamination rather than preventing future risks.

RISK ASSESSMENT AND CONTROL STRATEGIES

Key Components of Risk Assessment:

- **Identify Sources:** Screen raw materials, APIs, and excipients for nitrosamine precursors.
- **Process Evaluation:** Analyze every step of the synthesis process for potential nitrosation reactions.
- **Storage and Packaging:** Check the compatibility of packaging materials and storage conditions.

Control Strategies:

- **Process Optimization:** Replace amines and nitrosating agents with safer alternatives.Transition to green chemistry principles to minimize nitrosamine precursors.Develop catalytic processes that minimize byproduct formation.
- **Supplier Qualification:** Ensure raw materials meet stringent purity criteria. Enforce supplier quality agreements that mandate impurity thresholds.
- **Dedicated Equipment:** Prevent cross-contamination during multi-product manufacturing. Implement advanced monitoring tools like real-time release testing (RTRT).
- **In-Process Monitoring:** Regularly test intermediates and finished products.

Regulatory Requirements:

- Risk assessments must be filed for all products, with documented mitigation plans for identified risks.
- Periodic re-evaluation for lifecycle management.

References:

- *FDA Nitrosamine Control Plan Requirements*
- *EMA Q&A on Nitrosamin*

LESSONS LEARNED FROM RECENT NITROSAMINE RECALLS (2022-2024)

Product	Date	Issue	Key Lessons Learned
Duloxetine (Cymbalta)	October 2024	N-nitroso-duloxetine impurity detected, exceeding acceptable limits.	Conduct API-specific risk assessments for novel impurities.
Cinacalcet	November 2024	Presence of nitrosamine impurities exceeding acceptable intake limits.	Enforce stringent supplier audits and implement raw material specifications.
Dabigatran Etexilate Mesylate (Pradaxa)	March 2023	Contamination with N-nitroso-dabigatran impurity due to cross-contamination.	Implement in-process monitoring and control during manufacturing.
Quinapril Tablets	December 2022	Nitrosamine impurity levels above the FDA's proposed interim limit.	Perform degradation studies to identify risks early.
Sitagliptin	August 2022	Contamination with nitrosamine impurity NTTP.	Enhance stability monitoring to capture potential degradants.
Varenicline (Chantix)	September 2021	Detection of N-nitroso-varenicline above acceptable intake limits during long-term storage.	Conduct extended stability studies under real-world conditions.

Addressing nitrosamine impurities requires a paradigm shift toward prevention. The lessons from these recalls underscore the importance of predictive modeling, cross-functional collaboration, and embracing innovative control measures to ensure compliance and patient trust

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WHERE BIOTECHS SHOULD THINK DIFFERENTLY

Proactive Risk Modeling:

- Leverage AI and machine learning tools to predict impurity formation during API synthesis and storage.

Use predictive models for:

  - Reaction path analysis to avoid nitrosating conditions.
  - Degradation simulations under various storage environments.

Companies like Schrödinger and Certara provide AI-driven modeling software for predicting Impurity risk.

Cross-Functional Teams:

- Align R&D, manufacturing, and regulatory teams to create a unified impurity control strategy.
- Set up regular cross-functional reviews of impurity risk assessments during drug development.

Sustainable Practices:

- Transition to green chemistry principles to minimize or eliminate the use of nitrosamine precursors.options such as
  - Replace nitrosating agents with safer alternatives (e.g., avoiding tertiary amines).
  - Implement catalytic routes that reduce byproduct formation.
  - Use lifecycle strategies to make impurity management a competitive differentiator, highlighting compliance as a value proposition to partners and investors.

Move Beyond Compliance:

Implement lifecycle strategies where impurity control is not just a reactive measure but a competitive differentiator. Use nitrosamine control as a value proposition to potential partners and investors. Use robust impurity control frameworks as a competitive advantage in securing partnerships.Position impurity control as part of brand differentiation during licensing or M&A discussions.

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CREATIVE APPROACH TO CONTROL STRATEGIES

Go Beyond the Minimum:

- **Advanced detection techniques such as:**
  - High-Resolution Mass Spectrometry (HRMS): Precise detection of novel nitrosamines.
  - Surface-Enhanced Raman Spectroscopy (SERS): Emerging technology for rapid and trace-level impurity analysis.
  - Innovate in-process monitoring with real-time sensors to detect impurities during synthesis.
  - Implementing Process Analytical Technology (PAT) frameworks to minimize deviations.

Transform Supply Chains:

Conduct rigorous supplier audits to ensure compliance with nitrosamine risk controls.

Establish long-term partnerships with API and excipient suppliers to enforce strict impurity specifications.

Mandated traceability for all critical raw materials.

Design Safe Molecules:

Use computational chemistry to design APIs and formulations that inherently avoid nitrosamine precursors.

use of molecular design to eliminate degradation pathways leading to nitrosamines.

Innovate in Collaboration:

Collaborate with external CDMOs and academic institutions to explore cost-effective impurity control methods.

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CALL TO ACTION – THE PATH FORWARD

What's Next for Biotechs?

Adopt a Quality-First Culture:

- Make impurity control an integral part of organizational strategy, from early development to commercialization.
- Implement real-time release testing (RTRT) for rapid impurity detection and correction.
- Companies using RTRT techniques have faster FDA approvals due to demonstrated control.

Collaborate Globally:

- Leverage consortium efforts to standardize risk assessment tools and share analytical data.
- Example: Nitrosamine Consortium formed by multiple pharmaceutical companies to share best practices.

Invest in Knowledge:

- Train teams on:
  - Latest analytical methods (e.g., HRMS, SERS).
  - Regulatory updates from FDA, EMA, and WHO.
- Regularly refresh staff on root cause analysis techniques.

Closing Thought:

Addressing nitrosamines isn't just a compliance exercise—it's an opportunity to build trust with regulators, investors, and patients by prioritizing safety and innovation.

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With over 20 years of experience in the biotech, CDMO, and pharmaceutical industries, Dr. Kishore Hotha specializes in end-to-end CMC development operations. As the founder of Dr. Hotha's Life Sciences LLC, he provides strategic consulting in complex small molecules, ADCs, Oligonucleotides, and Peptides, supporting clients from discovery through regulatory submissions.

Dr. Hotha has led high-performing global teams, implemented scalable systems across international sites, and managed over 80 client projects. His contributions include supporting 90+ regulatory submissions (INDs, NDAs, ANDAs) and delivering 45+ successful commercializations. Known for his ability to navigate complex CMC challenges, he has transformed strategies to meet fast-to-market demands while enhancing R&D capabilities.

A prolific author with over 80 publications, Dr. Hotha also serves on editorial boards and frequently speaks at international conferences. His PhD in Analytical Chemistry and MBA in Project Management empower him to deliver innovative, results-driven solutions that advance drug development and commercialization.

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ABOUT US

Dr. Hotha's Life Sciences LLC is a Global biotech consulting firm specializing in comprehensive pharmaceutical and life sciences solutions. With more than two decades of expertise, we partner with clients to guide them through the entire drug development lifecycle—from early discovery to market entry. Our proficiency spans therapeutic areas, focusing on small and large molecules, ADCs, Oligonucleotides, and Peptides, ensuring successful outcomes for drug substances and products.

OUR MISSION

At Dr. Hotha's Life Sciences LLC, we transform complex challenges into clear, actionable strategies. Our mission is to simplify CMC drug development by providing bespoke solutions for regulatory submissions, including INDs, NDAs, and ANDAs. We are dedicated to delivering fast-to-clinic and fast-to-market strategies that maximize quality, accelerate project timelines, and meet stringent regulatory standards.

Complexity to Clarity Together

With a strong focus on early-phase to late-phase projects, Drug substances, and Drug products, we offer end-to-end consulting services that guide our clients through every development phase—from initial discovery to regulatory submission.

Our Approach:

Partner: We believe in solid collaborations. By partnering closely with our clients, we build tailored strategies that align with your unique goals and challenges.

Plan: We provide strategic planning that encompasses the entire development lifecycle. Whether navigating complex regulatory environments or optimizing lab operations, we ensure that your project is equipped for success.

Prosper: With our expertise and guidance, you can bring life-saving therapies to market faster, achieving sustainable growth and long-term success.

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