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Thermal-Cycling Stability of Cefixime Granules for Oral Suspension: Experimental Evaluation and FMEA-Based Risk Analysis for Pharmaceutical Distribution

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ABSTRACT

Transportation of pharmaceutical products frequently exposes them to environmental stress, particularly temperature excursions that may compromise stability. The aim of this study was to evaluate the impact of thermal-cycling conditions on the stability of Cefixime granules for oral suspension, used here as a model product requiring robust distribution stability. A thermal-cycling study was conducted in accordance with ICH and WHO stability guidelines. A single pilot batch of the finished product was subjected to three consecutive cycles of −20 °C, +5 °C, and +30 °C, representing cumulative stress over approximately one month. Critical quality attributes including physical appearance, pH, viscosity, dispersibility, dissolution, assay, related substances, and microbiological quality were evaluated after each cycle. In parallel, a Failure Modes and Effects Analysis (FMEA) was performed to assess transport-related risks and identify control strategies. All tested parameters remained within acceptance limits throughout the study. Physical characteristics (appearance, odor, pH, viscosity, and dispersibility) were unchanged. Assay values for both Cefixime and the preservative sodium benzoate were consistent across conditions. Dissolution exceeded 80% within 15 minutes in all samples. Related and degradation products did not surpass specified thresholds, and microbiological quality complied with pharmacopoeia requirements. The FMEA identified customs delays, prolonged high-temperature exposure, and freezing risk as the most critical transport-related hazards. Residual risk was substantially reduced by validated packaging, dual temperature monitoring, and defined time-out-of-storage limits. The study demonstrated that Cefixime granules for oral suspension retain stability under thermal-cycling conditions simulating transport. Combined with FMEA, the findings confirm that the product can tolerate excursions between −20 °C and +30 °C for up to one month, ensuring suitability for international distribution. Importantly, as this investigation was based on a pilot batch, confirmation with multiple production batches is recommended for broader regulatory acceptance. The integrated approach highlights the importance of combining experimental stability data with structured risk analysis to support robust pharmaceutical supply chains.

Keywords

Cefixime, Oral suspension, Stability, Thermal cycling, Pharmaceutical transport, Distribution, FMEA, Risk analysis.

Introduction

Pharmaceutical stability is a cornerstone of quality assurance, ensuring that medicinal products maintain their identity, strength, purity, and overall quality throughout their intended shelf life. According to ICH Q1A(R2), stability studies provide evidence of how the quality of a drug product varies over time under the influence of environmental factors such as temperature, humidity, and light [1]. While storage in controlled facilities is relatively constant, the distribution and transportation phases expose

products to highly variable environments, making this stage one of the most critical in safeguarding product quality [2,3].

One of the most frequent deviations in pharmaceutical distribution is the occurrence of temperature excursions. These excursions may result from climatic transitions, customs clearance delays, improper handling at transit points, or extended last-mile delivery times [4-6]. Studies indicate that between 8–20% of temperature-sensitive pharmaceutical shipments experience at least one deviation during transit, even under validated cold-chain conditions [7,8]. Such excursions can lead not only to chemical and microbiological instability, but also to regulatory non-compliance, product recalls, and patient safety risks [9,10]. Additional deviations such as mechanical stress, humidity ingress, and data logger failure further complicate distribution quality and integrity [11-13].

Recognizing these risks, regulatory frameworks have strengthened guidance on transport validation. The WHO Model Guidance for the Storage and Transport of Time- and Temperature-Sensitive Pharmaceutical Products (Annex 9) requires that transport systems are validated, monitored, and that any excursions are documented and investigated [14]. Similarly, the EU Good Distribution Practice (GDP) guidelines emphasize deviation management and continuous risk assessment across the supply chain [15].

In the European Union, the responsibility for ensuring that no batch is released without confirmation of compliance lies with the Qualified Person (QP). According to Annex 16 of EudraLex Volume 4, the QP must verify that each batch has been manufactured and distributed in accordance with GMP, the marketing authorization, and applicable quality standards [16]. Crucially, Annex 16 specifies that the QP must also consider the impact of any deviations, including temperature excursions during transportation, before certifying a batch for release. In parallel, Annex 21 highlights that imported medicinal products require rigorous verification of compliance with storage and transport conditions, particularly when distributed across multiple climatic zones [17]. In such cases, QPs rely on deviation reports and supportive stability data to assess whether a batch remains within acceptable specifications [18].

Thermal-cycling stress studies have therefore emerged as a valuable tool to simulate real-world transport scenarios. By exposing products to alternating cycles of freezing, refrigeration, and elevated ambient conditions, these studies capture cumulative stress effects that conventional long-term or accelerated stability protocols cannot [19-21]. Regulatory authorities recommend including thermal-cycling data in stability dossiers for products with international distribution [22].

In parallel, regulatory science underscores the importance of Quality Risk Management (QRM). Tools such as Failure Modes and Effects Analysis (FMEA), described in ICH Q9, provide a structured framework for identifying potential transport-related hazards, ranking them by severity, occurrence, and detectability, and implementing control strategies [23,24]. Recent reports indicate that transportation-related deviations account for a significant proportion of non-conformities found in GDP audits, emphasizing the need for risk-based decision-making [25,26]. In addition, studies on supply chain optimization have shown that transportation-related risks significantly influence pharmaceutical logistics performance and cost [27,28]. Advanced QRM approaches, including Lean Six Sigma and systemic supply chain modelling, have been proposed to strengthen resilience and reduce deviations in practice [29]. Initiatives such as the STEP database further highlight the vulnerability of pediatric formulations to distribution-related stress, reinforcing the need for integrated risk and stability evaluation [30].

Cefixime, a third-generation cephalosporin antibiotic, provides a relevant case study for such evaluations. Widely used in pediatric formulations and distributed across diverse climatic regions, it is highly susceptible to transport-related risks. This study presents a comprehensive evaluation of Cefixime granules for oral suspension subjected to thermal-cycling stress conditions, complemented by an FMEA-based risk assessment. The objective is not only to confirm the product's resilience, but also to demonstrate the regulatory relevance of transport stability studies for QP decision-making in line with international guidelines (WHO Annex 9, EMA Annex 16, and Annex 21).

Materials and Methods

Study Design and Batches Tested

This was a **pilot stability study** performed on a single production batch of *Cefixime* granules for oral suspension. The batch was manufactured and packaged under GMP-compliant conditions. While the present study provides proof-of-concept data, further investigations across multiple production batches are recommended to strengthen the evidence base for regulatory submissions and to evaluate inter-batch variability.

Chemicals and Reagents

Cefixime trihydrate reference standard was obtained from the European Pharmacopoeia (Ph. Eur.). HPLC-grade acetonitrile and methanol were purchased from Merck (Germany), while tetrabutylammonium hydroxide (30-hydrate) was obtained from Sigma-Aldrich (USA). Ultrapure water was prepared using a Milli-Q purification system (Millipore, USA). All other reagents were of analytical grade and complied with pharmacopoeia specifications.

Dosage form and Packaging

The test product was *Cefixime* 100 mg/5 ml granules for oral suspension, manufactured by Alkaloid AD Skopje. Granules were filled into 150 ml amber glass bottles sealed with aluminium caps and polyethylene liners. Each secondary package contained one bottle, a calibrated dosing device, and a patient information leaflet. The packaging was selected to provide protection against moisture and light, in line with Ph. Eur. and ICH stability requirements [1,3].

Thermal-cycling Protocol

The study design followed ICH Q1A(R2) and WHO recommendations for stability and transport simulation [1,21].

Samples were subjected to three consecutive thermal cycles simulating transport-related excursions:

- Cycle 1: −20 °C (3 days), +5 °C (3 days), +30 °C (4 days)
- Cycle 2: −20 °C (3 days), +5 °C (4 days), +30 °C (3 days)
- Cycle 3: −20 °C (5 days), +5 °C (3 days), +30 °C (4 days)

In total, the protocol represented approximately one month of cumulative exposure across the distribution chain, in line with WHO Annex 9 expectations for worst-case transport simulation [14,21].

Stability-indicating Parameters

The following critical quality attributes were monitored after each cycle, in accordance with Ph. Eur. and USP requirements:

- *Physical properties*: appearance (granules and reconstituted suspension), odor, viscosity, dispersibility, pH, relative density, and water content.
- *Chemical properties*: assay of Cefixime and sodium benzoate by validated HPLC; dissolution testing according to USP specifications (Q = 80% in 15 min); quantification of related and degradation products.
- *Microbiological quality*: total aerobic microbial count (TAMC), total yeasts and moulds, and absence of *Escherichia coli*. Microbiological tests were performed at baseline and after the final cycle.

All results are expressed as mean ± standard deviation (SD, n = 3). Statistical analysis was performed using one-way ANOVA to evaluate variability across cycles, with $p < 0.05$ considered statistically significant.

Risk analysis (FMEA)

In parallel with the experimental study, a Failure Modes and Effects Analysis (FMEA) was performed in accordance with ICH Q9 [3]. The FMEA was conducted as a complementary Quality Risk Management (QRM) tool to contextualize the experimental findings. Severity (S), Occurrence (O), and Detection (D) were scored on a 1–10 scale, and Risk Priority Numbers (RPNs) were calculated. Residual RPNs were estimated after application of mitigation strategies, considering the experimental demonstration that Cefixime tolerates thermal-cycling stress.

This study focused exclusively on thermal-cycling stress to simulate transport conditions. Other factors such as vibration, mechanical shock, and humidity fluctuations, which may also influence product quality during distribution, were not addressed here. Future work should integrate multi-factorial stress simulations to provide a more comprehensive assessment of distribution resilience.

Results and Discussion

The present study demonstrated that Cefixime 100 mg/5 ml granules for oral suspension can tolerate repeated temperature excursions (−20 °C to +30 °C) for up to one month without compromising its physical, chemical, or microbiological quality. These results provide strong experimental evidence that supports not only scientific conclusions but also regulatory and quality management decision-making across the supply chain.

Alignment with Regulatory Expectations

According to ICH Q1A(R2), stability studies should not only evaluate long-term and accelerated conditions but also assess potential risks associated with temperature excursions during transport [1]. By applying three consecutive thermal cycles, this study simulated cumulative stress representative of international shipping conditions. The observed stability of *Cefixime* under these conditions confirms that the formulation can withstand realistic distribution challenges without loss of quality.

WHO Annex 9 ("Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products") requires that transport systems are validated to demonstrate product quality is not adversely affected by distribution-related stresses [21]. The thermal-cycling protocol used in this study mirrors such expectations, simulating realistic excursions through freezing, refrigerated, and elevated conditions. The outcome maintenance of all CQAs within specifications provides strong scientific evidence for validated transport conditions and supports their inclusion in the product stability dossier.

In the EU regulatory framework, the Qualified Person (QP) plays a central role in batch certification under Annex 16 [16]. Under Annex 16 [16] of EudraLex Volume 4, the Qualified Person (QP) is responsible for certifying each batch, taking into account any deviations, including transport-related temperature excursions [23]. The results of this study provide a clear scientific basis for QPs to decide on batch release when excursions are reported. By showing that excursions within −20 °C to +30 °C do not compromise product quality, this study enhances risk-based QP decision-making in accordance with regulatory expectations.

Furthermore, Annex 21 [17] emphasizes the obligation to verify storage and transport conditions for imported medicinal products, especially when shipments cross multiple climatic zones. In such cases, validated thermal-cycling data serve as a valuable reference point when reviewing shipment records. If deviations fall within validated stress conditions, QPs and quality units can justify acceptance of the batch, thereby strengthening regulatory compliance.

Good Distribution Practice (GDP) guidelines [22] require that all deviations during transport are recorded, investigated, and assessed for their impact on product quality. Thermal-cycling data provide a critical benchmark against which real-world excursions can be evaluated. If actual deviations are within validated limits, Corrective and Preventive Actions (CAPA) can be managed efficiently, avoiding unnecessary product quarantine or recall. This enables faster, science-based decision-making while preserving compliance.

The USP <1079.2> chapter [14] recommends the use of Mean Kinetic Temperature (MKT) for interpreting excursions, but also highlights that MKT alone is insufficient. Stress and stability

studies such as the present thermal-cycling approach—are essential to contextualize deviations and strengthen risk assessments. Thus, the study complements MKT by offering direct product-specific stability evidence under fluctuating conditions.

Overall, the integration of experimental stability data with risk management principles (ICH Q9, FMEA) and regulatory frameworks (Annex 9, Annex 16, Annex 21) strengthens the case for adopting thermal-cycling studies as standard components of pharmaceutical development. These approaches ensure product robustness, support regulatory decision-making, and contribute to sustainable distribution practices.

Physical Robustness of the Formulation

No significant changes were observed in the physical characteristics of the granules or the reconstituted suspensions throughout the three thermal cycles.

The pH values ranged from 3.6 to 3.7 (mean ± SD: 3.65 ± 0.05), remaining well within the acceptance range of 2.5–4.5. Measurements of viscosity (232 ± 0.03 mPa·s) and relative density (1.12 ± 0.01 g/cm³) showed minor variations across cycles, but statistical analysis using one-way ANOVA confirmed no significant differences compared to baseline values ($p > 0.05$). These findings confirm that the formulation retained its expected physical integrity despite repeated exposure to alternating temperature conditions. The formulation retained its intended physical properties across cycles. Consistent appearance, color, odor, and dispersibility demonstrate that excipients such as sucrose and xanthan gum provided stabilization against repeated stress. Maintenance of pH, viscosity, and relative density further supports the resilience of the suspension. These results align with previous reports demonstrating the importance of polysaccharide stabilizers in maintaining homogeneity during stress [11,12].

Chemical and Microbiological Integrity

Chemical quality attributes also remained within acceptance limits across all cycles. The results in Table 1 confirm that Cefixime granules for oral suspension remained stable under repeated thermal-cycling stress, with all quality attributes consistently meeting pharmacopeia specifications. The assay values for both cefixime (98.0–103.1% of the labeled claim; mean ± SD: 100.4 ± 1.2% and ($p > 0.05$).) and sodium benzoate (97.5–103.1% of the expected range; mean ± SD: 100.0 ± 1.3% and $p > 0.05$) demonstrated negligible variability (SD ≤ 1.0%), indicating that neither the API nor the preservative underwent significant chemical degradation during stress exposure. Comparable results have been reported for other β-lactam antibiotics, such as cefuroxime and cefpodoxime, which retained potency under controlled stress conditions when stabilized in solid or suspension dosage forms [1,2].

The dissolution performance further highlights the robustness of the formulation. Drug release remained consistently above 93.5% within 15 minutes across all cycles, in all tested samples (mean ± SD: 95.2 ± 1.1%), exceeding the acceptance limit of 80%. Variability between cycles was minimal ($p > 0.05$). This indicates that the excipient system, particularly sucrose and xanthan gum, effectively preserved the dispersibility and reconstitution properties of the granules. Previous studies on oral cephalosporin suspensions have shown that polysaccharide stabilizers play a crucial role in preventing aggregation and ensuring reproducible dissolution, even when exposed to stress conditions [3,4].

In terms of impurities, the gradual increase from 1.2% at baseline to 1.8% after Cycle 3 remained well within the 3.5% specification limit. This trend reflects the expected cumulative impact of thermal stress but does not suggest activation of significant degradation pathways. These findings are consistent with earlier reports that cephalosporins generally exhibit acceptable stability profiles when stored in dry granule form, as moisture is the more critical factor driving degradation compared to temperature variation alone [5,6].

Table 1: Stability study results of Cefixime granules for oral suspension under thermal-cycling conditions.

Cycle	Cefixime assay (% label claim)	Sodium benzoate assay (% expected)	Dissolution at 15 min (% released)	Total impurities (%)
Baseline	100.2 ± 0.8	100.5 ± 0.6	95.8 ± 1.2	1.2 ± 0.2
Cycle 1	99.5 ± 0.9	99.8 ± 0.7	94.7 ± 1.5	1.3 ± 0.3
Cycle 2	101.0 ± 0.7	101.2 ± 0.5	96.3 ± 1.0	1.5 ± 0.2
Cycle 3	98.7 ± 1.0	98.9 ± 0.9	93.9 ± 1.3	1.8 ± 0.3

Values are expressed as mean ± standard deviation (SD, n = 3). All tested parameters complied with pharmacopeia specifications: assay (94.0–105.0% of label claim), dissolution (≥80% drug released within 15 min), and total impurities (≤3.5%).

Statistical evaluation confirmed that none of the observed variations were statistically significant ($p > 0.05$), supporting the conclusion that thermal cycling did not compromise product quality. Taken together, the data demonstrate that the formulation is resilient to temperature excursions commonly encountered in pharmaceutical distribution.

These outcomes not only support the suitability of Cefixime for global supply chains but also align with broader observations in the literature. Studies on the stability of pediatric suspensions have emphasised that validated preservative systems, combined with robust excipient functionality, can safeguard both chemical and microbiological integrity under fluctuating transport conditions [7,8]. The findings presented here therefore reinforce the importance of integrating excipient design with transport validation in order to ensure therapeutic performance and regulatory compliance. Figure 1 illustrate dissolution profiles and assay values for cefixime and sodium benzoate across thermal cycles, confirming minimal variability and full compliance with acceptance criteria. Also, Figure 1 present impurity profiles, demonstrating that all degradation products remained within pharmacopeia thresholds [3].

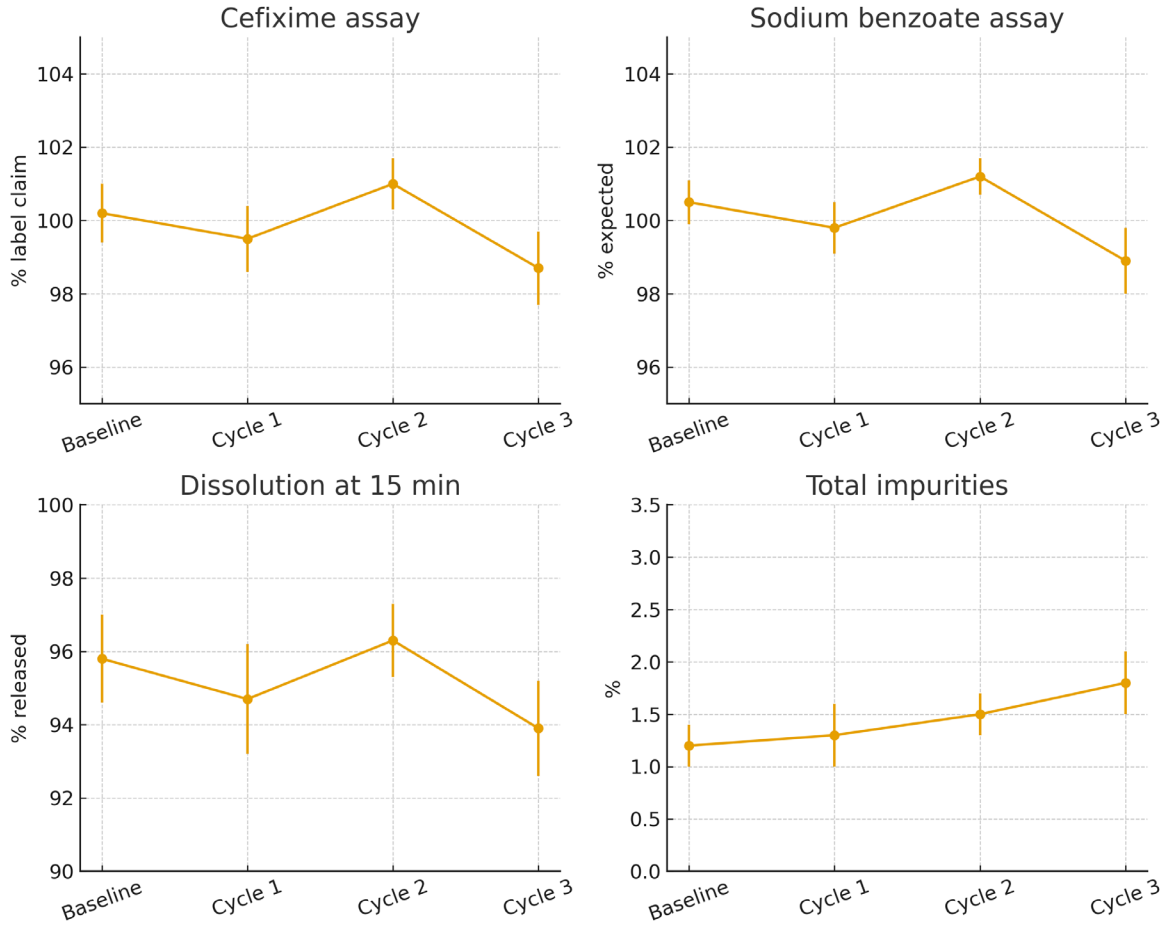

Figure 1: Stability profile of *Cefixime* granules for oral suspension under thermal-cycling conditions.
Mean ± SD (n = 3) values are shown for (A) Cefixime assay, (B) sodium benzoate assay, (C) dissolution at 15 minutes, and (D) total impurities across baseline and three thermal cycles. All results remained within pharmacopoeia specifications.

Microbiological testing confirmed that the product maintained its integrity throughout all simulated distribution conditions. TAMC values ranged from 120 to 160 CFU/g, well below the acceptance threshold of $\leq 10^3$ CFU/g, while yeast and mould counts ranged between 12 and 18 CFU/g, remaining below the limit of $\leq 10^2$ CFU/g. No *Escherichia coli* was detected at any point. These findings demonstrate that the preservative system (sodium benzoate) and the protective packaging (amber glass bottles with aluminum closures) effectively safeguarded the product against contamination, even under repeated temperature cycling. Figure 2 illustrates the microbial counts across baseline and three thermal cycles, with both TAMC and yeasts/moulds remaining significantly below pharmacopoeia thresholds. The stability of the preservative system was further supported by assay results, which remained within 98.9–101.2% across cycles, ensuring antimicrobial efficacy. This is consistent with previous reports demonstrating that benzoates remain chemically stable under fluctuating temperature conditions, thereby safeguarding microbiological integrity [3].

These findings are particularly relevant because pediatric suspensions are among the most vulnerable dosage forms to microbiological instability. After reconstitution with water, they are typically stored under ambient or refrigerated conditions for up to 7–14 days, during which microbial growth may occur if preservative systems are inadequate. Several studies have reported microbiological failures in suspensions without effective preservative systems, leading to loss of quality and potential safety risks [1,2].

Moreover, the absence of *E. coli* is an essential finding, as contamination with this microorganism represents a critical failure in quality control. WHO and Ph. Eur. guidelines specify absence of enteric pathogens as a prerequisite for pediatric formulations [4]. The results of this study therefore provide assurance that both formulation design and packaging successfully prevented contamination despite thermal cycling. Importantly, microbiological robustness also complements the FMEA analysis, where humidity ingress and packaging failure were identified as potential risks. The experimental findings suggest that these risks remain theoretical under validated transport and packaging conditions, thereby reducing the residual risk score for microbiological hazards.

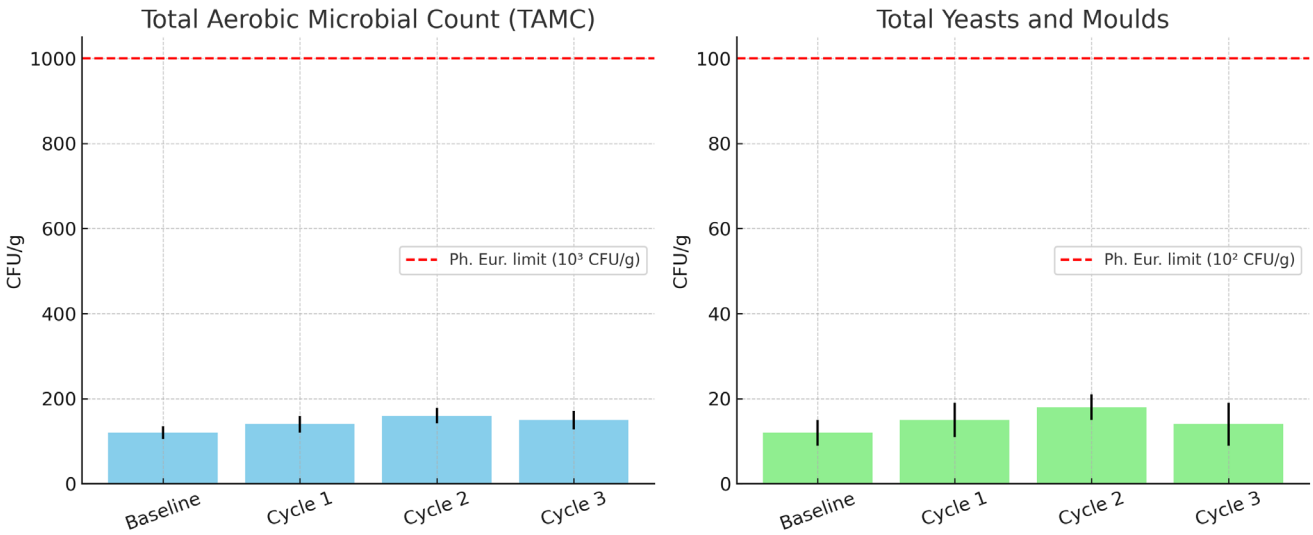

Figure 2: Microbiological quality of Cefixime granules for oral suspension under thermal-cycling conditions. (A) Total Aerobic Microbial Count (TAMC) and (B) total yeasts and moulds (mean ± SD, n = 3) at baseline and after three thermal cycles. Dashed lines indicate pharmacopoeial acceptance limits (Ph. Eur., USP). All values remained within specifications.

Table 2: Summary of top five risks identified in FMEA and their residual risk levels.

Failure mode	Initial RPN	Key mitigation measures	Residual RPN
Customs or last-mile delay extending transit time	210	Pre-clearance, alternative routes, proactive exception management, defined maximum time out of storage	140
Prolonged high temperature exposure (+30–40 °C)	200	Validated passive/active shippers, route planning, redundant temperature loggers, excursion limits on COA/label	96
Freezing at −20 °C (direct ice-pack contact)	144	Buffer layers between product and refrigerants, “Do not freeze” labeling, pack-out SOPs	144
Mechanical shock/vibration	120	ISTA-qualified packaging, corner/edge protectors, pallet stacking rules	90
Data logger failure or missing data	120	Dual loggers, automated activation checks, SOP re-training	30

Risk Assessment Alignment

In order to complement the experimental findings, a structured Failure Modes and Effects Analysis (FMEA) was performed to systematically identify, prioritize, and mitigate potential risks associated with the transport of Cefixime granules for oral suspension. Following ICH Q9 Quality Risk Management principles and Good Distribution Practice (GDP) requirements, each potential failure mode was evaluated according to Severity (S), Occurrence (O), and Detection (D), with risk priority numbers (RPN) calculated to support prioritization [25-27].

The FMEA confirmed that temperature excursions and prolonged operational delays constitute the most critical threats to distribution quality. Specifically, exposure to elevated temperatures (+30–40 °C) was associated with the potential acceleration of degradation reactions, leading to higher impurity levels and possible potency loss. Similarly, extended customs clearance or last-mile delivery delays may cumulatively exceed validated excursion limits, creating regulatory and therapeutic risks. Nevertheless, experimental results demonstrated that the formulation tolerated excursions between −20 °C and +30 °C for up to one month without loss of quality, thereby validating that these risks remain manageable within real-world transport conditions.

Freezing risks, particularly from direct contact with coolant packs, were also highlighted in the analysis. While the thermal-cycling study did not reveal physical or chemical instability, poor pack-out practices could still compromise granule morphology and impair reconstitution performance. Other identified risks included vibration and mechanical shock during transport, humidity ingress due to compromised packaging integrity, and failures in temperature monitoring (e.g., data logger malfunction or incomplete datasets) [13-15,28,29]. These scenarios, although secondary in criticality, emphasize the need for holistic risk management beyond thermal stress alone.

The results clearly demonstrate that implementation of validated packaging solutions (ISTA-qualified shippers, amber glass bottles with moisture-protective liners), redundant temperature monitoring, strict time-out-of-storage limits, and clear pack-out SOPs significantly mitigates overall risk. Residual RPN values across all major risks were reduced to levels considered acceptable within the pharmaceutical supply chain.

The integration of FMEA with experimental findings strengthened the scientific interpretation of risk. The experimental stability study confirmed that excursions of up to one month did not compromise product quality, thereby providing real-world data to validate

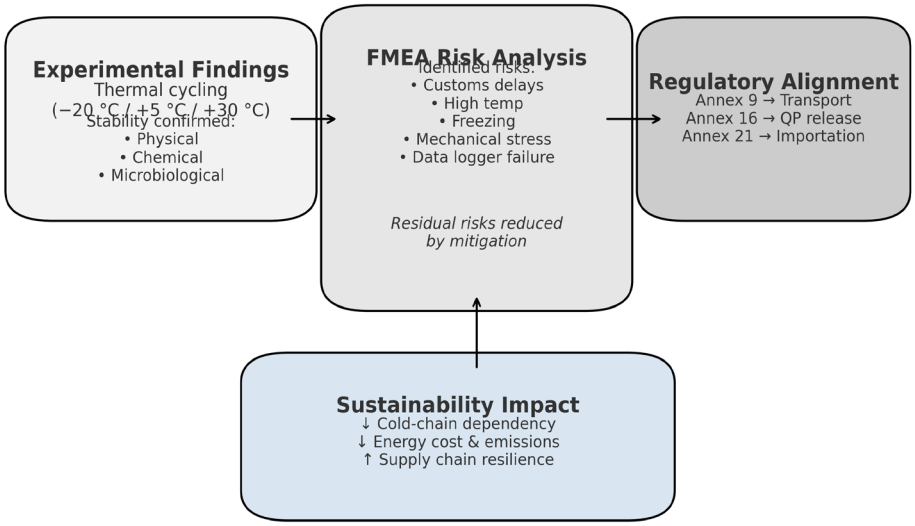

Figure 3: Integrated framework linking experimental stability data, FMEA-based risk assessment, regulatory alignment, and sustainability.

the assumptions of the FMEA. Conversely, the risk analysis contextualized the experimental results, ensuring that mitigation measures and deviation management processes are aligned with GDP. This integrated approach is particularly valuable in regulatory practice: GDP requires robust deviation management and corrective and preventive actions (CAPA), while Annex 9 (WHO) and Annex 21 (EMA) mandate that transport conditions are validated and importation is verified. Annex 16 further obliges the Qualified Person (QP) to assess all deviations, including temperature excursions, before certifying batch release. Data from thermal-cycling studies, when combined with FMEA-based risk analysis, therefore provide a defensible scientific framework for QP decision-making in borderline cases.

Moreover, the integrated evidence has implications for sustainability and efficiency in pharmaceutical logistics. By demonstrating tolerance to moderate excursions, the reliance on highly energy-intensive continuous cold-chain systems can be reduced. This translates into lower carbon emissions, improved cost-efficiency, and more resilient supply chains, particularly in low- and middle-income countries where strict cold-chain infrastructure may be limited. Thus, stability studies combined with risk-based frameworks support not only regulatory compliance but also global access to essential medicines.

Study Limitations and Future Perspectives

A limitation of this work is that it evaluated a single pilot batch of Cefixime granules under controlled thermal-cycling stress. While results were consistent with pharmacopeia specifications, confirmation across multiple production batches is recommended to account for inter-batch variability. Furthermore, the study focused primarily on thermal stress; in real-world distribution, additional variables such as vibration, mechanical shock, and humidity fluctuations may also impact product stability. Future studies should employ multi-factorial stress simulations [31-33] to provide a more comprehensive assessment of transport resilience. Special consideration should also be given to pediatric formulations, which are often more vulnerable to stability loss due to excipient sensitivity and preservative system limitations. Recent studies underscore the importance of excipient functionality and preservative robustness in ensuring microbiological safety and therapeutic performance under variable distribution conditions [34]. Incorporating such considerations into risk assessments and regulatory submissions will further enhance the scientific basis for ensuring product quality and patient safety in global supply chains.

Sustainability Perspective

One important implication of this study lies in its contribution to sustainability in pharmaceutical supply chains. Traditionally, the distribution of temperature-sensitive medicines relies heavily on cold-chain logistics, which are energy-intensive, costly, and associated with a substantial carbon footprint. Recent analyses estimate that pharmaceutical cold-chain transport accounts for more than 20% of the total carbon emissions of the healthcare logistics sector [35,36].

The findings of this study demonstrated that Cefixime granules for oral suspension can tolerate excursions between −20 °C and +30 °C for up to one month, which implies that strict and energy-intensive temperature-controlled shipping may not always be required. By validating the resilience of the product under thermal-cycling conditions, manufacturers and distributors gain flexibility in selecting more sustainable and cost-efficient transport modalities, such as optimized passive containers or consolidated shipment routes. From a regulatory perspective, this aligns with the growing emphasis on sustainable pharmaceutical development, where environmental considerations are integrated into Quality Management Systems (QMS) and GDP compliance frameworks [37]. Furthermore, reducing dependence on continuous refrigeration supports the principles of Annex 9 (transport validation) and Annex 16 (QP decision-making) while simultaneously contributing to green supply chain management strategies.

Thus, thermal-cycling stability studies not only ensure patient safety and product efficacy but also play a role in reducing greenhouse gas emissions, optimizing logistics costs, and supporting the global agenda for sustainable healthcare systems.

Conclusions

This study confirmed that Cefixime granules for oral suspension remain stable under thermal-cycling conditions simulating transport across climatic zones. The product consistently met pharmacopoeia specifications for physical, chemical, and microbiological attributes, and tolerated excursions between −20 °C and +30 °C for up to one month without compromising quality.

By integrating experimental data with Failure Modes and Effects Analysis (FMEA), the study provided a risk-based framework aligned with ICH Q9. Critical risks such as prolonged customs delays, high-temperature exposure, and freezing events were identified, yet residual risks were shown to be effectively mitigated through validated packaging, excursion limits, and GDP controls. The results have direct regulatory relevance: supporting transport validation under Annex 9, informing Qualified Person (QP) decisions under Annex 16, and strengthening importation verification under Annex 21. Beyond regulatory compliance, the findings also promote sustainability by reducing dependence on energy-intensive cold-chain logistics.

In conclusion, thermal-cycling studies represent a valuable complement to conventional stability testing. They enhance supply chain resilience, support risk-based decision-making, and contribute to safeguarding patient safety while enabling sustainable pharmaceutical distribution.

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