IPEC Europe Position Paper

Mandatory Diethylene Glycol and Ethylene Glycol Testing in Excipients: addressing the surge in Fraudulent and Unintentional Contamination events

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1. Introduction

Global contamination incidents involving fraudulent adulteration of excipients with diethylene glycol (DEG) and ethylene glycol (EG) continue to draw international attention, particularly following the tragic series of events between 2022 and 2025, which resulted in more than 300 deaths, many of them children. These events revealed persistent weaknesses in supply chain oversight, including failures in supplier qualification, insufficient incoming goods testing, and misplaced reliance on inadequate or falsified certificates of analysis.

However, not all reported cases involve intentional adulteration. WHO has reported incidents where DEG/EG levels were below 1%, a finding more consistent with cross-contamination rather than deliberate substitution. Such events can arise from poor handling practices of packaging materials (including the reuse of containers), or from inadequate standards in filling equipment and filling processes. These issues are particularly prevalent in non-regulated markets and point to GDP failures rather than fraud. The IPEC GDP Guide addresses these scenarios and provides relevant advice on preventing such unintentional contamination through proper handling, storage, and processing controls.

In response, several regulatory authorities introduced mandatory identity testing for DEG/EG, often requiring testing of every individual container of specified excipients. While these measures aim to protect patients, especially in regions where supply chains are more vulnerable, they also introduce significant technical and logistical challenges for manufacturers, distributors, and users of pharmaceutical excipients.

This position paper aims to:

- Recommend enhancements to supply chain security that more effectively address the root causes of contamination events;
- Advocate for a harmonised, risk-based approach to DEG/EG control;
- Provide a basis for constructive dialogue with regulators, industry partners, and other stakeholders;
- Highlight key issues associated with mandatory container-level testing.

This position paper focuses on excipients identified as at high-risk of contamination due to fraudulent activities, for which regulators mandate DEG/EG laboratory testing to verify their authenticity.

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2. Regulatory Landscape

International regulatory expectations are evolving quickly and often inconsistently. Requirements now exist, or are emerging, in the United States, European Union, India, Pakistan, China, The Gambia, Indonesia, Thailand, and others. These initiatives reflect heightened attention to excipient safety and may foreshadow future tightening of pharmaceutical requirements worldwide.

2.1 Countries and Regions with Testing Requirements (applicable to the whole supply chain, from manufacturers to user)

- United States: FDA issued an Immediately-in-Effect Guidance (May 2023) requiring DEG/EG testing for high-risk drug components such as glycerol and propylene glycol. USP intends to publish a specific test method for DEG/EG in finished dosage forms;
- European Union: EMA incorporated questions on DEG/EG contamination into GMP and GDP guidance considering global incidents;
- European Union: EMA has published Q&As related to DEG/EG in February 2025 and April 2025. EU GMP Guide annexes have been updated particularly Annex 8, which covers the sampling of starting and packaging materials such as glycerol;
- European Pharmacopoeia: a "Potential adulteration" section describing an analytical procedure for the quantification of DEG/EG when suspected to be present in harmful amounts has been included in the four Ph. Eur. monographs concerned, Sorbitol, liquid, partially dehydrated (2048), Sorbitol, liquid (non-crystallising) (0437), Sorbitol, liquid (crystallising) (0436) and Maltitol, liquid (1236), all of which have been published in PharmEuropa 37.4 for comment;
- WHO: issued guidance for strict control of high-risk ingredients prone to DEG/EG contamination - such as glycerol, propylene glycol - requiring DEG/EG testing on every container of every lot, ensuring safe limits and secure, qualified supply chains; the WHO also offers validated, low-cost TLC screening methods for resource-limited labs.
- India: CDSCO and the Indian Pharmacopoeia introduced strengthened requirements, including revised monographs and mandatory testing for DEG/EG in all oral liquid formulations (as part of Amendment List 09 to IP 2022);
- Pakistan: DRAP issued warnings and expectations for stringent control of DEG/EG contamination;
- China: Requirements continue to evolve within the excipient registration scheme and the Chinese Pharmacopoeia;
- The Gambia: Introduced pre-shipment testing measures;
- Indonesia: Implemented DEG/EG expectations for food supplements containing propylene glycol (2022–2023) and introduced EG/DEG testing in the national Pharmacopoeia;
- Thailand: Set contamination limits for food additives from October 2023.
- Malaysia's National Pharmaceutical Regulatory Agency (NPRA) sets testing requirements for ethylene and diethylene glycol in February 2026 (aligned with the EMA position and does not include alkoxylation products).

Although food and food-additive regulations fall outside the pharmaceutical scope, they may anticipate regulatory trends and therefore warrant acknowledgement.

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2.2 Pharmacopoeia Developments

The European Pharmacopoeia recently published draft monographs for consultation, including DEG/EG limits for materials such as certain liquid polyol monographs (see above), following safety alerts. IPEC Europe recommends focusing on finalised pharmacopeial requirements to avoid creating expectations around content still under revision.

3. Key Issues and Challenges

3.1 Discrepancy Between Adulteration Levels and Control Limits

Documented adulteration cases typically involve extremely high contamination levels, often 30 to 50 percent, consistent with intentional substitution of glycerol or propylene glycol with cheaper industrial chemicals. In contrast, regulatory limits and pharmacopeial thresholds as low as < 0.1%, reflecting sensitivity needed to control process-related impurities.

This creates analytical and operational challenges. Highly sensitive methods are required to detect low-level impurities, while different methods may be more appropriate for screening massively adulterated materials. It was agreed that this discrepancy should be acknowledged; however, IPEC will not propose alternative limits.

3.2 Not All Excipients Are Capable of DEG/EG Adulteration

FDA-mandated mandatory testing requirements include excipients for which adulteration is chemically not possible, such as solid-state materials (e.g., high-molecular-weight PEGs, powdered polyols). For these materials, container-level testing neither increases safety nor provides meaningful data.

Regulation should instead focus on high-risk liquid materials, primarily polyols and glycols, which share properties making substitution or contamination more likely. Harmonised global agreement is needed to identify and maintain a list of high-risk excipients.

3.3 Differentiating Adulterants from Process-Related Impurities

DEG/EG used deliberately as adulterants must not be confused with legitimate process-related impurities, such as residual ethylene glycol in ethoxylated excipients. The intent and source of contamination differ, and analytical interpretation must reflect this distinction. Moreover, ICH Q3C Residual Solvents guideline has been already covering the potential presence of EG (option 1 limit 620 ppm) in ethoxylated and polyol excipients.

3.4 Supply Chain Complexity

The recent incidents demonstrate that contamination often occurs outside the excipient manufacturing site, particularly during distribution, repackaging/relabelling, transport, or storage. Full traceability and documented oversight of all intermediaries are therefore essential.

Key challenges identified include:

- Incomplete or unclear supply chains;

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- Use of non-pharmaceutical grades to manufacture medicines;
- Absence of robust incoming inspection practices;
- Limited auditing of distributors and brokers, despite their central role;
- Insufficient change control systems and poor communication of supply chain changes.

It should be emphasized that supply chain security, rather than repeated container testing, should be recognised as the main safeguard against intentional adulteration.

4. IPEC Europe Position and Recommendations

IPEC Europe supports the goal of protecting patients from toxic adulteration and recognises the gravity of past incidents. However, measures must be effective, proportionate, and scientifically grounded. Mandatory testing of every container may not always represent the most appropriate or efficient means of preventing recurrence.

4.1 Risk-Based Testing Approaches

IPEC Europe supports a risk-based approach to DEG/EG sampling and testing, grounded in:

- Proven supply chain integrity and transparency;
- Reliable supplier qualification;
- Audit outcomes;
- Awareness and training of sampling personnel;
- Historical performance and monitoring results.

Such an approach aligns with international risk management principles and allows regulators and manufacturers to focus resources where they truly matter. IPEC recognises that in some regions, where supply chain risks are significantly higher, more stringent testing may be necessary.

4.2 Supply Chain Security Measures

IPEC Europe believes that strengthening supply chain controls offers the most effective long-term protection. Established industry guidelines, such as the IPEC GDP Guide, provide detailed expectations for supply chain traceability, security, and handling standards, and should be applied consistently to prevent both fraudulent adulteration and unintentional contamination.

The following elements are essential:

- Purchase excipients only from qualified and approved suppliers, including manufacturers and distributors that work under appropriate excipient GMP/GDP's;
- Cosmetic/personal care and industrial/technical grades should not be labelled as pharmaceutical grade, even if they meet pharmacopoeia specs, when not made under GMP conditions suitable for pharmaceutical excipients;
- Perform robust incoming goods inspection and testing using applicable pharmacopeial methods or validated internal methods, meeting the appropriate pharmacopeial requirements;
- Ensure full and documented traceability back to the original manufacturer, including the original manufacturer's CoA for each delivery. Consider implementing Supply chain maps and distribution

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risk assessments to include details of handling and storage of materials by third parties in the supply chain;
- Maintain and apply formal quality risk management, integrating supplier risk, route-of-supply vulnerabilities, and material characteristics;
- Implement rigorous change control procedures and timely notification of significant changes, in alignment with the IPEC Significant Change Guide;
- Ensure appropriate training, competency management, and documentation for all personnel involved in procurement, analysis, warehousing, Quality Control, and Quality Assurance;
- For high-risk materials, prioritise on-site supplier audits rather than remote or desktop assessments.

These measures directly address the root causes of the global incidents, unlike container-level testing which can only detect problems after they have entered the supply chain.

4.3 Harmonisation of Requirements

When testing for adulteration, IPEC Europe calls for global harmonisation of:
- Lists of high-risk excipients;
- Testing methods for DEG/EG when possible;
- Reporting limits and acceptance criteria; based on relevant safety limits;
- Sampling and container-testing requirements.

Fragmented requirements create unnecessary burden and inconsistency without improving patient safety.

4.4 Use of Existing Guidance

IPEC Europe emphasises that the industry already possesses extensive tools to ensure excipient quality and integrity. Existing IPEC guides, pharmacopoeial standards, regulatory guidance documents, and auditing frameworks should be applied consistently. The challenge is not the absence of guidance, but uneven adoption and implementation.

5. Proposed Actions and Next Steps

To advance this work, IPEC Europe will:
- Refine the position paper to incorporate feedback from member experts;
- Compile regulatory developments from additional countries to ensure global completeness;
- Work with volunteers to draft supporting rationale and scientific justifications for each recommendation;
- Engage with regulators, partner associations, and media outlets to promote correct understanding of excipient risk management;
- Continue emphasising adherence to established IPEC guidance, including supplier qualification, change control, and risk management.

A follow-up meeting will be scheduled to review the expanded draft, evaluate feedback, and agree on a path toward publication.

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6. Conclusion

Preventing DEG/EG contamination is a shared global responsibility. While container-level identity testing may be appropriate as an immediate risk-mitigation measure in certain regions, it is not a sustainable or universally necessary long-term solution. The most effective safeguard for patients lies in robust, transparent, and well-controlled supply chains, grounded in qualified suppliers, full traceability, rigorous change control, and risk-based oversight.

IPEC Europe remains committed to collaborating with regulators, industry partners, and other stakeholders to promote harmonised, science-based approaches that reduce patient risk while enabling efficient and secure global supply of pharmaceutical excipients.

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