

Update on incidents of over-the-counter syrups for children with confirmed or suspected contamination with high levels of diethylene glycol and ethylene glycol

Report by the Secretariat

BACKGROUND

1. The WHO Global Surveillance and Monitoring System for substandard and falsified medical products (GSMS) is responsible for recording, assessing and using data concerning substandard and falsified medical products to improve their prevention, detection and response in order to protect public health. The aim of GSMS is to facilitate accurate assessments of the scope, scale and socioeconomic harm caused by substandard and falsified medical products and support affected Member States.

2. Recorded incidents of fatal levels of diethylene glycol and ethylene glycol in medical products date as far back as 1937 and have been reported in all WHO regions, with a particularly devastating impact on children. This threat is therefore not new and is widely recognized within the global health community. Since January 2020, GSMS has recorded 21 incidents of over-the-counter syrups for children with confirmed or suspected contamination with high levels of diethylene glycol and ethylene glycol. Diethylene glycol and ethylene glycol are hazardous chemicals that have been used, both accidentally and deliberately, as cheaper substitutes for pharmaceutical-grade solvents like propylene glycol, glycerol and sorbitol in the production of liquid oral medicines. In all the incidents reported to GSMS, the contaminated medical products were oral syrup formulations, many of which were specifically marketed for children, and they have reportedly been linked to hundreds of cases of acute kidney injury and more than 350 deaths, mainly of children under the age of five, in at least five Member States.

Substandard (contaminated) medical products

3. Since 2012, GSMS has recorded at least 56 substandard medical products, most of which were indicated for treating the symptoms of coughs, colds and allergies, with confirmed or suspected contamination with high levels of diethylene glycol and/or ethylene glycol. The recorded contaminated medical products include syrups whose manufacture, export and supply had been authorized both at the point of manufacture and in the market where they were consumed. Some of the products were not, however, authorized to be on the market in the country in which they were consumed. The labels indicate that, to date, all the recorded contaminated medical products have been manufactured in the WHO South-East Asia Region (84%), the WHO Eastern Mediterranean Region (9%) and the WHO Western Pacific Region (7%), and they have so far been detected in five of the six WHO regions –

European (43% of the products), South-East Asia (20%), African (14%), Eastern Mediterranean (12%) and Western Pacific (11%).

WHO medical product alerts

4. Through GSMS, WHO can issue medical product alerts in response to incidents arising from substandard and falsified medical products that pose a significant threat to public health. Since October 2022, WHO has issued six medical product alerts following the identification in seven Member States of 11 medical products and 39 affected batches with confirmed or suspected contamination with high levels of diethylene glycol and ethylene glycol.¹ As a result of the alerts, valuable information on the source and distribution of these medical products has been received by WHO, and other Member States have been able to identify contaminated products and take immediate steps to remove them from circulation within their respective jurisdictions.

WHO response

5. In January 2023, WHO issued a call to action to all Member States and national health authorities to: detect and remove contaminated medical products from circulation within their respective jurisdictions; increase surveillance and diligence within the supply chains of countries and regions likely to be affected by contaminated medical products; notify WHO immediately following the identification of contaminated medical products; and inform the public of the dangers and potentially fatal effects of contaminated medical products.

6. The WHO Incidents and Substandard/Falsified Medical Products technical team responds immediately to reported confirmed or suspected incidents of contaminated medical products by engaging with national regulatory authorities in the affected Member State(s). Guidance and support are provided for market surveillance, sampling of suspected contaminated medical products and, if necessary, laboratory analysis. With the support of the national regulatory authority of the country of manufacture, WHO seeks to identify the source of the contaminated medical products as well as any regional or global distributors. If this information is made available, it is then immediately shared with any potentially affected Member State(s).

7. WHO has encouraged Member States that have detected over-the-counter syrups for children with confirmed or suspected contamination to continue risk-based post-market surveillance programmes and identify and sample more products for analysis. WHO has also called on Member States to improve the reporting and monitoring of potential signals of suspected or confirmed adverse events that may be linked to contaminated syrups, such as a spike in the number of cases of acute kidney injury.

8. The Steering Committee addressed this matter during its meetings in March and June 2023. It was agreed that the Working Groups would explore ways to tackle this issue as part of their ongoing activities. Proposals for work to be performed in 2023 by existing Working Groups were discussed, together with a zero-draft set of terms of reference for a potential future Working Group on excipients for 2024–2025.

9. WHO has undertaken to review and update WHO guidance on the control of raw materials, manufacturing processes and quality control for excipients and products that are either potential sources of or at a high risk of contamination. WHO is also developing screening and detection testing methods

¹ Full list of WHO medical product alerts [website]. Geneva: World Health Organization; 2023 (<https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts>, accessed 4 October 2023).

for the presence of diethylene glycol and ethylene glycol in raw materials, excipients and medicines. Furthermore, efforts are ongoing to identify Member State needs regarding access to appropriate laboratory testing facilities and to support the improvement of regional capacity for testing confirmed or suspected contaminated medical products.

10. WHO is collaborating with international business associations and researchers through formal and informal engagements to improve understanding of the market for pharmaceuticals and develop responses to ameliorate the situation.

11. In partnership with stakeholders such as UNODC, WHO will support research aimed at improving understanding about whether illicit networks and/or actors are involved in the production of contaminated excipients, as well as the vulnerability of supply chains. The aim of the research will be to:

- (a) assess the risk of the accidental or deliberate adulteration, substitution and/or falsification of pharmaceutical-grade solvents with diethylene glycol and ethylene glycol;
- (b) determine the scale and nature of the involvement of illicit networks and/or actors; and
- (c) propose interventions for Member States to consider.

ACTION BY THE MEMBER STATE MECHANISM

12. The mechanism is invited to note the report. In its discussions, it is further invited to provide comments and guidance in respect of the following questions:

- how can Member States be encouraged and supported to promptly, openly and comprehensively report incidents involving substandard and falsified medical products that could have an immediate and far-reaching impact on other Member States?
- in what ways can the mechanism support and advocate for this kind of systematic reporting of incidents and exchange of information thereon in order to mitigate the international impact of such incidents?

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