ARTICLE

The history, regulatory journey and Fortrea's revival of Rifampin in DDI studies

A KEY QUESTION

When safety concerns emerged over the use of rifampin in DDI studies, and the available alternatives less than ideal, what did it take to safely reintroduce it?

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Drug-drug interaction (DDI) studies are a cornerstone of modern clinical pharmacology, ensuring that new therapies and existing medications are safe and effective when administered alongside each other. Among the tools available to researchers, rifampin has long stood out as the preferred agent for inducing the cytochrome CYP3A enzyme, a pathway responsible for metabolizing approximately 30% of all small molecule drugs. However, recent years have seen rifampin's role in DDI studies decline due to safety concerns related to levels of impurities[1], resulting in a search for suitable alternatives. This article traces the history of rifampin in DDI research, the FDA's evolving response to nitrosamine impurities, the limitations of alternative inducers and Fortrea's innovative solution in collaboration with Emery Pharma.

Rifampin: The gold standard for CYP3A induction

Rifampin, a semi-synthetic antibiotic derived from amycolatopsis mediterranei, was introduced in the late 1960s for the treatment of tuberculosis and other serious infections. Its unique pharmacological profile—potent induction of CYP3A and other drug-metabolizing enzymes—establish it as the preferred CYP3A induction agent for DDI studies. For decades, rifampin enabled researchers to reliably assess how investigational drugs interact with the body's metabolic pathways, providing clinical data and supporting regulatory submissions worldwide.

Rifampin exhibits desirable properties liked by researchers when investigating medicinal products:

- **Potency and predictability:** Rifampin exhibits a strong induction of CYP3A. It also significantly induces other isoenzymes, including CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2B6. This broad induction is why rifampin can reduce the effectiveness of many other medications by increasing their metabolism

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- **Safety and tolerability:** Compared to other strong index inducers of CYP3A, rifampin has a more favorable safety profile and is generally well tolerated in healthy participants
- **Clinical relevance:** The data generated from rifampin-based DDI studies are directly applicable to real-world clinical scenarios, making it the preferred precipitant for sponsors

The nitrosamine challenge: FDA scrutiny and market disruption

Discovery of nitrosamine impurities

Nitrosamines are a class of compounds with known carcinogenic potential and their presence in pharmaceuticals has prompted global regulatory action. In 2020, the FDA announced the detection of 1-methyl-4-nitrosopiperazine (MNP), a nitrosamine impurity, in rifampin. The FDA initially set an acceptable intake limit for MNP at 0.16 ppm, but in 2021 published results from tested batches where they found that every lot of rifampin tested exceeded this threshold.

To mitigate shortages and enable continued access for patients with tuberculosis, the FDA temporarily allowed rifampin with MNP levels up to 5.0 ppm for patient use. But many health authorities suggested alternatives to the use of rifampin in healthy participant studies. This decision caused contract research organizations (CROs) and sponsors to seek alternative CYP3A inducers for DDI studies, disrupting established protocols and delaying drug development timelines.

Key FDA actions

- **2020:** Detection of unacceptable MNP levels in rifampin
- **2021:** FDA publishes laboratory analysis results of MNP levels of some lots of rifampin and recommend an acceptable limit; temporary increase in allowable limits for patient use
- **2023:** Release of final guidance on nitrosamine impurities which recommends establishing the acceptable intake limits (RAILs) for drug substance-related impurities based on the predicted carcinogenic potency categorization approach[2]
- **Current guidance:** The FDA has published a RAIL for MNP of 400 ng/day (which equates to a control limit of 0.67 ppm based on a 600 mg/day dose of rifampin), with an interim control limit of 5.0 ppm, or an interim RAIL of 3000 ng/day, for rifampin injection and capsules[2]

The search for alternatives: Carbamazepine and phenytoin

Alternative induction agents

With rifampin sidelined, researchers turned to carbamazepine and phenytoin as alternative strong index CYP3A inducers. While these agents do not carry the same nitrosamine impurity risk, they present other significant challenges:

Carbamazepine

- **Requires dose titration:** Unlike rifampin, carbamazepine must be titrated to the target dose level to manage tolerability, prolonging study timelines
- **Genetic testing needed:** Subjects must be screened for HLA-B*15:02 and HLA-A*31:01 alleles to reduce the risk of severe dermatologic reactions
- **Higher drop-out risk:** Adverse events are more common, increasing the number of subjects needed and raising costs
- **Longer study duration:** Extended dosing schedules mean longer trials and higher expenses

Phenytoin

- **Narrow therapeutic index:** May require careful monitoring to avoid toxicity
- **Genetic exclusions:** Poor metabolizers of CYP2C9 and CYP2C19, as well as carriers of HLA-B*15:02, must be excluded
- **Intermediate study duration:** Not as well studied or as strong of an inducer as part of a DDI study when compared to rifampin, presents risks to the conclusion of the trial

Comparative table

Source: Fortrea generated data, 2025

Feature	Rifampin	Carbamazepine	Phenytoin
Doses titration	Not required	Required	Not required
Safety profile	Good	Rash, dizziness	Narrow index, rash
Study duration	Short	Long	Medium
Nitrosamine risk	Present (now managed)	None	None
Regulatory support	U.S.—Conditional	Supported	Supported

Why alternatives are less than ideal

The shift away from rifampin toward carbamazepine has in some cases resulted in longer, more expensive studies and introduced additional risks to participant safety. While carbamazepine lacks the robustness and predictability of rifampin as an inducer, the other alternative, phenytoin, more closely approximates rifampin's induction strength, but brings its own safety concerns and does not replicate the broader range of induction effects seen with rifampin. As a result, neither agent represents a fully optimal substitute for DDI research.

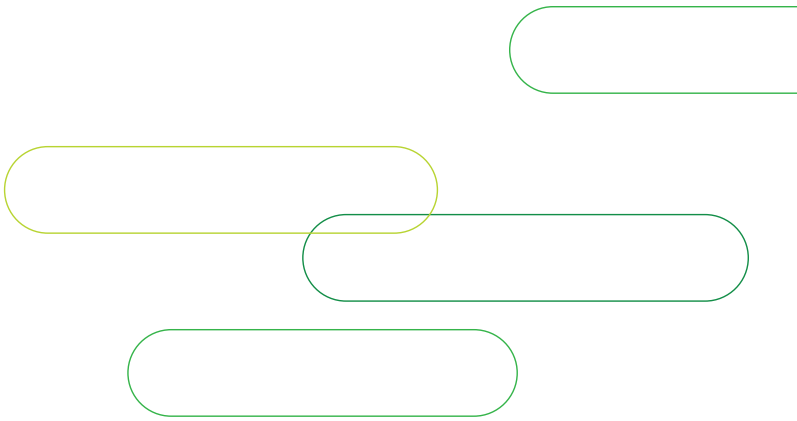
Fortrea and Emery Pharma: Restoring rifampin's role

The strategic collaboration

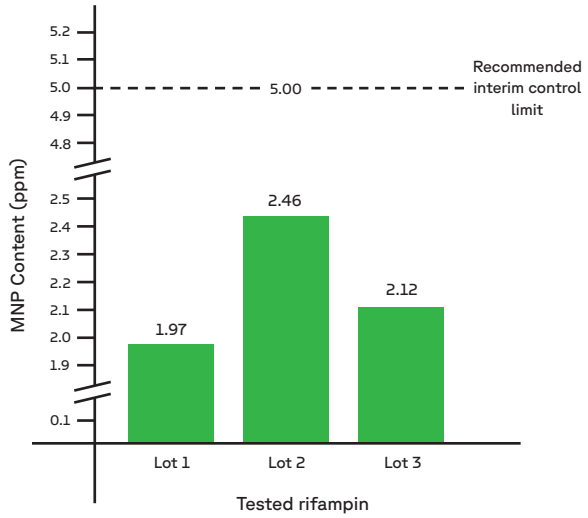
Recognizing the critical need for rifampin in DDI studies, Fortrea has collaborated with Emery Pharma to implement a rigorous lot-by-lot testing protocol for nitrosamine impurities. Emery Pharma's expertise in analytical and bioanalytical testing under Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) assures sponsors that only rifampin lots that fall below the current FDA guidance threshold of 5.0 ppm MNP* are used in clinical trials.

How the collaboration works

- **GMP MNP testing:** Each lot of commercial rifampin is tested for MNP levels prior to dosing in a DDI clinical trial
- **Rapid turnaround:** Testing is completed within four weeks of arrival at Fortrea using established GMP-qualified methods. The testing of rifampin takes place in parallel to other study startup activities, meaning no impact on overall timelines
- **Compliance:** Only rifampin lots that meet the current FDA recommended interim control limit (<5.0 ppm) are used
- **Sponsor flexibility:** Fortrea can source and test rifampin lots as needed, providing real data analysis for each batch
- **Regulatory assurance:** This approach establishes compliance with FDA's latest guidance and reassures sponsors and regulators of participant safety



* Per current August 2025 FDA acceptance requirements



Published here are the results of three batches of rifampin tested by Emery Pharma and made available to Fortrea sponsors for DDI studies. The GMP certification provides the proof regulators are seeking that MNP content is below the FDA threshold, permitting the DDI study to proceed with each tested batch.

Impact on clinical research

By restoring access to rifampin for DDI studies, Fortrea and Emery Pharma are enabling sponsors to:

- **De-risk early-phase trials:** Reliable induction of CYP3A with a well-characterized agent
- **Accelerate timelines:** Shorter study durations compared to alternatives
- **Enhance data quality:** Consistent, high-quality pharmacokinetic data
- **Improve participant safety:** Reduced adverse event risk and drop-out rates

The wealth of clinical data, better safety and tolerability and limited impact of nitrosamine impurities (when managed appropriately) all support the continued use of rifampin.

FDA guidance

The FDA's evolving guidance on nitrosamine impurities reflects a balance between safety and the need for effective clinical research tools. By raising the acceptable intake limit for MNP and endorsing rigorous testing protocols, the FDA has paved the way for rifampin's return to DDI studies—provided that sponsors adhere to strict compliance measures.

Scientific and regulatory endorsement

Supporting evidence

Recent presentations at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) conference have highlighted the reliability and benefits of rifampin in DDI studies.

Conclusion

The journey of rifampin in DDI research is a testament to the dynamic interplay between scientific innovation, regulatory oversight and clinical need. While nitrosamine impurities posed a significant challenge, the collaborative efforts of Fortrea and Emery Pharma—supported by FDA guidance—have restored rifampin's role as the gold standard for CYP3A induction in DDI studies. Sponsors can now conduct efficient, safe and compliant trials, accelerating the development of new therapies and enhancing patient outcomes.

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