

# PHARMACEUTICAL NEWSLETTER

CONSTANTLY PURSUING NEW CHALLENGES TO CONTRIBUTE TO BETTER HUMAN HEALTH



Fuji Chemical Industries

## Fujicalin®: Your Partner in Mitigating Nitrosamine Impurities in Drug Products

# Fujicalin®

This newsletter highlights how **Fujicalin®**, a low nitrite content Dicalcium Phosphate Anhydrous (DCPA), can support manufacturers in mitigating these risks effectively.

### THE ISSUES

The rise of nitrosamines in pharmaceuticals is a significant concern due to their potential cancer risk. The FDA has released updated guidelines urging manufacturers to actively manage the risks linked to nitrosamine impurities.

#### Regulatory Challenges:

The presence of nitrosamines can lead to regulatory actions including product recalls, stringent testing requirements, and the need for risk assessments, which can be costly and complex for pharmaceutical manufacturers.

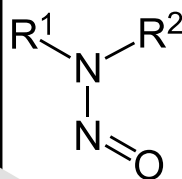


#### Reputational Damage:

Companies facing issues with nitrosamine contamination can suffer from reputational damage, impacting consumer trust and potentially leading to decreased sales and market share.



### UNDERSTANDING N-NITROSAMINES IN PHARMACEUTICALS



Nitrosamines are classified as probable human carcinogens, posing a significant health risk as they can potentially lead to cancer when present in significant quantities over extended periods. The primary risk for the presence or formation of N-nitrosamines in drug products arises from the interplay of **three critical factors**:

#### Vulnerable Amines:

The presence of secondary or tertiary amines, which are more susceptible to nitrosation.



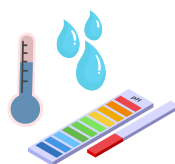
#### Nitrosating Agents:

The availability of nitrosating agents that can react with these amines to form N-nitrosamines.



#### Favorable Conditions:

Specific environmental conditions, such as elevated temperatures, acidic environments, and the presence of moisture in the liquid phase, which can facilitate the nitrosation process.



### THE TIMELINE

#### July 2018:

EMA recalls products containing Valsartan contaminated with NDMA.

#### September 2020:

FDA releases guidelines titled "Control of Nitrosamine Impurities in Human Drugs."

#### September 2024:

FDA updates these guidelines to enforce stricter monitoring and mitigation strategies.

### NITRITES IN EXCIPIENTS

- ⚠️ Nitrite concentration varies by excipient chemistry, manufacturer, and batch.
- ⚠️ Process water, raw materials, and processing conditions can introduce nitrites, but process water typically poses low risk, with levels usually below WHO limits.
- ⚠️ While nitrites are present in many excipients, reducing them is challenging; complete elimination is impractical and alternatives like scavengers should be considered.
- ⚠️ Each drug product should assess the potential risk of nitrites in its specific excipient.

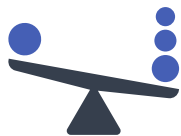
## STRATEGIC MEASURES TO MINIMIZE NITROSAMINE RISKS IN PHARMACEUTICAL MANUFACTURING

To effectively manage the risk of N-nitrosamines in drug formulations, manufacturers should implement control strategies based on thorough risk assessments:



### Nitrites Alone Are Not Sufficient:

The presence of nitrites in an excipient does not automatically lead to nitrosamine formation; a vulnerable amine and specific reaction conditions are also required.



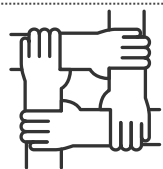
### Excipient Contribution:

The nitrite contribution from an excipient depends on its quantity in the formulation, highlighting the importance of careful selection.



### Mitigation Strategies:

Manufacturers can reduce risks by using scavenger substances and minimizing moisture through formulation, processing, and packaging techniques.



### Collaborative Communication:

Open discussions between excipient suppliers and drug manufacturers are essential for ensuring a clear understanding of excipient information and effective risk management.

## RESPONSIBILITIES OF EXCIPIENT SUPPLIERS

To effectively manage the risk of N-nitrosamines in drug formulations, manufacturers should implement control strategies based on thorough risk assessments:

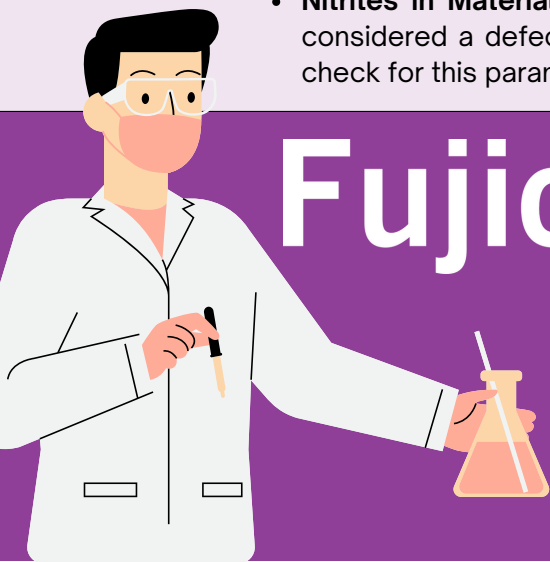
- **IPEC Questionnaire Assistance:** The IPEC questionnaire helps excipient suppliers give detailed information about their products and the processes used to make them. This supports drug manufacturers in conducting thorough risk assessments.
- **Voluntary Testing:** While not mandatory, excipient manufacturers can choose to test their products for N-nitrosamines or nitrites and share the results if necessary
- **Nitrites in Materials:** Finding nitrites in materials, either current or from past batches, is not considered a defect. Standard Certificates of Analysis and Pharmacopeia tests usually do not check for this parameter.

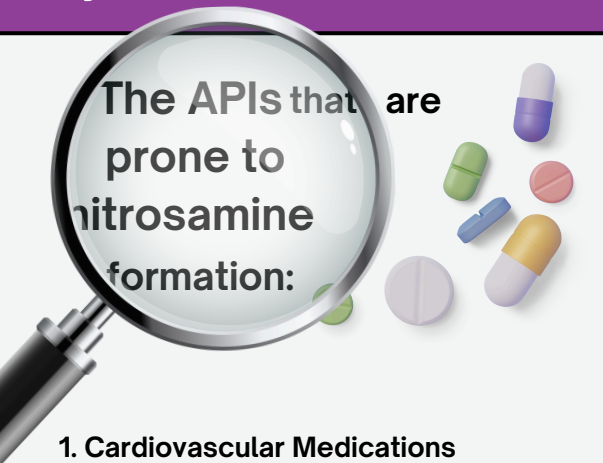
Research indicates that approximately **40%** of APIs could be potential nitrosamine precursors, particularly those containing secondary or tertiary amines, emphasizing the need for vigilant risk assessment and mitigation strategies in pharmaceutical formulations.



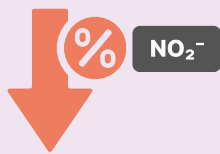
# Fujicalin® A Strategic Solution

Fujicalin® is a specialized excipient that enhances tablet formulations while reducing nitrosamine formation risk. Its low nitrite content prevents harmful impurities, and its high specific surface area from a patented spray-drying process improves blending and uniformity. Fujicalin® also provides excellent flow and compression properties, enabling robust tablet production and reducing equipment wear.





## Fujicalin® 3 Key Benefits



### Low Nitrite Content

Reduces the risk of harmful nitrosamines by maintaining low nitrite levels.



### High Specific Surface Area

Its unique spray-drying process creates porous spheres, enhancing blending and uniformity in formulations.



### Excellent Flow and Compression Characteristics

Produces strong tablets with minimal abrasion on tableting machines, ensuring smoother operations and less equipment wear.

### 1. Cardiovascular Medications

- Beta Adrenoreceptor Blockers and Beta Agonists: *Propranolol, Atenolol, Bisoprolol, Metoprolol*
- ACE Inhibitors: *Enalapril, Ramipril, Quinapril, Lisinopril*

### 2. Migraine Treatments

- Triptans: *Sumatriptan, Rizatriptan, Naratriptan, Almotriptan*

### 3. Gastrointestinal Medications

- H2 Blockers: *Ranitidine, Nizatidine*

### 4. Diabetes Management

- Antidiabetics: *Metformin*

### 5. Miscellaneous APIs

- Sitagliptin, Verenicline, etc.*

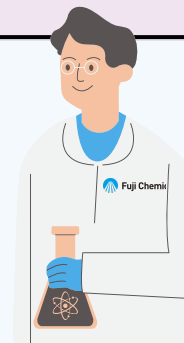
Please contact us to know the detailed list of APIs prone to nitrosamine formation.



## Fuji Chemical Industries

### Let Us Help You Navigate Nitrite Challenge

Fuji Chemical Industries offers a robust nitrosamine risk assessment for **Fujicalin®** (DCPA), adhering to the latest IPEC guidelines. This assessment enables drug manufacturers to evaluate and mitigate



the risks associated with nitrosamines effectively. Our findings indicate that the risk of nitrosamine contamination in **Fujicalin®** is extremely low, as we do not use any raw materials containing amines, nitrites, or nitrosating agents in its production.

**Fuji Chemical Industries** is dedicated to supporting customers through every step of the formulation process. Our commitment includes:



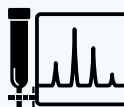
**Nitrosamine Risk Assessment:** Manufacturers can collaborate with Fuji Chemical Industries for a comprehensive nitrosamine risk assessment related to Fujicalin®, ensuring FDA compliance and product safety.



**Regulatory Compliance:** Fuji Chemical Industries actively monitors regulatory changes and has rigorously tested Fujicalin® for nitrate and nitrite content using ion chromatography, aligning with current standards.



**Expert Guidance:** A team of experts offers technical support and training to help customers optimize Fujicalin® use in various formulations, especially those sensitive to heat and moisture.



### Rigorous Testing Protocols:

We extensively tested Fujicalin® with ion chromatography, and the results from three separate lots demonstrate remarkably low levels of nitrates and nitrites:

Lot Number	Nitrate Ion (ppm)	Nitrite Ion (ppm)
CP304511	1.2	N.D.
CP304512	N.D.	N.D.
CP304513	N.D.	N.D.

With nitrites detected at only 0.004 ppm in the water used for **Fujicalin®**'s manufacturing process, our commitment to quality is clear.

## REGULATORY UPDATES FROM USFDA AND HEALTH CANADA

- The September 2024 **USFDA** guidance on nitrosamines introduces detailed recommendations for assessing and controlling NDSRIs, alongside updated acceptable intake limits and implementation timelines.<sup>3</sup>




- Health Canada** has recently updated its guidance on nitrosamine impurities, adding ten (10) additional nitrosamine impurities along with their corresponding CPCA-derived Acceptable Intake (AI) limits.<sup>4</sup>



## SUMMARY

**Fujicalin®** is your ultimate ally in the fight against nitrosamine risks in drug formulations. As a leading excipient, it provides a low-risk solution for manufacturers seeking to ensure the safety of their products.

By partnering with Fuji Chemical Industries, you can access comprehensive nitrosamine risk assessments tailored specifically for **Fujicalin®**, empowering you to make informed decisions that prioritize patient safety.



What sets **Fujicalin®** apart? Rigorous Testing and Compliance. Fuji Chemical Industries stays ahead of the curve by continuously monitoring regulatory changes and conducting thorough tests for nitrate and nitrite content in **Fujicalin®**. Utilizing ion chromatography, a trusted analytical method, we confirm that **Fujicalin®** contains extremely low levels of nitrates and nitrites, further minimizing the risk of nitrosamine formation.

With **Fujicalin®**, you gain peace of mind knowing that no raw materials containing amines or nitrosating agents are used in its production. This commitment to quality means that you can confidently incorporate Fujicalin® into your formulations, knowing it meets the highest safety standards.

**Choose Fujicalin® - where innovation meets safety.**

Let us help you navigate the complexities of nitrosamine risks, ensuring your drug products are not only effective but also safe for consumers. Partner with us today for a future of worry-free manufacturing!



**Fuji Chemical Industries**

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#### References:

- [https://ipec-federation.org/wp-content/uploads/2024/02/20240227\\_IF\\_Nitrosamines-Position-Paper-v2\\_F.pdf](https://ipec-federation.org/wp-content/uploads/2024/02/20240227_IF_Nitrosamines-Position-Paper-v2_F.pdf)
- EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU. Press Release, 05 July 2018.
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits>
- <https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/nitrosamine-impurities/established-acceptable-intake-limits.html>