MCAZ Medicines Control Authority of Zimbabwe

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To: All Pharmaceutical Manufacturers

PREVENTION OF DIETHYLENE GLYCOL (DEG) AND ETHYLENE GLYCOL (EG) CONTAMINATION IN PHARMACEUTICALS

The Authority has noted with concern the recurring cases of oral liquid formulations that are contaminated with Diethylene Glycol (DEG) and Ethylene Glycol (EG). Diethylene Glycol (DEG) and Ethylene Glycol (EG) are toxic substances that can be fatal, when taken in small amounts. DEG and EG in liquid dosage forms such as cough, allergy, analgesic, and antiemetic syrups will result in toxicity and fatalities once they exceed concentrations of 0.10%. Since 2022 to date, there have been reports of DEG and EG poisoning cases due to consumption of contaminated medicines in several parts of the world, resulting in more than three hundred deaths of which most of these fatalities were children.

Findings from investigations by the World Health Organisation (WHO) indicated that the root causes of DEG and EG contamination of medicinal products were:

- A lack of, or insufficient Quality Control (QC) testing of starting materials.
- Use of industrial grade starting materials.
- Falsification of records, namely, certificates of analysis (COAs) and reliance on supplier COAs by finished pharmaceutical product (FPP) manufacturers.
- Supply chain complexity - the chain of custody or distribution history of high-risk ingredients was not readily known or apparent from the COA.

Regarding DEG and EG contamination, starting materials of concern which are considered as high-risk starting materials for pharmaceutical formulations are: **Glycerine (Glycerol)**, **Propylene Glycol**, **Maltitol Solution**, **Hydrogenated Starch Hydrolysate**, **Sorbitol Solution**, and other pharmaceutical ingredients whose synthesis or degradation might result in the generation of DEG and EG.

Considering the above, pharmaceutical manufacturers making use of high-risk starting materials should conduct rigorous testing of such materials as per current Good Manufacturing Practices (cGMP) requirements and in particular test for DEG and EG contamination as described in the respective pharmacopeial monographs of each starting material.

The purpose of this circular is to outline the regulatory position and pro-active measures to be taken by pharmaceutical manufacturers to ensure that all oral liquid formulations registered with MCAZ are not contaminated with DEG or EG.

The Authority hereby instructs all finished pharmaceutical product (FPP) manufacturers of oral liquid formulations registered in Zimbabwe which could potentially be contaminated with DEG and EG to implement the following preventative measures with immediate effect:

1. Upon receipt of raw materials from suppliers, FPP manufacturers must conduct adequate testing of all containers of all lots of high-risk starting materials to be used in pharmaceutical formulations. Testing for DEG and EG contamination in the high-risk materials should be done in accordance with respective pharmacopeial monographs. Skip-lot testing of these high-risk materials will not be acceptable. Proof of testing will be verified during routine cGMP audits.
2. FPP manufacturers making use of high-risk starting materials should not rely on supplier COAs for DEG and EG test results.
3. In cases where the FPP manufacturer outsources DEG and EG testing, copies of raw data should accompany the COA from the contract laboratory.
4. Finished product testing for DEG and EG as described in the International Pharmacopeia (currently stated in the WHO Working Document QAS/23.922/rev3) should be done on formulations containing high-risk starting materials.
5. FPP manufacturers should only make use of pharmaceutical grade starting materials. The use of non-pharmaceutical grades e.g. industrial grade will not be acceptable.
6. Vendors and/or manufacturers of high-risk starting materials should be adequately qualified. FPP manufacturers should be able to trace the supply chain and custody of starting materials right from the starting material manufacturer to their warehouse.
7. FPP manufacturers are required to test for DEG and EG in retention samples of oral liquid formulations whose batches are currently on the market, if these had been released without testing for DEG and EG.

Yours faithfully

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

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R.T. RUKWATA (Mr.)
DIRECTOR GENERAL