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BANNED EXCIPIENT COMBINATIONS IN COUGH SYRUPS: A REVIEW ON GLOBAL SAFETY AND REGULATORY CONCERNS

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ABSTRACT

The safety of pharmaceutical excipients used in cough syrup formulations has emerged as a critical global issue due to several incidents of contamination and toxicity. Although excipients are considered pharmacologically inactive, recent evidence indicates that they can significantly affect product safety, especially in paediatric formulations. Contaminants such as Di-Ethylene Glycol (DEG) and Ethylene Glycol (EG) have led to fatal poisonings, prompting worldwide recalls and regulatory interventions. Between 2022 and 2025, the World Health Organization (WHO) and National Drug Authorities including the U.S. Food and Drug Administration (FDA) and India's Central Drugs Standard Control Organization (CDSCO) issued multiple alerts on substandard cough syrups. The 2021 study by Zupanets et al. provided critical insights into the cumulative risks of excipients in paediatric Phyto mucolytic syrups, reinforcing the need for regulatory vigilance and comprehensive safety evaluation of excipients. This review highlights the significance of recent global bans, mechanisms of toxicity, and the urgent call for harmonized excipient testing standards.

KEYWORDS: Banned excipients, cough syrup, Di-Ethylene Glycol, Ethylene Glycol, WHO alert, Excipient toxicity, Paediatric safety, Pharmaceutical regulation.

1. INTRODUCTION

Cough syrups are widely used pharmaceutical preparations for symptomatic relief of respiratory conditions. They typically contain active ingredients such as Dextromethorphan, Ambroxol, or Guaifenesin, combined with excipients like solvents, sweeteners, preservatives, and flavouring agents to improve stability and palatability. Although these excipients are conventionally viewed as inert, multiple global health emergencies have demonstrated that they can become toxic or even lethal when contaminated or improperly used.

Excipient's are substance other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug-delivery system to assist in processing, protect or enhance stability or bioavailability, aid patient acceptability, or improve other aspects of the final drug product.

The contamination of excipients such as Glycerin, Sorbitol, or Propylene Glycol with toxic substances—mainly Diethylene glycol (DEG) and Ethylene Glycol (EG)—has caused catastrophic incidents. The earliest known tragedy, the 1937 Elixir Sulphanilamide disaster in the United States, resulted in over 100 deaths and led to the establishment of the Food, Drug, and Cosmetic Act. Despite this historical lesson, similar incidents have recurred globally. Between 2022 and 2025, cough syrups contaminated with DEG and EG caused hundreds of paediatric deaths in Gambia, Uzbekistan, and India, leading to multiple WHO Medical Product Alerts.

The toxicology of these glycols is well-documented: upon ingestion, DEG and EG are metabolized into glycolic acid and oxalic acid, leading to severe renal failure and metabolic acidosis. Their presence in paediatric formulations is therefore unacceptable, and both WHO and national agencies have classified DEG and EG as prohibited excipients in oral liquid medications.

Zupanets et al. (2021) contributed significantly to this area by assessing the cumulative risks of excipients in paediatric Phyto mucolytic syrups. Their study highlighted that even permissible excipients, when used in high quantities or in combinations, can have adverse effects on metabolic, hepatic, and renal systems of children. They emphasized that excipient safety must be viewed in the same light as API toxicity, especially for chronic or paediatric use. This reinforces the urgent need for excipient toxicity profiling and risk-benefit assessment before formulation approval.

Regulatory responses have included WHO's call for global DEG/EG testing, FDA's guidance on mandatory analytical verification for glycerin-based solvents, and CDSCO's directive for DEG/EG testing in all Indian-manufactured liquid orals. These measures aim to establish a consistent and traceable quality assurance framework across the pharmaceutical supply chain.

Case study: 1

A fresh drug safety scare has emerged in India after the Union Health Ministry confirmed that a batch of Coldrif cough syrup manufactured at a Tamil Nadu facility contained Diethylene Glycol (DEG) above permissible limits. While samples of the syrup collected earlier from Madhya Pradesh tested negative, contamination was detected when Tamil Nadu regulators tested products directly at the manufacturing site in Kanchipuram.

The states of Madhya Pradesh and Tamil Nadu have now banned the sale of Coldrif, and the Centre has ordered risk-based inspections at 19 pharmaceutical manufacturing units across six states, the Ministry of Health and Family Welfare (MoHFW) said on Sunday in an official release. According to the Health Ministry, these inspections aim to identify systemic quality control gaps in drug manufacturing, especially among smaller firms where oversight may be weaker.

At the same time, a multidisciplinary team of experts from the National Institute of Virology (NIV), Indian Council of Medical Research (ICMR), National Environmental Engineering Research Institute (NEERI), Central Drugs Standard Control Organisation (CDSCO), and All India Institute of Medical Sciences (AIIMS) Nagpur is investigating whether DEG exposure could be linked to recent child deaths reported in Chhindwara, Madhya Pradesh.

What are DEG and EG, and why are they dangerous?

According to the World Health Organization (WHO), Di-Ethylene Glycol (DEG) and Ethylene Glycol (EG) are industrial solvents widely used in antifreeze, paints, brake fluids, and plastics. They have no therapeutic role in medicines but can enter pharmaceutical formulations when contaminated or cheaper industrial-grade raw materials are used instead of pharmaceutical-grade excipients such as glycerine or propylene glycol.

Once ingested, DEG and EG break down into toxic metabolites that damage the kidneys, liver, and nervous system, says WHO.

Symptoms of poisoning include

Nausea

Vomiting

Abdominal pain

Drowsiness

Reduced urination

In children, this can escalate rapidly to acute kidney failure, seizures, and death. “DEG and EG can be fatal even in small amounts, especially for children,” the WHO said.

Earlier in 2022, The Gambia saw at least 70 children die after consuming cough syrups contaminated with DEG and EG. Similar incidents have been documented in Panama, Nigeria, and Haiti over the past decades.

WHO’s global warning on cough syrup contamination

WHO has repeatedly raised alarms about the dangers of DEG and EG in cough syrups. In its alerts, the organisation linked such contamination to more than 300 child deaths worldwide since 2022.

To strengthen safeguards, WHO has recommended a two-step testing approach

1. Thin-layer chromatography (TLC) for quick screening of syrups
2. Gas chromatography for confirmatory analysis

The agency has also urged governments to

1. Tighten surveillance of pharmaceutical supply chains
2. Remove substandard or falsified medicines from circulation
3. Ensure manufacturers only procure pharmaceutical-grade ingredients

Why this matter for India?

India is the world’s largest producer of generic medicines, often referred to as the “Pharmacy of the World.” Incidents like this not only raise public health concerns domestically but also threaten India’s global pharmaceutical reputation.

For parents and patients, the discovery serves as a reminder to always check government advisories before using over-the-counter syrups. For policymakers, it underscores the urgency of closing regulatory gaps in raw material sourcing, manufacturing oversight, and supply chain transparency.

As the probe continues, the MoHFW (Ministry of health and family welfare) has said that the priority remains on removing contaminated products from circulation and ensuring accountability in the pharmaceutical ecosystem to prevent another tragedy.

Global lessons from DEG incidence

The World Health Organization (WHO) issued an alert on Monday identifying oral cough syrups manufactured in India that contain Diethylene Glycol (DEG), a substance typically used as an industrial solvent and in antifreeze. According to the BBC, at least 20 children in India have died after ingesting these cough syrups.

WHO said it received a notice from India's Central Drugs Standard Control Organization (CDSCO) on 8 October alerting it to the presence of DEG in at least three oral liquid drugs. WHO said it first identified "localized clusters of acute illness and child fatalities" on 30 September 2025.

CDSCO has confirmed to WHO that state authorities ordered an immediate halt to production at the implicated manufacturing sites and suspended product authorizations. The affected products have since been recalled by state authorities.

CDSCO also informed WHO that none of the contaminated medicines have been exported from India and there is no evidence of illegal export of the drugs. WHO "encourages National Regulatory Authorities (NRAs) to consider targeted market surveillance, with particular attention to informal and unregulated supply chains where products may circulate undetected. NRAs are also advised to carefully evaluate the risks associated with any oral liquid medicines originating from the same manufacturing sites—particularly those produced since December 2024."

WHO said it is working closely with Indian health authorities to monitor the situation, identify the source of contamination, and mitigate potential public health risks.

The US Food and Drug Administration (FDA) also issued a warning addressing the contaminated cough syrups, noting that the drugs have not been shipped to the US.

FDA said there are reports of a fourth cough medicine has been linked to adverse events in children in India, Dextromethorphan Hydrobromide syrup manufactured, which has also been

recalled by Indian authorities. However, testing of that drug in India has not detected DEG or Ethylene glycol (EG) contamination. FDA said it is in contact with CDSCO and is coordinating its response efforts with WHO.

DEG-tainted cough syrups have been a global problem in recent years. In 2022, contaminated cough syrups from India were tied to 70 child deaths in Gambia and 18 in Uzbekistan.

According to WHO's health alert issued in January 2023, reports of contaminated cough syrups containing DEG and EG were linked to 300 deaths in three countries in 2022, with most of the fatalities occurring in children. (RELATED: WHO proposes updated excipient GMPs in wake of contaminated cough syrup, Regulatory Focus 10 April 2023).

CONCLUSION

The recurrent episodes of cough syrup-related fatalities underscore systemic deficiencies in the regulation, testing, and certification of Pharmaceutical Excipients. Banned excipients such as diethylene glycol and ethylene glycol continue to pose a global threat due to inadequate quality monitoring and supply chain oversight. The study by Zupanets et al. (2021) further reinforces the concept that excipients, though pharmacologically inactive, can have cumulative toxic effects, particularly in vulnerable paediatric populations.

To prevent further tragedies, global harmonization of excipient standards is essential. Each batch of solvent-based excipients must be analytically verified, and manufacturers must adhere strictly to WHO and national guidelines. A paradigm shift is required in pharmaceutical formulation design—where excipient safety is treated with the same rigor as active ingredients. Through vigilant regulation, transparent sourcing, and responsible manufacturing, the pharmaceutical industry can eliminate preventable harm from excipient-related toxicity.

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