

Different regulatory approaches to excipient requirements: the case of EG/DEG contamination risk in pharmaceuticals

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ABSTRACT

Review

Ethylene glycol (EG) and diethylene glycol (DEG) contamination of pharmaceutical excipients has repeatedly resulted in severe poisoning events, particularly in oral paediatric medicines, with fatalities continuing to be reported outside highly regulated regions. These incidents have largely been attributed to economically motivated adulteration of widely used excipients such as glycerol and propylene glycol. In response, regulatory authorities and pharmacopeial bodies have implemented measures to mitigate this risk; however, the scope, stringency, and regulatory philosophy of these measures vary significantly across jurisdictions. This article reviews and compares the current regulatory approaches adopted by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the World Health Organization (WHO) and major Pharmacopoeias (USP and Ph. Eur.) with respect to EG/DEG detection and control in pharmaceutical excipients. Particular attention is given to differences in the definition of “high risk” excipients, the setting of EG/DEG limits as identity or impurity tests, and the different considerations for excipients in which EG/DEG may occur as process related by-products, such as ethoxylated excipients. This review highlights the critical role of supply chain integrity, traceability, and supplier qualification in preventing EG/DEG adulteration events. Furthermore, it identifies opportunities for risk based, harmonized regulatory strategies that would enhance patient safety while avoiding unnecessary and inefficient testing burdens across global pharmaceutical supply chains.

INTRODUCTION

In 1937 the sulfanilamide elixir tragedy caused more than 100 fatalities in U.S. due to the presence of diethylene glycol (DEG) that was used to dissolve the drug substance in the medication. In response to this event, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act, which required proof of safety before the release of a new drug, fundamentally shaping the modern FDA's authority (1). This action was effective in eliminating deaths associated with DEG contamination in the US but, sadly, many different cases of ethylene glycol (EG) and diethylene glycol (DEG) fatal poisoning of children syrups continued to be reported in the 1990's and in more recent years (2019-2023), in several parts of the world, mainly in LATAM, African and Asian countries (including Haiti, Panama, Gambia, India, Indonesia and Cameroon). During this time period there have been no contaminated-related deaths reported in the US and EU. In most of the fatal poisoning cases, the contamination was the result of a deliberate economically motivated adulteration of glycerol or propylene glycol excipients with less expensive EG and/or DEG at levels up to 30% in the finished product (2).

In response to these more recent cases, the FDA issued in May 2023 the guidance "Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol" (3) to prevent the risk of economically motivated adulteration of high-risk drug components. The guidance also extends to ethoxylated excipients, such as polysorbates, polyethylene glycol (PEG) grades, PEG esters, PEG ethers, etc., that may contain low levels of EG/DEG as by-products of the ethoxylation reaction.

The FDA guidance has the same requirements i.e., EG and DEG limits of 0.10%, for excipients regarded as high-risk drug components identified in the title of the document (including glycerin, propylene glycol, maltitol solution, hydrogenated starch hydrolysate and sorbitol solution) and for excipients where EG/DEG is a minor by-product of production processes (see footnote 32 of FDA Guidance (3)).

Following publication of the FDA guidance, other regulatory authorities have issued their own requirements to prevent EG/DEG contamination of excipients.

It is worth noting that the EG content of excipients in medicinal products was already controlled because of the

requirements of the ICH Q3C residual solvents guideline (4) in which residual EG was required to be below 0.0620% (620 ppm) under option 1 (oral) for excipients.

DISCUSSION

U.S. FDA and USP requirements

Under the FDA guidance, pharmaceutical product manufacturers are required to perform identity testing (ID) to check for EG/DEG presence in all individual containers of high-risk drug components, to maintain awareness of the supply chain for these specific excipients and to ensure all personnel involved in the receipt and release of high-risk drug components are aware to the criticality of proper EG/DEG contamination testing (3).

The FDA guidance does not include a list of all excipients considered high-risk drug components; however it does emphasize that the recommendations are also important precautions when determining supplier and lot acceptability of "other excipients" that may be at risk for DEG or EG contamination even though they are not specifically named in the guidance.

Information from the FDA Warning Letters database (5a) shows an alarming lack of compliance as reflected in more than a hundred warning letters in the last three years citing 21 CFR 211.84(d)(1) non-conformity ("Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality"). In these cases, it appears that drug manufacturers often rely solely on supplier Certificates of Analysis (CoA's) and take the ID results from them without conducting their own ID tests. Such actions could result in a failure to detect cases where there has been deliberate contamination of the excipient at some point of the supply chain after manufacture.

FDA has clearly stated that for ID testing, drug product manufacturers cannot rely on a supplier COA and must conduct their own raw material ID testing (6). It is worth noting that the FDA warning letters mentioned glycerin and propylene glycol but none of them mentions, for instance polysorbate (5b) a widely used excipient (and that is mentioned on footnote 32 of the FDA guidance), highlighting FDA's strong focus on evaluating the risk of economically motivated adulterations.

Table 1. Current situation of relevant USP monographs regarding EG/DEG requirements

Monograph	Pharmacopeia	EG limit	DEG limit	Monograph Section	Monograph date
Glycerin	USP	0.10%	0.10%	ID	2024
Propylene Glycol	USP	0.10%	0.10%	ID	2020
Maltitol Solution	USP	0.10%	0.10%	ID	2025
Sorbitol Solution	USP	0.10%	0.10%	ID	2025
Polyethylene Glycol (MW<1000)	USP	620 ppm	0.10% *	ID	2025
Polyethylene Glycol (MW>1000)	USP	620 ppm	0.10%	Tests	2025
Polyoxyl 35 castor oil	USP	620 ppm	EG+DEG nmt 0.25%	Tests	2020
Polyoxyl stearate	USP	No requirement	No requirement	N.A.	2020
Polyoxyl 20 cetostearyl ether	USP	No requirement	No requirement	N.A.	2025
Polysorbate 80	USP	No requirement	No requirement	N.A.	2020

* For Polyethylene Glycol with molecular weight (MW) 200 to 400 the limit is as follows: NMT 0.062% (620 µg/g) of ethylene glycol; NMT 0.25% (2500 µg/g) of the sum of ethylene glycol and diethylene glycol

While the FDA guidance places emphasis on the ID testing of all containers for EG/DEG, these warning letters also include recommendations to identify additional appropriate corrective actions and preventive actions (CAPA) that protect supply chains in the future, including, but not limited to, ensuring that all incoming raw material lots are from fully qualified manufacturers and are free from unsafe impurities.

Almost three years after the publication of the FDA guidance, the corresponding USP monographs include EG/DEG as identity tests for the materials named in the guidance title, i.e., glycerin, propylene glycol, etc, but not for excipients where EG/DEG is a by-product of production processes, i.e., polysorbates, polyoxyl stearate, etc., as shown in Table 1.

Therefore, USP is not completely aligned with the FDA approach of having EG/DEG testing as part of the monograph ID tests, at least for ethoxylated excipients.

EU EMA and Ph. Eur. requirements

The EMA in a published GMP Q&A document (January 2025) defined a list of materials identified as high-risk materials that was limited to only glycerol, propylene glycol and PEGs with a relative molecular mass below 1000 (liquid PEGs) (7)

In addition, instead of as ID tests specified in the USP, the European Directorate for the Quality of Medicines & Healthcare (EDQM) includes EG/DEG testing on the Tests section of the Ph. Eur. monographs for glycerol and pro-

pylene glycol materials (Table 2). Moreover, EDQM has decided to incorporate a “Potential adulteration” new section (defined in 1.5.1.6 of General Notices) describing an analytical procedure for the quantification of EG and DEG when suspected to be present in harmful amounts for the Ph. Eur. Liquid Sorbitol and Maltitol monographs, as published recently as drafts for comment in *Pharmeuropa* 37.4 (8). This “Potential adulteration” section would apply to “monographs of substances for which an incident has occurred or which are at risk of deliberate contamination” and “the requirements listed in the section apply to the whole supply chain, from manufacturers to users”.

For excipients where EG/DEG is a by-product of production processes, i.e., polysorbates, polyoxyl stearate, etc, Ph. Eur. monographs have no requirements for EG/DEG testing, presumably because the possibility of any EG/DEG economically motivated adulteration is regarded as low risk for these materials (Table 2). It is worth noting that prior to 2000, the Ph. Eur. Polysorbate 80 monograph had an impurity test for “ethylene chlorhydrine, ethylene and diethylene glycol” with a limit of EG+DEG max 0.4%. This requirement was removed a few years later as polysorbate 80 supplies in the market showed very low levels of EG/DEG and testing was consequently considered unnecessary (and also because the presence of EG was limited by ICH Q3C residual solvents requirements).

Table 2. Current situation of relevant Ph. Eur. monographs regarding EG/DEG requirements

Monograph	Pharmacopeia	EG limit	DEG limit	Monograph Section	Monograph date
Glycerol (0496)	Ph. Eur.	0.1%	0.1%	Tests (impurities)	2022
Propylene Glycol (0430)	Ph. Eur.	620 ppm	0.10%	Tests	2025
Maltitol Solution (1236)	Ph. Eur.	620 ppm	0.1%	Potential Adulteration	Published in Pharmeuropa 37.4 (Oct 2025)
Sorbitol Liquid (crystallising) (0436)	Ph. Eur.	620 ppm	0.1%	Potential Adulteration	Published in Pharmeuropa 37.4 (Oct 2025)
Polyethylene Glycol (MW<1000) (1444)	Ph. Eur.	EG + DEG nmt 0.4%		Tests	2026
Polyethylene Glycol (MW>1000) (1444)	Ph. Eur.	No requirement	No requirement	N.A.	2026
Macrogolglycerol ricinoleate (1082)	Ph. Eur.	No requirement	No requirement	N.A.	2017
Macrogol stearate (1234)	Ph. Eur.	No requirement	No requirement	N.A.	2019
Macrogol stearyl ether (1340)	Ph. Eur.	No requirement	No requirement	N.A.	2008
Polysorbate 80 (0428)	Ph. Eur.	No requirement	No requirement	N.A.	2025

WHO requirements

The WHO Annex 3 Good manufacturing practices for excipients used in pharmaceutical products (9) (Appendix 2) defines excipients at high-risk of EG/DEG adulteration as follows: Ethanol, 2-Propanol, Glycerol, Hydrogenated Starch Hydrolysates, Maltitol solution, Propylene Glycol and Sorbitol solution. Furthermore, it defines a list of other excipients that may be contaminated by DEG and EG including: Polyethylene Glycol (Macrogol), Diethylene Glycol Stearates, Polyethylene Glycol Monomethyl Ether 350/550 (molecular weight below 600 only), Polyoxyl 35 Castor Oil, Polysorbate 20/40/60/80, Polyoxyl 15 Hydroxystearate, Polyoxyl 20 Cetostearyl Ether, Polyoxyl 8 Stearate, Octoxynol 9, Nonoxynol 9.

WHO have developed a two-level testing strategy for finished liquid oral preparations that can be adapted also to analyze samples of excipients. Suspect samples are first screened for non-compliance using a semi-quantitative thin-layer chromatography (TLC) method with a limit of detection of 0.20%. If the result is positive the material is subjected to a quantitative gas chromatography (GC) test. Note: This testing methodology is intended mainly for National Quality Control Laboratories (NQCLs) for screening of finished products (10, 11).

In addition to materials testing, WHO strongly advocates for supply chain integrity to improve compliance and regulatory oversight of high-risk excipients. Pharmaceutical manufacturers using these materials should be ensuring that sourcing, distribution, supply, documentation, use and disposal of packaging, are all being conducted in compliance with GMP and GDP requirements (2).

Risk of economically motivated adulteration on excipient ethoxylates

There are a few factors mitigating the risk of economically motivated adulteration of solid excipients with a liquid substance (EG/DEG). For instance, after manufacture, it is not physically feasible to incorporate a liquid into the solid material using a simple mixing process.

In addition, most excipient ethoxylate monographs contain a requirement for testing of the hydroxyl value (OHV) to characterize the ethylene oxide chain length. Economically motivated adulteration with significant amounts of EG and/or DEG will cause the OHV value to be out-of-specification. For example, consider a calculation of the theoretical OHV of blends of Polyoxyl Stearate 8 adulterated with EG (OHV= 1807 mgKOH/g) or DEG (OHV= 1057 mgKOH/g) (Table 3) (Note: For the purposes of this example, we have assumed

Table 3. Calculated hydroxyl value (OHV) for blends of Polyoxyl Stearate 8 with EG and DEG

PEG8 stearate (%)	EG or DEG (%)	blend with EG (OHV)	blend with DEG (OHV)
100	0	92,5	92,5
99,9	0,1	94,2	93,5
99,5	0,5	101,1	97,3
99,2	0,8	106,2 *	100,2
99	1	109,6	102,1
98,5	1,5	118,2	107,0 *
90	10	264,0	189,0
75	25	521,1	333,6
50	50	949,8	574,8
20	80	1464,1	864,1
0	100	1807	1057

* OHV in red correspond to first values above the upper OHV specification limit (i.e 105 mgKOH/g)

a batch of Polyoxyl Stearate 8 with a OHV value 92.5, i.e. in the middle of the OHV specification (80 - 105 mgKOH/g)). It is very clear that a contamination of just 0.8% EG or 1.5 % DEG is enough for this ethoxylated excipient to fail the OHV specification (see OHV data in red in the table that are above the 105 mgKOH/g limit). Thus, these adulterated excipients would not meet the compendial specification and would be rejected and not used in the production of pharmaceuticals.

Safety levels

It is generally recognised that a 0.10% maximum content for EG and DEG is considered an adequate safety level for ingestion by humans and for this reason, the limits are set at this level in most Pharmacopeial monographs.

ICH Q3C guidance on residual solvents permitted daily exposure for EG is defined as 6.2 mg/day (calculated from

the NOAEL of 150 mg/kg/day and considering several safety modifying factors) that corresponds to a limit of 620 ppm (= 0.0620%) based on a maximum daily intake of 10g of the ingredient. There is no mention of DEG in the ICH Q3C guidance, but its toxicity is considered lower than EG given that the NOAEL for DEG is 300 mg/kg/day (12).

Despite these safety considerations, both USP and Ph. Eur. monographs for Ethylene Glycol Stearates and Diethylene Glycol Stearates (that correspond to esters of EG and DEG mainly used in topical applications) have EG and DEG residual limits well above the 0.10% threshold, i.e., 5.0% for EG and 2.5% DEG respectively (Table 4)

Moreover, the recently revised USP Polyethylene Glycol (PEG) monograph which became official in August 2025 states limits of NMT 0.062% (620 µg/g) for EG and NMT 0.25% (2500 µg/g) for the sum of EG+DEG for PEG's 200, 300 and 400.

These examples highlight that the 0.10% threshold is a safe limit to avoid cases of economically motivated adulterated materials, but higher limits might be reasonable for excipients that contain EG/DEG as by-products of their synthesis process.

Supply chain integrity

Although the FDA, EMA and the WHO have different EG/DEG views on testing requirements in terms of product scope and frequency (as ID or as impurity testing), they all agree that improving the integrity of the supply chain is critical because the cases of EG/DEG contamination have happened outside of excipient manufacturing sites. Ensuring fully documented traceability to the excipient manufacturer, documented supply chain maps and proper excipient manufacturer and distributor qualifications, should avoid new cases of economically motivated adulteration with EG/DEG without the need for testing of every single container (13-14)

Table 4. Current situation of USP and Ph. Eur. monographs for EG/DEG esters regarding residual EG/DEG

Monograph	Pharmacopeia	EG limit	DEG limit	Monograph Section	Monograph date
Ethylene Glycol stearates	USP	5.0%	No requirement	Tests	Prior 2013
Ethylene Glycol monopalmitostearate	Ph. Eur.	5.0%	No requirement	Tests (impurities)	2020
Diethylene Glycol stearates	USP	No requirement	2.5%	Tests (impurities)	2025
Diethylene Glycol palmitostearate	Ph. Eur.	No requirement	2.5%	Tests	2020

CONCLUSIONS

The lack of alignment on the scope of excipients considered at risk from EG/DEG contamination, and differences in the testing requirements from various regulatory authorities are causing unnecessary challenges to excipient manufacturers and users.

Global harmonised risk-based regulatory requirements are essential to reduce the likelihood of new cases of EG/DEG contamination, especially in regions where the risk of fraudulent activities in the supply chain may be more common. However, these measures need to be efficient and must provide a high degree of safety against EG/DEG

adulteration. This can be achieved, not only by mandatory EG/DEG ID testing of all excipient containers but also by ensuring integrity and full traceability of the supply chain (chain of custody) and through proper supplier qualification processes.

In addition, without compromising patient safety, it would be beneficial to have a distinction between testing regimes and limits prescribed to prevent cases of economically motivated adulteration from situations where EG/DEG are present at low levels as process impurities, and for which gross adulteration would be detected by the hydroxyl value compendial testing (such as for excipient ethoxylates).

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