IPEC Position Paper

Latest fatal incidents with contaminated medicinal syrup during 2022/2023 - an updated IPEC Federation Position Paper

August 2023

Introduction

This is an update of an IPEC Position Paper on the above subject initially published in 2019 [1].

Below is an extract from a media briefing given by Tedros Adhanom Ghebreyesus, the World Health Organization (WHO) Director-General, on 24 January 2023 [2].

"…over the past four months, several countries have reported incidents of contaminated cough syrups for children. Last year, WHO raised the alarm by issuing medical alerts in October focused on the Gambia, in November about Indonesia, and earlier this month regarding Uzbekistan. The cases in these three countries are associated with more than 300 deaths, but we know that at least seven countries have been affected. Most of the deaths have been in children under the age of five. These contaminants are toxic chemicals used as industrial solvents and antifreeze agents that can be fatal even in small amounts, and should never be found in medicines. This week, WHO released an urgent call for countries, manufacturers and suppliers to do more to prevent, detect and respond quickly to contaminated medicines. Governments must increase surveillance so they can detect and remove from circulation any substandard medicines identified in the WHO medical alerts. They must also enforce legal measures to help stop the manufacture, distribution and use of substandard and falsified medicines. And manufacturers must purchase pharmaceutical grade ingredients from qualified suppliers and conduct comprehensive testing before using them; And suppliers must always check for signs of contaminated medicines and only distribute or sell medicines authorized by, and from sources approved by, competent authorities; All unnecessary deaths hurt but when children die that pain is magnified and demands a requisite response."

Each of these recent cases relates to the use of medicinal syrups that were manufactured using non-pharmaceutical grade excipients such as propylene glycol, glycerine, sorbitol or polyethylene glycol, all of which were contaminated with ethylene glycol (EG) and/or diethylene glycol (DEG).

Historical background

Since 1937, when the first similar adulteration case of this kind was identified, there have been numerous cases that have caused several hundred deaths due to the use of excipients of inappropriate quality in pharmaceutical formulations (for an overview see [3]).

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WHO published a communication in 1998, summarizing the numerous cases to date, stating that there were more than 500 deaths in the past 60 years with contaminated/mislabelled/falsified excipients [4].

Guides, Standards, Regulations and Monographs

The initial document targeting this severe and reoccurring problem was the WHO Good Trade and Distribution Practices for Pharmaceutical Starting Materials (GTDP) first published in 2003 and updated in 2016 [5]. It was developed to provide guidance on how to assure security in the supply chain for pharmaceutical starting materials including how to maintain excipient quality, traceability and integrity from the excipient manufacturing sites downstream to the finished dosage form manufacturer. Subsequently, further Guides, Standards and Regulations were established, e.g.

- the International Pharmaceutical Excipients Council (IPEC) Good Distribution (GDP) Guide for pharmaceutical excipients, first published in 2006 [6] and updated in 2017 to provide industry guidance for supply chain security by applying appropriate GDP principles.
- the “Falsified Medicines Directive“ (2011/62/EC), published by the EU commission in 2011 explicitly targeting falsified medicinal products [7].
- the IPEC GDP Guide was supplemented in 2012 by an IPEC-sponsored certifiable standard for GMP and GDP for excipient manufacturers and suppliers – EXCiPACT [8] as well as the NSF/IPEC/ANSI 363 standard [9].

The IPEC Federation Guides were initially developed along with new guides to improve the security of the supply chain, for the current versions see [10].
Additionally, the United States Pharmacopeia - National Formulary (USP-NF) [11], European Pharmacopoeia (Ph. Eur.) [14] and the Japanese Pharmacopoeia (JP) [15] added the testing of Glycerine for traces of residual ethylene glycol and diethylene glycol into the corresponding monographs. Similar tests are part of the corresponding monographs for Propylene glycol in the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia - National Formulary (USP-NF).

Recurrence of issues during 2022 and 2023

There were no significant new cases reported between 2012 and 2022, implying that the new guides, standards and regulations, and their application, had improved the overall situation.
Nevertheless, some new cases of contaminated medicinal syrups occurred during 2022 and 2023 resulting in more than 300 deaths in different countries in Africa, Asia and the Pan-Pacific region, see recent Medical Product Alert communications by the WHO [12].
Initial findings from the WHO indicate the following areas require more focus and in-depth investigation:

- Criminal activity
- Falsification of records (namely CoAs)
- Supply Chain complexity
- Lack of, or insufficient QC testing

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- Use of industrial grade material

These findings suggest that the current issues are similar to issues identified in cases prior to 2012.
In general, the blending or falsification of well-known pharmaceutical excipients such as propylene glycol, glycerin, maltitol, sorbitol and polyethylene glycol with industrial products seems to be the underlying principle of all the cases referred to in this Position Paper. The majority of reported cases since 1937 is in connection with the contamination of medicinal products with ethylene glycol and diethylene glycol [12].
The U.S. FDA recently published a new guidance in May 2023 for immediate implementation by industry: Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol [13].
It contains a general introduction section, a background section, listing the various previous cases and similarities, a section about applicable regulatory requirements in the United States and a fourth section with recommendations to safeguard the quality and safety of medicines from DEG and EG contamination.
Section three highlights three similarities in all cases:

1. No full identity testing of glycerin, including tests to quantify the DEG content, by the manufacturers of the liquid drug products
2. Reliance on the certificates of analysis (COA) provided by the supplier of glycerin, by the manufacturers of the liquid drug products
3. Unknown chain of custody or distribution history, because the origin of the glycerin was not readily apparent from the COA, and the COA of the original manufacturer was not provided by the supplier

Major recommendations in section four include:

- Ensure specific identity analysis for each lot, with samples from all containers of all lots, and a limit test for DEG and EG with a safety limit for DEG and EG of NMT 0.10%, even if there is no testing for DEG and EG in the identity test of the corresponding product USP-NF monograph
- Drug product manufacturers to maintain current knowledge of the supply chain, including the origin of the original manufacturer and any subsequent repackers or distributors of high-risk drug components
- Awareness of personnel of the importance of DEG and EG contamination testing and potential hazards
- Repackers and others who distribute and prepare should test high-risk components for use in drug products, with issuance of accurate and complete COAs, which identify the original manufacturer [14] [15].

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Toxicity Aspects

IPEC Federation wishes to reemphasize the points made in the Introduction that ethylene glycol and diethylene glycol are chemicals for use in industrial applications only, such as for example, industrial solvents, coolants and antifreeze agents. Ethylene glycol and diethylene glycol are not approved for use in pharmaceutical applications. When consumed by human beings, especially young children, e.g., as components of a medicinal syrup or other liquid pharmaceutical formulations, they lead to significant toxicity effects. Depending on the dose, these effects may include severe kidney damage potentially resulting in death.

IPEC Federation Position and proposed actions

In general, the IPEC Federation believes that the tools to ensure security of the excipient supply chain are already available (see section above on guides, standards and the references), but believes that the following areas require greater awareness and compliance by all actors involved with the supply chain of pharmaceutical excipients:

- Awareness and robust application of guides, standards and regulatory requirements
- Starting materials to be purchased from qualified and approved suppliers
- Purchase of ingredients suitable for use in pharmaceutical products/pharmaceutical grade excipients, no use of industrial grade chemicals as pharmaceutical excipients
- Robust incoming goods inspection, quality control testing and product release according to applicable monographs or equivalent validated and appropriate internal method(s)
- Full traceability of the supply chain back to the original excipient manufacturer
- Awareness and application of Risk Management principles
- Training system and records

The IPEC Federation will consider the findings of the WHO investigation and the FDA guidance to identify if any updates are required to be made to GMP and/or GDP Guides in order to ensure an ongoing robust supply chain.
This Position Paper should be brought to the attention of all stakeholders in the supply chain of pharmaceutical excipients. Additionally, IPEC Federation believe that this issue should also be brought to a wider public attention through mass media.

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