

STUDY OF CONTAMINATION CONTROL IN THE PHARMACEUTICAL INDUSTRY: ETHYLENE GLYCOL AND DIETHYLENE GLYCOL

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ABSTRACT

Study of Contamination Control in The Pharmaceutical Industry: Ethylene Glycol and Diethylene Glycol.

Contamination cases in health products are on the rise, mainly due to ethylene glycol and diethylene glycol contaminants, which contribute to the high number of child deaths. Contamination caused by toxic compounds should be controlled and minimized to ensure public safety and security. Therefore, contamination control needs further review. This paper aims to discuss HACCP and GMP procedures for controlling and minimizing contaminants in the pharmaceutical industry, as well as policies and coordination between actors to prevent the recurrence of cases of ethylene glycol and diethylene glycol contamination. The research used the literature study method, with hazing's publication or perish as a search tool. The results of this paper show that in the application of HACCP, there are several critical control points, namely the manufacture of drugs, the removal of materials, screening of raw materials, dry mixing, mixing, and packaging. GMP implements controls on sanitation and hygiene, equipment, self-inspection and supplier approval audits, personnel, training, personal hygiene, and locations and buildings. In order to prevent the recurrence of contamination cases, it is necessary to apply policies related to suppliers of raw materials, raw materials, and the application of GMP. Coordination between actors at the country and company scales is necessary to prevent the recurrence of ethylene glycol and diethylene glycol contamination cases.

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INTRODUCTION

A safe production process is crucial to maintaining public health and meeting consumer demand for safe products without contamination. Contamination can cause various losses to society and can even result in death. Cases of contamination in health products are increasing due to the high mortality they cause. Ethylene glycol and diethylene glycol triggered these cases in Gambia and Indonesia. In Gambia, the case resulted in the deaths

of 69 children⁽¹⁾. Meanwhile, cases in Indonesia resulted in the deaths of 169 children due to the consumption of cough syrup⁽²⁾. Figure 1 details the timeline of ethylene glycol and diethylene glycol contamination cases in Indonesia.

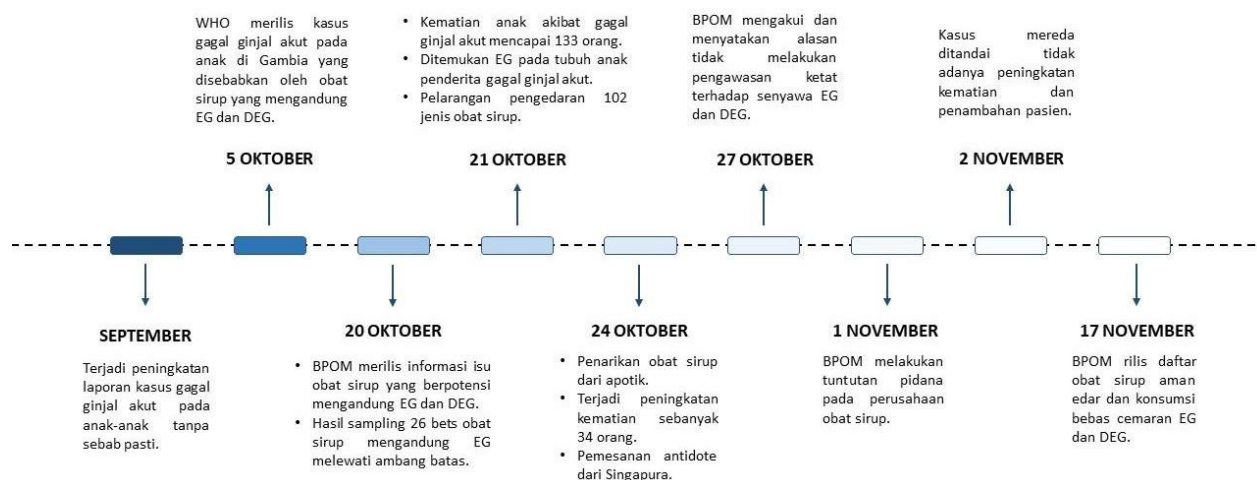


Figure 1. Timeline of Ethylene glycol (EG) and Diethylene glycol Contamination Poisoning Cases (DEG) in Indonesia in 2022.

Ethylene glycol and diethylene glycol are used by several industries as solvents, a toxic compound that, if misused, can lead to high mortality rates^(3,4). When ethylene glycol is consumed, it causes a buildup of calcium oxalate in the kidneys, resulting in kidney failure⁽⁴⁾. Meanwhile, diethylene glycol will obstruct the citric acid cycle, causing necrosis in kidney cells. Numerous factors can trigger contamination⁽³⁾. Contamination occurred in The Gambia as a result of a production process disruption. Meanwhile, in Indonesia, contamination occurs due to supplier changes and a lack of coordination of raw material imports⁽²⁾.

Controlling contamination in the production process is important. We can carry out control through Hazard Analysis, Critical Control Point (HACCP), and Good Manufacturing Practice to control the production process and minimize contamination. Regulations must also support the control and minimization of contaminants. In addition, the interconnection of actors is necessary to maintain community security as part of biosecurity. Therefore, this paper aims to discuss how to control and minimize contaminants through HACCP and GMP procedures in the production process, as well as discuss policies and coordination between actors to avoid the recurrence of contamination cases.

MATERIALS AND RESEARCH METHODS

The research method used is a literature study; all the data collected comes from journals, books, or other sources. The literature study method exclusively relies on written works, encompassing both published and unpublished research results. This methodical approach can provide knowledge about controlling ethylene glycol and diethylene glycol contaminants. Types of data used.

In literature studies, data is either textual or conceptual. We obtained data using search tools like Harzing's publish or perish. The software Harzing's publish or perish streamlines the process of finding neatly arranged articles connected to various publication sites like Google

Scholar, Scopus, and Web of Science, providing valuable reference material for literature studies.

We conducted an analysis on 20 related pieces of literature about contamination control in the pharmaceutical industry. This literature focuses on the topic of preventing ethylene glycol and diethylene glycol contamination in the pharmaceutical industry, especially regarding HACCP, GMP, regulations, and actor coordination, with a research period of 10 years. We carried out data analysis through a process that included data reduction, data display, and content analysis.

RESULTS OF RESEARCH AND DISCUSSION

The HACCP method analyzes, evaluates, prevents, and controls hazards that arise from product design, development, production, and use ⁽⁵⁾. HACCP can ensure the quality and safety of products from contaminants and has an effect on improving the quality of pharmaceutical products because it identifies critical points for handling toxins and contaminants and ensures product safety. ^(6,7). Figure 2 illustrates the seven principles that underpin HACCP.

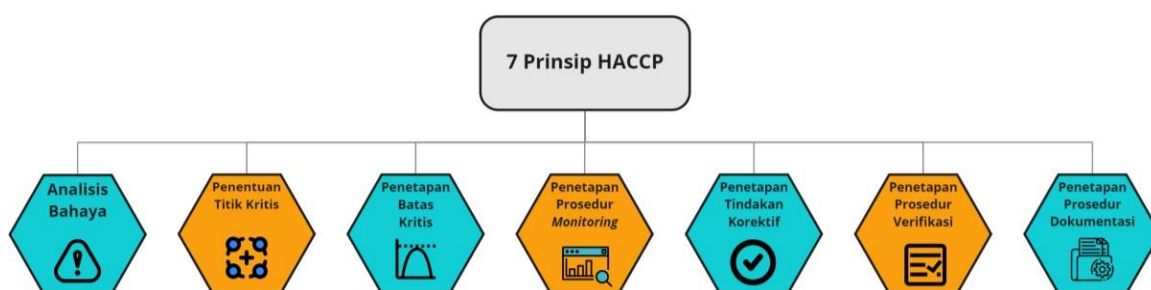


Figure 2. Seven Principles of HACCP⁷.

A special team handles HACCP in the pharmaceutical industry, and they must implement a pre-requested program (PRP) in the form of HACCP training in accordance with WHO guidelines ⁽⁸⁾. The stages of HACCP that require execution are as follows ⁽⁹⁾:

1. Process characterization

We carry out characterization starting from the release of raw materials, product processing, and delivery.

2. Product Description

To prepare preventive measures to protect workers during the production process, we describe medicines according to their type.

3. Critical Control Point Analysis and Corrective Actions

The analysis of critical control points serves to identify monitoring points. Next, we identify hazard monitoring procedures and develop them into corrective actions. Table 1 illustrates the critical control points in the pharmaceutical industry that require consideration.

We compile the results of HACCP analysis regarding critical control points and corrective actions into quality control documents and SOPs to serve as a foundation for control ⁽⁹⁾. Periodically, we carry out and verify checks, then record them for further HACCP improvements.

HACCP implementation employs risk assessment tools that have been proven to reduce production deviations by 50% and improve company performance. Effective assessment tools for HACCP: (1) Use check sheets and process flow to identify hazards and make decisions based on their severity and suitability between processes. (2) Hazard assessment using Pareto analysis and cause-and-effect diagrams to identify problem sources and critical control points, and facilitate the search for appropriate corrective actions; (3) Determining hazard controls using Kaizen and Six Sigma analysis approaches to handle contamination⁽⁸⁾.

GMP (Good Manufacturing Practice)

GMP is a method that plays a role in ensuring that the drugs produced are controlled according to quality standards and marketing authorization requirements to produce quality products, as it can be challenging for customers to identify high-quality drugs ⁽¹⁰⁾. GMP's application closely aligns with HACCP, as GMP serves as the initial prerequisite for HACCP, thereby reducing risk, as it forms the foundation of processing security. The aim of GMP is to maintain public health and reduce risks in the production process⁽¹¹⁾. Many countries have implemented GMP regulations in the pharmaceutical industry to reduce drug damage and ensure higher quality and safety⁽¹²⁾.

In order to follow GMP, there must be a clear, standardized, and consistent manufacturing process; operators must be trained to follow procedures correctly; all processes must be accurately recorded; and any problems must be looked into and dealt with in a firm way. We keep records in a form that is simple to understand and access, minimize product damage through storage and distribution, and have a system to recall each batch of products from sale. ⁽⁷⁾

Workers or operators influence the effectiveness of GMP, so it is necessary to carry out training and quality assurance for workers⁽¹³⁾. The government must conduct systematic monitoring in the pharmaceutical industry to minimize the use of substandard medicines. ⁽¹²⁾ We can keep an eye on aspects of control such as:

1. Sanitation and Cleanliness

Sources of contamination must be eliminated through an integrated sanitation and hygiene program, including workers, premises, equipment, and products for cleaning and disinfection. This can be maintained by cleaning the equipment or building, before and after use⁽⁷⁾.

2. Equipment

Manufacturing equipment is designed to be easy to clean. The surface of the tool in contact with the product must be flat and smoothly polished without gaps, and there are no parts that harbor contaminants⁽¹¹⁾

3. Supplier Self-Inspection and Approval Audit

An inspection program is designed to detect deficiencies in GMP implementation and for corrective action ⁽¹⁴⁾. The inspection team is workers appointed by management and can evaluate GMP implementation objectively. In the supplier audit section, the purchasing department sends orders to suppliers that have been approved by QA, QC and production. Different supplier batches in one shipment must be separated with different internal lot numbers. Each container is in good condition, labeled "Quarantine", "Code Number", "Material Name", "Lot Number", and "Date Received"⁽⁷⁾.

4. Personnel, Training, and Personal Hygiene

Implementation must be carried out by experts specifically tasked with monitoring GMP. Expert workers can explain rules and training that are easy to understand, and take notes.

GMP supervisors must have a high level of experience, skills and knowledge to monitor activities effectively. All workers will receive initial GMP training (7).

5. Places and Buildings

Buildings must pay attention to the design of water, steam, electricity and other channels that minimize the risk of errors, and are easy to clean to avoid contamination⁽¹¹⁾. The building wall design is made of concrete. Walls and floors are coated with epoxy for easy cleaning and resistance to chemical use. The ceiling must be strong, made of asbestos, non-flammable, and plastered using gypsum board. Door and window frames ownlayers that are hard, smooth, waterproof, tightly sealed, and installed facing inside the production area⁽¹¹⁾.

Policies in Handling Ethylene glycol and Diethylene glycol Cases in the Pharmaceutical Industry

Policy has an important role in ensuring the quality, safety, and efficacy of medicines, as well as protection for the community. ⁽¹⁵⁾ Policies exist to address quality system errors caused by the absence of an effective control system, timely quality reviews, and prevention and improvement plans ^[16]. There are several institutions that regulate production policies for pharmaceutical companies globally, such as the US Food and Drug Administration (FDA), the EU European Medicines Agency (EMA), and the Australian Therapeutic Goods Administration (TGA). Each institution implements policies differently. For instance, the TGA centrally implements GMP, while the EMA allows state authorities to determine the procedures⁽¹⁷⁾.

In the pharmaceutical industry, policies alone are insufficient to regulate the production process. The emergence of cases of ethylene glycol and diethylene glycol contamination in cough syrups in Indonesia highlights the need for changes in raw material suppliers. Several Indonesian factories switched from pharmaceutical to chemical raw material suppliers to mitigate high raw material prices⁽²⁾. The shift from pharmaceutical to chemical raw material suppliers compromises the purity of the obtained raw materials, rendering them unsuitable for processing into medicines⁽²⁾. Pharmaceutical suppliers provide raw materials that are clearly pure and suitable for use in drug and food production. The impure solvent used causes contamination of ethylene glycol and diethylene glycol.

The case in Indonesia highlights the need for the pharmaceutical industry to prioritize other policies, specifically those related to raw material suppliers and raw material policies. This is particularly important when handling cases involving ethylene glycol and diethylene glycol. Suppliers play an important role in pharmaceutical production because they can change processes and facilities. Therefore, maintaining the quality of operations requires an inspection system. ⁽¹⁸⁾ Companies can determine policies by integrating suppliers and practices according to standards.

Companies can integrate suppliers by establishing the following policies: (1) providing a key performance index (KPI) for measuring supplier performance; (2) communicating regarding material quality; (3) engaging with the best suppliers; and (4) utilizing data to determine risk impact. ^(18.) The Food and Drug Supervisory Agency (BPOM) regulates raw material suppliers in Indonesia under Presidential Decree No. 80 of 2017. BPOM supervises the administration, manufacturing, and distribution of drugs within the community. Producers will face sanctions as outlined in Articles 60 to 63 UUPK19 if fraud occurs ⁽¹⁹⁾.

To ensure the production of quality medicines, policies for raw material selection are crucial. There are various raw materials used in a single process; some materials can pose risks to the process and final product⁽²⁰⁾. Raw materials that do not meet the requirements will have an impact on the quality, safety, and efficacy of medicines. Causes side effects and drug withdrawal⁽²¹⁾.

Implementation of policies as part of quality risk management aids in assessing the quality of raw materials and medicinal products ⁽²²⁾. You can implement two policies to ensure the quality of raw materials ⁽²⁰⁾:

1. Qualification Programs

Formal program to meet raw material requirements. When choosing a supplier, a company must consider the supplier's quality system through CoA. Certificates of analysis (CoA) provide information about raw material specifications, which need to be considered when evaluating the impact on the finished product.

2. Risk Based

This policy is used to determine the criticality of raw materials which will determine the level of testing required, beyond the CoA information. The standard standards for materials used in pharmacy are contained in the Pharmacopoeia. Testing procedures and standard standards can prove the quality of materials as excipients and raw materials in industrial processes⁽²¹⁾. The importance of regulations to ensure raw materials meet requirements and are suitable for their intended use has been recognized by many parties. This has led to the emergence of regulations that require the pharmaceutical industry to use pure ethylene glycol, not a mixture that can cause contamination in syrup drugs. This regulatory control is carried out by BPOM which regulates policies in the process of receiving raw materials in BPOM Regulation No. 34 of 2018.

Coordination of Actors in Handling Ethylene glycol and Diethylene glycol Cases in the Pharmaceutical Industry

In the case of ethylene glycol and diethylene glycol contamination that occurred in Indonesia, coordination between actors played an important role in handling the case. It is critical to identify who is involved and who holds the primary role ⁽²⁾. Actors who play a role in handling cases of ethylene glycol and diethylene glycol contamination on a national scale are the ministry of health, the BPOM agency, and pharmaceutical companies. Therefore, these actors are the ones who need to make efforts to overcome and prevent contamination from occurring again. Figure 1 illustrates the government's and BPOM's responsiveness in handling contamination cases.

We initiated coordination by analyzing WHO data about children in Gambia experiencing acute kidney failure as a result of syrup medication contamination. BPOM received this information, which depicted a similar situation to the surge in acute kidney failure cases in Indonesia. We then coordinated with the government to withdraw the drug, resulting in a drastic reduction in kidney failure cases, without any increase in deaths or additional patients. The time interval for reducing contamination cases with drug withdrawals in Figure 1 shows the effectiveness of the drug withdrawal policy in minimizing instances. So, in handling contamination cases in the pharmaceutical industry, government action to reduce policies based on coordination from several actors is important.

BPOM also plays an important role in cases of ethylene glycol and diethylene glycol contamination. This is because BPOM and the government both play a role in carrying out periodic production supervision to ensure that the drugs produced always meet quality requirements ⁽²³⁾. In this case, BPOM plays a role in coordinating with pharmaceutical companies to ensure the use of raw materials according to regulations, carry out periodic monitoring and evaluation, and carry out laboratory tests on critical parameters. This aims to explore all risk factors that cause kidney failure, both from drug sources and other potential causes. If drugs fail to meet quality standards, BPOM and pharmaceutical companies coordinate by stopping the production and distribution process, and recalling all products based on laboratory results indicating contamination or exceeding the threshold.

The government and BPOM's coordination plays a crucial role. Pharmaceutical companies and their actors must also coordinate to ensure drug quality. The actors involved in ensuring the quality of medicines within the company⁽²⁴⁾ need to coordinate:

1. Quality Assurance (QA)

QA coordinates with management and workers to ensure production activities comply with SOPs, carry out validation, training, mastery of infrastructure, and management of corrective and preventive actions.

2. Expert Team

A team of experts such as chemists, engineering and pharmaceutical experts play a leadership role to ensure GMP compliance. Coordination of the expert team is carried out with internal and external projects so that production runs according to SOP.

3. Laboratory Worker

Laboratory workers have a role important as a key to the GMP process and analysis related to drug quality. Coordination of laboratory workers is carried out with a team of experts and QA to inform the quality of the drugs produced.

An external coordination network is also needed to maintain drug safety. External coordination can be carried out with universities, pharmacies, hospitals, companies and other institutions so that development (clinical trials), research and development (R&D) of drugs with safety, efficacy and quality can be carried out ⁽²⁵⁾.

CONCLUSIONS AND RECOMMENDATIONS

Improvements to the production system, the implementation of regulations, and coordination among actors can handle cases of ethylene glycol and diethylene glycol contamination. In the production process, HACCP can be an alternative control by monitoring critical control points, namely releasing materials, sieving raw materials, dry mixing, mixing, and packaging. We can also implement GMP to reduce contaminants by focusing on sanitation and cleanliness, equipment, self-inspection, supplier approval audits, personnel, training, personal hygiene, and premises and buildings.

Implementing policies that focus on regulating raw material suppliers and the use of medicinal raw materials can also control cases of ethylene glycol and diethylene glycol contamination, ensuring the production of appropriate medicines. In case control, coordination among actors is crucial, not only with national-scale actors like the government, but also with internal companies and external actors like hospitals, pharmacies, and university researchers, to prevent the recurrence of contamination cases. If the contamination case reoccurs, we can implement the following treatment recommendations:

1. The government needs to respond quickly to cases of increasing disease or high mortality.
2. When a case arises, BPOM and the laboratory team must conduct an investigation right away.
3. To reduce the increase in cases, the government must take firm action immediately, such as recalling goods.
4. We must distribute case information equitably.

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