United Nations
Office on Drugs and Crime

World Health Organization

CONTAMINATED MEDICINES AND INTEGRITY OF THE PHARMACEUTICAL EXCIPIENTS SUPPLY CHAIN

THE UNITED NATIONS OFFICE ON DRUGS AND CRIME VIENNA
AND THE WORLD HEALTH ORGANIZATION

Contaminated Medicines and Integrity of the Pharmaceutical Excipients Supply Chain

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Abbreviations

AKI	Acute Kidney Injury
API	Active Pharmaceutical Ingredient
CDSCO	Central Drugs Standard Control Organization (India)
COA	Certificate of Analysis
CPP	Certificate of Pharmaceutical Product
DEG	Diethylene Glycol
DRAP	Drug Regulatory Authority of Pakistan
EG	Ethylene Glycol
FPP	Finished Pharmaceutical Product
GBT	Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products (WHO)
GC-MS	Gas Chromatography-Mass Spectrometry
GSDP (cGSDP)	(Current) Good Storage and Distribution Practice
GMP (CGMP)	(Current) Good Manufacturing Practice
GSMS	Global Surveillance and Monitoring System for Substandard and Falsified Medical Products (WHO)
GXP	Good Practice Guidelines
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHR	International Health Regulations
IPEC	International Pharmaceutical Excipients Council
IPR	Intellectual Property Rights
LMIC	Low and Middle Income Countries
MLAT	Mutual Legal Assistance Treaty
MQCL	Medicine Quality Control Laboratory
NRA	National Regulatory Authority
OCG	Organised Crime Group
PG	Propylene Glycol
PIC's	Pharmaceutical Inspection Cooperation Scheme
PPM	Parts Per Million
PQS	Pharmaceutical Quality System
QA	Quality Assurance
QC	Quality Control
QRM	Quality Risk Management
SDG	Sustainable Development Goals (UN)
SFMP	Substandard and Falsified Medical Product
SMACS	Starting Material Certification Scheme
TLC	Thin Layer Chromatography
UNODC	United Nations Office on Drugs and Crime
UNTOC	United Nations Convention against Transnational Organised Crime
USFDA	United States Food and Drugs Administration
WCO	World Customs Organization
WHO	World Health Organization
WLA	World Health Organization Listed Authority

Glossary

Active pharmaceutical ingredient

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

Adverse Event

Any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with this treatment.

Excipient

A substance, other than the active pharmaceutical ingredient, that has been appropriately evaluated for safety and is included in a drug delivery system to:

a) Aid in the processing of the drug delivery system during its manufacture.
b) Protect, support or enhance stability, bioavailability or patient acceptability.
c) Assist in product identification; and
d) Enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

Falsified medical product

Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Finished Pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container or labelling.

High risk excipients

Excipients that pose a greater risk of contamination or quality issues, which can significantly impact the safety and efficacy of the final pharmaceutical product.

Incident

A documented occurrence of detecting a suspected or confirmed substandard/falsified medical product at a specific time and location.

National Regulatory Authority

A government agency or department responsible for ensuring the safety, efficacy, and quality of medicines and other health products within a country.

Organised Crime Group

A structured group of three or more persons, existing for a period of time and acting in concert with the aim of committing one or more serious crimes or offences established in accordance with UNTOC, in order to obtain, directly or indirectly, a financial or other material benefit.

Pharmacopoeia
A legally binding collection of standards and quality specifications for medicines, and their ingredients used in a country or region.

Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Rapid alert
A notification system used to quickly communicate urgent information about serious risks to public or animal health. This system is employed by National Regulatory Authorities when a significant threat from substandard or falsified medical products is identified.

Raw Material
A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or excipients for pharmaceutical use.

Serious Crime
Conduct constituting an offence punishable by a maximum deprivation of liberty of at least four years, or a more serious penalty.

Substandard medical product
Also called 'out of specification' these are authorized medical products that fail to meet either their quality standards or their specification, or both.

Starting Material
A pharmaceutical starting material is an active pharmaceutical ingredient, or an excipient intended or designated for use in the production of a pharmaceutical product.

Unregistered/unlicensed medical product
Medical products that have not undergone evaluation and/or approval by the National or regional medicines regulatory authority for the market in which they are marketed and/ or distributed.

WHO Global Surveillance and Monitoring system for substandard and falsified medical products (GSMS)
The WHO system which maintains a centralized global database of incidents of substandard and falsified medical products identified and reported by Member States and stakeholders.

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Foreward

With a profound sense of responsibility, we present this joint report by the United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO). For nearly a century, a recurring and preventable tragedy has claimed the lives and compromised the health of countless patients, predominantly children, through the ingestion of medicines contaminated with dangerously high levels of toxic chemicals.

This report exposes the persistent nature of this preventable harm, revealing that what were once considered isolated incidents are, in fact, symptoms of systemic vulnerabilities within the global pharmaceutical supply chain, mostly facilitated by criminal actors.

The joint research by the United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO) examines a web of weaknesses and vulnerabilities that plague the excipient supply chain, a component of medicines manufacturing that is often ignored by regulatory authorities.

The report scrutinizes the adequacy of existing legislation, regulation, and guidance, and sheds light on the dangerous nexus between criminal exploitation, deficient manufacturing practices, and inadequate regulatory oversight.

In view of these challenges, this report culminates in a set of targeted and actionable recommendations for key stakeholders – National Governments, National Regulatory Authorities, criminal justice actors, law enforcement agencies, pharmaceutical manufacturers, suppliers, and distributors.

The implementation of these recommendations is not merely a policy option; it is an urgent imperative and call to action. Only through coordinated, decisive actions can we break the cycle of preventable harm and ensure that the tragic lessons of the past ninety years are finally addressed. Failure to act now will risk condemning future generations to the same unacceptable risks.

Contribution to the UN Sustainable Development Goals[1]

SDG 3 Good Health and Well being

Sustainable Development Goal 3 seeks to ensure healthy lives and promote well-being for all at all ages. Within the broader SDG, target 3.8 seeks to "achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all." This report helps Member States understand the vulnerabilities in the excipient supply chain and how criminal actors exploit these vulnerabilities. This assists Member States reduce the preventable and unnecessary harm caused to patients, predominantly children, through ingesting medicines contaminated with high levels of toxic chemicals.

SDG 16 Peace, Justice and Strong Institutions

Sustainable Development Goal 16 seeks "To promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels." Target 16.4 of SDG16 aims to "by 2030, significantly reduce illicit financial and arms flows, strengthen the recovery and return of stolen assets and combat all forms of organized crime." This report identifies how criminals seek to profit from the trade in contaminated excipients. Furthermore, target 16.5 emphasises the need to "substantially reduce corruption and bribery in all its forms." The report also details how bribery and corruption within private and governmental organisations is a contributing factor in the trade of contaminated excipients and medicines.

Executive Summary

The preventable and unnecessary harm caused to patients, predominantly children, through ingesting medicines contaminated with high levels of toxic chemicals (diethylene glycol (DEG) and ethylene glycol (EG)) has continued for the past 90 years.

At least 25 reported cases have led to over 1300 reported deaths and many more hospitalizations leading to life changing injuries. Reports suggest that these cases are isolated, unusual, and anomalies, often reported following a cluster of obviously linked adverse events in patients. Recent developments indicate that this issue is more common than first thought.

Since October 2022 the World Health Organization (WHO) have issued 7 Medical Product Alerts concerning multiple batches of contaminated liquid oral medicines, many of which were marketed for paediatric use and exported widely to low- and middle-income countries (LMIC). WHO also issued 2 Alerts concerning falsified bulk chemicals masquerading as pharmaceutical quality excipients.

Following a particularly serious case in The Gambia in which at least 66 children lost their lives attention was once again focused on this issue. The case in The Gambia was quickly followed by similar incidents in Indonesia and Uzbekistan with a further 268 reported deaths and two further WHO Medical Product Alerts.

Most of the recent cases involve inexpensive oral liquid medicines that can be bought without a prescription. In most cases these medicines were marketed specifically for children and are registered medicines available in pharmacies, medicine stores or informal street markets.

The widespread attention of the public, regulators, international organizations and the media together with a WHO call to action aimed at all stakeholders led to an increased level of vigilance. A widely accessible screening methodology to detect the presence of the toxic contaminants was also developed and rolled out.

The heightened awareness, global attention and availability of testing led to an increase in the detection and reporting of more oral liquid medicines containing toxic levels of contaminants. Further global and national alerts and recalls of contaminated oral liquids or excipients have followed in all 6 WHO regions.

Initial suspicions focused on volatility in the excipient markets during the COVID-19 pandemic. Whilst this may have been a contributory factor in the most recent upsurge of cases, it fails to explain the numerous historic cases where no apparent contributory factor exists. Rather, more embedded and deep rooted behaviours and bad practices existent in the supply chain together with weak oversight of excipients combine to create a fertile environment for the tragedies that have followed.

What has become clear during this research is that intentional criminal behaviours including the falsification of excipients, accentuated by poor compliance with regulatory requirements is a persistent and pervasive threat to public health. In some cases, detailed investigations have been carried out, resulting in the successful prosecution of those involved. In other cases, prosecutions have failed due to poor investigations and prosecutors inexperienced in pharmaceutical related crimes.

Incidents of contaminated medicines result in a range of negative social and economic consequences from serious harm to public health, damage to confidence in the quality, safety and efficacy of medicines and their regulatory oversight, and financial losses. Due to the globalization of the pharmaceutical market the actions of a few small traders and manufacturers have a disproportionately negative impact, often on a global scale.

This joint United Nations Office on Drugs and Crime (UNODC) and WHO research focuses on weaknesses and vulnerabilities in the excipient supply chain, and the adequacy of existing legislation, regulation and guidance. Through a literature review, subject matter expert interviews, a series of case studies, and a field study it examines the nexus between criminal actions and poor manufacturing and distribution practices.

Finally, it suggests a set of recommendations for key stakeholders, the implementation of which is an effort to prevent the unfortunate certainty of history repeating itself.

Key Findings

Criminal Actors

1. Criminal actors have recognised that a market exists for certain pharmaceutical grade excipients that are vulnerable to availability and price fluctuations.
2. Certain high-risk excipients have been subject of intentional dilution, substitution, and mislabelling.
3. Falsified labels purporting to be from multinational excipient manufacturers are being affixed to drums of toxic chemicals to lend credibility to the product, claiming to be pharmaceutical grade excipients, and offered for sale to the pharmaceutical, food and cosmetic industries.
4. E-commerce and social media platforms are being used by unlicensed and unregulated traders to market these falsified excipients.
5. Corruption of public officials has been used to facilitate access to markets of finished pharmaceutical products.

Manufacturers of High Risk Excipients

6. Manufacturers of high risk pharmaceutical grade excipients are not currently subject to regulatory oversight.
7. There is a lack of control on recycling or reuse of empty drums of pharmaceutical excipients resulting in packaging being passed on to third parties for reuse.
8. There is a lack of traceability systems used in relation to high-risk excipients.

Distributors of High Risk Excipient

9. Distributors of high risk pharmaceutical grade excipients are not currently subject to regulatory oversight
10. Certificates of analysis for pharmaceutical excipients are being altered, falsified, or are missing, causing uncertainty about excipient origin, quality and hindering traceability.
11. Commonly high-risk excipients pass through the hands of multiple intermediaries in different jurisdictions rendering traceability difficult.

Medicine manufacturers

12. Some medicine manufacturers are purchasing pharmaceutical excipients from untraceable traders and brokers without conducting any due diligence or vendor assurance.
13. Some medicine manufacturers, when required, are failing to test high-risk pharmaceutical excipients for the presence of impurities before use.
14. Medicines produced with contaminated pharmaceutical excipients are being marketed nationally and/or widely exported to low- and middle-income countries (LMIC)
15. Medicine manufacturers are improperly disposing of empty drums of pharmaceutical excipients to 3rd parties, with some drums still bearing their original labelling.
16. Some pharmaceutical manufacturers have accepted contracts to produce medicines from third parties having failed to conduct due diligence on their client's identity and background.

Regulation

17. There is currently insufficient regulatory oversight of medicines manufactured for export only purposes.
18. There is currently insufficient regulatory focus during inspections of the source or quality of high-risk excipients.
19. The incidents of contamination have revealed deficiencies in regulatory capacity, both in countries where these medicines were manufactured and those where they were used.
20. There is a lack of implementation, enforcement, and where necessary timely sanctioning of critical non-compliance with regulations regarding the use of contaminated high-risk excipients in some countries.
21. There is a lack of risk-based post market surveillance of medicines produced with high-risk excipients.

Healthcare Professionals

22. There is generally delayed identification, linking and reporting of cases involving hospitalizations or deaths associated with medicines contaminated with DEG/EG.
23. There is an absence of national poison centres in some countries that have suffered contaminations, and when available there is lack of coordination between the pharmaceutical, food and cosmetic sectors in supporting management of DEG/EG related poisoning.

Testing

24. There is a lack of reliable, robust, portable, and affordable screening devices capable of detecting impurities down to permissible levels in high-risk excipients.

Toxicity

25. Whilst there is a widely accepted tolerance level of certain impurities safely permitted in medicines for regulatory purposes, there is a lack of recent research into the toxicity levels of DEG and EG in humans.

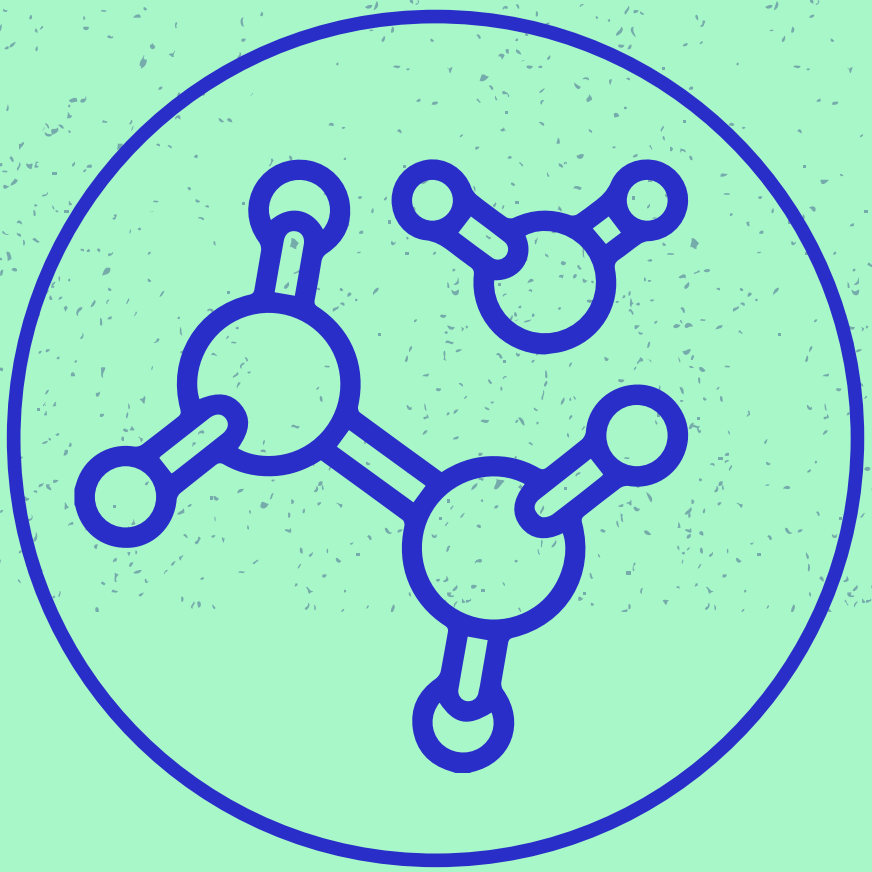
Reporting

26. Some countries are slow or entirely fail to report substandard/falsified medical products, including contaminated products, to the WHO Global Surveillance and Monitoring System (GSMS) for Substandard and Falsified Medical Products (SFMP), or via their International Health Regulations (IHR) focal points.

Investigation

27. Information exchange, collaboration and cooperation between law enforcement, customs and regulators enabling timely investigation and prosecutions is lacking in some jurisdictions.

PART 1



1. Introduction

The contamination of medicines due to the use of substandard/ falsified and toxic excipients is not a new phenomenon.

Since 1937 clusters of hospitalizations and deaths have occurred in all 6 WHO regions attributed to the presence of high levels of DEG and/or EG.

DEG and EG are industrial chemicals better known for use in the manufacture of engine coolant, lubricants, brake fluid, solvents, paints and in the manufacture of anti-freeze. They are colourless, odourless, sweet to taste and toxic in humans. The presence of DEG/EG as an impurity in pharmaceuticals is banned in some countries and is accepted in very small quantities in most others (0.10% (1000ppm)). They are being used as either a diluent or substitute for the more expensive pharmaceutical grade propylene glycol (PG), glycerine (also called glycerol) or sorbitol, which in their purest forms are safe to use in the manufacture of pharmaceuticals as solvents or sweeteners.

Frequently the medicines involved are cough, pain or fever oral liquid medicines intended for paediatric use which have led to many of the victims of these contaminations being aged under 5 years. The initial symptoms of EG & DEG poisoning are similar to other common diseases, but as the effects of the contaminated medicine progress they lead to acute kidney injury (AKI). In the absence of early diagnosis, advanced treatment or intensive care units, this condition may result in death, or in some cases permanent disability.

The WHO issued an alert on medicines contaminated with DEG in 1992[2]. The alert referred to three apparently unconnected incidents which had occurred in Argentina, Bangladesh and Nigeria. Those cases involved over 400 deaths due to either the mistaken use of DEG or the intentional mislabelling of PG.

From 2020 to date a surge of cases have arisen in all of the 6 WHO regions.

Since 2022 the WHO have issued 9 global Medical Product Alerts[3] relating to contaminated medicines and falsified excipients containing high levels of DEG/EG. Some of the cases subject of these alerts will be discussed more fully in this report.

These cases have often been identified due to healthcare professionals noticing a sudden increase in patients, often children, suffering from AKI, over a short period of time and in a very limited geographic area, sometimes at the same hospital. This pattern is linked to the distribution of the contaminated batch or batches of medicine. When the contaminated batch is distributed in a single location the sudden surge of patients will arise from that location and trigger further investigation. If the contaminated batch is more widely distributed and consumed over a longer period of time, the cluster of cases may be less obvious to healthcare professionals and is more likely to go unreported.

The WHO alerts have led to increased vigilance and risk based post market surveillance in some Member States, which in turn has resulted in further reports. This suggests that the issue of contamination is likely to be more widespread than originally thought and requires further investigation.

This report deals with identified/confirmed incidents attributed to medicines contaminated with DEG/EG through a series of case studies. It is suspected that there are many more incidents that may not have been recognized and have gone unreported.

1.1. Purpose and Focus

This research study has been conducted jointly by UNODC and WHO. It examines a subset of case studies involving contaminated medicines which are part of a wider series of similar cases that have led to over 1300 recorded deaths stretching back over a period of almost 90 years. The cause of the contaminations has been widely attributed to the use of a few substandard or falsified pharmaceutical ingredients, known as excipients, containing toxic levels of certain common contaminants.

This study is intended for a mixed audience of policy makers, medicine regulators, law enforcement officials, customs and border control, prosecutorial authorities and pharmaceutical industry. Some will be familiar with the complex set of regulations and guidance surrounding the manufacture and distribution of medicines, others not so. This study will not discuss the full set of existing guidance relating to the manufacture and distribution of medicines but will focus on the parts of that guidance with particular relevance to this research. Links will be provided in the endnotes to enable the reader to research the detailed regulatory requirements and guidance further.

This study examines the history, causes, and consequences of pharmaceutical contamination incidents, distinguishing between intentional crimes, negligence, and non-compliance. It analyzes supply chain vulnerabilities, motivations behind contaminations, the link between criminal activity and poor practices, and the effectiveness of current regulations, to identify potential mitigation strategies.

This report is structured in 4 parts.

- **Part 1** is designed to provide the reader with a better understanding of the purpose and background to the issue.
- **Part 2** provides a summary of the regulatory landscape including the manufacture, distribution, testing and regulatory enforcement of pharmaceutical excipients and finished pharmaceutical products (FPP).
- **Part 3** examines 8 case studies and a field study exposing the weaknesses and non-compliance with current regulation, and the vulnerabilities exploited and methods used by criminal actors.
- **Part 4** analyses the motivators, methods, enablers, criminality and responses leading to DEG/EG contamination of medicines and offers key recommendation from both a public health and a criminal justice perspective.

Finally, four annexes include a full set of recommendations, a guide to early identification, diagnosis and reporting, an aide memoire for the implementation of risk based inspections of pharmaceutical manufacturers and research methodology.

Through a clearer understanding of the underlying causes, actors involved and their methods, a better strategy can be developed to mitigate the risks and prevent reoccurrence.

This study and annexes will be submitted to the WHO for the information of the Member State Mechanism on substandard and falsified medical products for their consideration and any necessary action.

1.2. Background

The contamination of medicines with DEG/EG has been widely reported since it was first identified in the United States in 1937[4]. The incident happened following the discovery of a new drug which was effective in the treatment of a wide range of common and very serious ailments including serious infections. Pharmaceutical manufacturers were quick to produce the medicine, and market demand was very strong, outstripping the ability to meet those demands. At the time regulatory oversight was all but absent and manufacturers began to take short cuts in the manufacturing process. One company began using a cheaper alternative excipient known as DEG as a sweetener, but also toxic, solvent.

During a four week period 105 people died from ingesting the contaminated medicine.

The owner of the manufacturing company was prosecuted under the existing legislation and fined for the adulteration and misbranding of the medicine.

This case led to the enactment of the US Food, Drug and Cosmetic Act 1938 and the formation of the US Food and Drugs Administration (US FDA), creating strict oversight of the manufacturing of medicines and a requirement for premarket testing.

From 1937 to 2019, at least 21 recorded incidents of mass poisonings involving contamination with DEG/EG have been recorded (see table 1) leading to over 1000 reported deaths. These incidents mainly involved medicines but also toothpaste and alcoholic drinks.

Table 1. Incidents of DEG/EG Contaminations 1937-2019

Date	Member State	Contaminated product	Contaminated Excipient	Contaminant	Approximate Reported Fatalities
1937	USA[5] [6]	Sulfanilamide	DEG**	DEG	105
1969	South Africa[7] [8]	Sedative	PG	DEG	7
1973	India[9]	Paracetamol syrup	PG	DEG	15
1985	Spain[10]	Burn cream	Sodium Lauryl Nitrate	DEG	5
1985	Austria[11]	Wine	Unknown	DEG	0
1986	India[12] [13]	Glycerine	Glycerine	DEG	21
1990	Nigeria[14] [15]	Paracetamol Syrup	PG	DEG	47
1990-92	Bangladesh[16]	Paracetamol Syrup	PG/Glycerol	DEG	339
1992	Argentina[17] [18]	Propolis syrup	PG	DEG	29
1994	Venezuela[19]	Paracetamol Syrup	PG	DEG	Unknown
1995	Haiti*[20]	Paracetamol Syrup	Glycerine	DEG	100
1998	India[21] [22]	Paracetamol Syrup	PG	DEG	33
1998	India [23]	Cough syrup	Unknown	DEG	8
2004	France[24]	Herbal Remedy	Unknown	DEG	0
2006	China*[25]	Amillarisin A	PG	DEG	14
2006	Panama*[26]	Cough syrup	Glycerine	DEG	291
2007	Multiple[27]	Toothpaste	Unknown	DEG	Unknown

2008	Nigeria[28 29]	Teething formula	PG	DEG	84
2009	Bangladesh[30]	Paracetamol Syrup	DEG	DEG	28
2019	Brazil[31 32]	Beer	DEG	DEG	1
2019	India*[33]	Cough Syrup	PG	DEG	12

**Subject of case studies in this report*
*** In this case DEG was used as the excipient*

Following many of these earlier reported cases there were calls for a tightening of the excipient supply chain to prevent further incidents occurring. Good manufacturing and distribution practices were established, and regulatory inspections of pharmaceutical manufacturers improved. Whilst progress was made some incidents were occurring in low- and middle-income Member States, where regulatory practises were less mature, under resourced and where no medicine quality control laboratories existed.

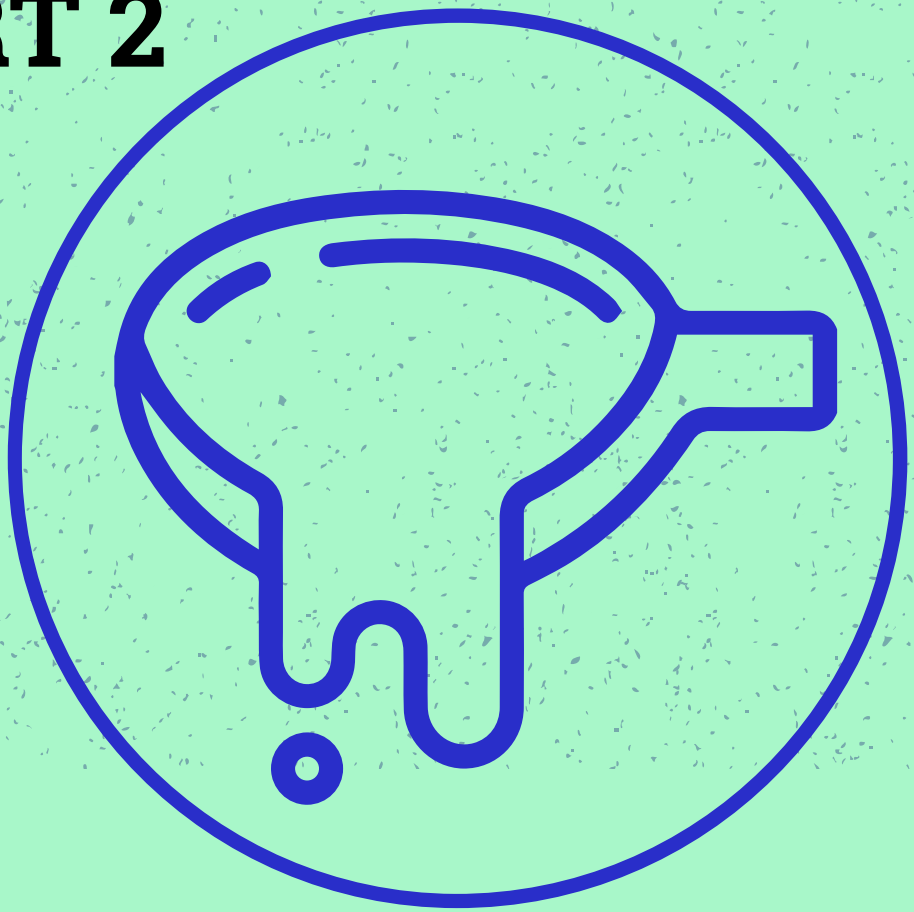
The most recent series of reported incidents have arisen since 2022 and have affected all 6 WHO regions[34]. Since 2022, WHO have issued 9 Medical Product Alerts relating to the contamination of medicines or excipients with DEG/EG as reported by Member States. Four of these incidents led to serious adverse events in patients including over 300 deaths (see table 2).

Table 2. WHO Alerts concerning DEG/EG Contaminations 2022-2024

WHO Alert Issued[35]	WHO Alert Number	Member State	Contaminated product	Country of origin	Contaminant	Reported fatalities
05/10/2022	6/2022	The Gambia*	4 x Imported Cough Syrups	India	DEG and EG	Y 66
02/11/2022	7/2022	Indonesia*	8 x locally manufactured syrups	Indonesia	DEG and EG	Y 200
11/01/2023	1/2023	Uzbekistan*	2 x Imported syrups	India	DEG and EG	Y 68
25/04/2023	4/2023	Marshall Islands and Micronesia	Imported syrup	India	DEG and EG	N
19/07/2023	5/2023	Cameroon*	Imported Syrup	India	DEG	Y 12
07/08/2023	6/2023	Iraq	Imported Syrup	India	DEG and EG	N
07/12/2023	8/2023	Maldives, Pakistan, Belize, Fiji, Lao PDR	5 x Imported syrups	Pakistan	EG	N
15/04/2024	1/2024	Pakistan**	Falsified PG	Unknown	EG	N
10/10/2024	4/2024	Pakistan**	Falsified PG	Unknown	EG	N

** Subject of case studies*
***Subject of Field study*

PART 2



2. International Guidance & Regulatory framework for pharmaceutical excipients

All aspects of the development, production, distribution, inspection, quality control, and regulation of medicines are included in a set of good practice guidelines collectively known as GXP (or current GXP, (cCXP)). The principles of the guidelines focus on consistently achieving the safety, quality and efficacy of medicines through a process of quality and risk management systems.

A number of international organizations, regional and national medicine regulatory authorities as well as industry bodies, have collaborated to establish comprehensive sets of guidelines. Many of these guidelines represent regulatory requirements, the application of which are necessary to achieve regulatory compliance.

Consistent application of the guidelines is crucial for protecting patient safety. Non-compliance has contributed to numerous tragic incidents including mass poisonings due to the contamination or cross-contamination of medicines with DEG/EG subject of this report.

It is in this context that this report examines two specific aspects of GXP in relation to incidents of DEG/EG contamination concerning excipients. Firstly, Good Manufacturing Practice (GMP or cGMP) and secondly Good Storage Distribution Practice (GSDP or cGSDP) focusing both on pharmaceutical excipients and finished pharmaceutical products (FPP). This report does not set out to describe the detailed procedures and processes required by these guidelines and regulations but rather discusses the core elements required to mitigate the threat of contamination through their application and enforcement and point the reader to the relevant sections within the guidelines.

This report draws upon WHO guidelines[36], the International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH)[37], the Pharmaceutical Inspection Co-operation Scheme (PIC/S)[38] and guidelines published by the Federation of the International Pharmaceutical Excipients Council (IPEC)[39].

> Responsibility for ensuring the safety, quality and efficacy of a medicine, and that it meets the regulatory requirements of the market in which it will be distributed lies firmly with the manufacturer of that medicine.

2.1. Pharmaceutical Excipients

Excipients are used in many different industries and are manufactured in different grades (purities) according to their intended end use. Those used in the manufacture of pharmaceuticals are required to meet the highest grades or specifications of purity excluding as far as possible any impurities that may be generated during the manufacturing processes. If not carefully controlled, they can go on to affect the quality of the finished pharmaceutical products in which they are used. Those specifications are published in national and international pharmacopoeias in the form of monographs.

Pharmaceutical grade excipients represent a fraction of the chemicals produced globally and are usually more expensive than industrial grade alternatives due to their higher specifications, purity and production costs.

Pharmaceutical excipients[40] are defined by the WHO as follows:

A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a medicine delivery system to:

- aid in the processing of the medicine delivery system during its manufacture.
- protect, support or enhance stability, bioavailability, or patient acceptability.
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during storage or use

Some guidance documents include pharmaceutical excipients under the broader term 'starting materials' this term includes all components of a finished pharmaceutical product (FPP) including active pharmaceutical ingredients (API) and excipients, but for the purposes of this report the above definition of excipients will be used throughout.

Pharmaceutical excipients cover a wide range of substances and chemicals which are manufactured on an industrial scale. They rely on raw materials from animal, mineral, agricultural and petrochemical sources. The estimated size of the global pharmaceutical excipients market in 2024 was US $9.94 billion[41]. There are approximately 1000 pharmaceutical excipients[42] used as fillers, diluents, binders, solvents, suspension and viscosity agents, coatings, flavouring agents, disintegrants, colorants and preservatives.

The safety profiles of new pharmaceutical excipients need to be evaluated systematically for potential risk in humans. Excipients should also be evaluated for their source, quantity, purity, degradation profiles, and potential interactions with APIs and other components in the dosage form.

Excipient manufacturers are not themselves subject of regulatory oversight, but WHO guidelines call for the implementation of an appropriate level of GMP during the production, packaging, repackaging, labelling, quality control, release, storage and distribution of excipients intended for use in pharmaceuticals. Regulatory inspections of finished pharmaceutical product manufacturers should already be seeking assurances that the excipients being used have been sourced from excipient manufacturers demonstrating these standards.

2.2. Manufacturing of Pharmaceutical Excipients

WHO reviewed and published 'Good manufacturing practices for excipients used in pharmaceutical products'[43] in 2024 as part of their Technical Report Series. This document sets out the requirements for establishing and maintaining the quality and purity of pharmaceutical grade excipients. It extends through the receipt of raw materials, production, packaging, testing, release, storage and distribution.

The guidelines call for additional measures to be taken when manufacturing excipients for which scientific literature, information in the public domain or historical data indicate the presence of higher risk due to the potential formation of toxic impurities during manufacturing or contamination during storage and distribution.

The founding principles of good manufacturing practice are based on the implementation of comprehensive quality and risk management systems. Those systems should ensure, amongst others, full traceability and testing of materials used in the manufacture of excipients, complete batch records documenting the history of each batch of excipient produced, and full testing, including for known impurities to ensure it is of the required standard, together with a complete record of storage and distribution.

The guidelines state:

- Raw materials and packaging materials should be sourced from approved suppliers, and a procedure for supplier approval and monitoring should be followed.
- Specific tests based on risk of the material should be carried out and impurities should be identified and controlled to ensure each batch meets the required specification.
- Reference and retention samples should be kept allowing subsequent investigation and testing if required.
- Test results should be incorporated into a certificate of analysis (COA).

The guidelines further state the minimum requirements for labelling of excipients should include the following information.

- The name of the excipient and grade
- The batch number assigned by the manufacturer
- The expiry or retest date, if applicable
- Any storage conditions or handling precautions that may be necessary
- Warnings and any other appropriate precautions
- The name and address of the manufacturer

2.3. Distribution of pharmaceutical excipients

Supply chains for pharmaceutical excipients are commonly international and complex. These supply chains can involve combinations of intermediaries including importers, agents, brokers, traders, wholesalers, distributors, repackers, relabellers and freight carriers in multiple jurisdictions rendering traceability challenging. Documents, labelling and certificates of analysis can be lost, altered or supplied in various languages.

In 2016 the WHO published 'Good trade and distribution practices for pharmaceutical starting materials'[44].

The guidelines are applicable to those who engage in the trade or take possession, repack, relabel, manipulate, distribute or store a pharmaceutical excipient other than the original manufacturer.

Excipients for pharmaceutical use should be distributed through traceable routes. Product, batch, container identity and integrity should be maintained at all times. All labels should remain legible.

The guidelines state, COAs issued by the original manufacturer should be provided. If additional testing is carried out by an intermediary, all COAs should be provided.

COAs should document product traceability back to the manufacturer by naming the original manufacturer and the manufacturing site. COA's should indicate which results were obtained by testing the original material and which results came from skip-lot testing (pre-selected batches at pre-selected intervals) or other testing and should specify the organization responsible for issuing the COA.

Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results meet the required specifications.

The original manufacturer and the intermediaries handling the material should always be traceable and transparent; and this information should be made available to authorities and end-users, downstream and upstream, when requested.

2.4. Repackaging and Relabelling of pharmaceutical excipients

Pharmaceutical excipients are manufactured and supplied in bulk quantities, ranging from large-scale tanker shipments via sea, road, or rail, to the more manageable 1000-liter (1 metric tonne) intermediate bulk containers (IBCs) and 200-liter (approximately 215 kg) plastic or steel drums. Often repackaging is required to supply the excipients in smaller quantities which involves decanting the excipient into smaller containers and relabelling them. This process introduces risks requiring meticulous monitoring to prevent errors, while also complicating the supply chain and traceability.

The WHO guidelines[45] set out requirements of relabellers and re-packagers which include:

- In all cases, traceability back to the original excipient manufacturer should be documented by identifying the original manufacturer of the specific batch of the material and its manufacturing site.
- If the integrity and quality of the batch is maintained during repackaging and relabelling, then the original COA of the original manufacturer should be provided.
- If retesting is conducted, both the original and the new COA should be provided as long as the batch integrity is maintained. The batch referred to on the new COA should be traceable to the original COA.
- The reuse of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed in them will not be adversely affected.
- Containers of repackaged material and relabelled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.
- Each batch of repackaged material should be tested to ensure that the material conforms to documented specifications.
- Only official pharmacopeial methods or validated analytical test methods should be used for the analysis. Where alternatives to the test methods specified in a monograph are used to provide test results, those alternative methods should be demonstrated to be suitable and equivalent.

2.5. High risk pharmaceutical excipients

In 2025 WHO published guidance on high-risk excipients[46] In response to the recent incidents involving medicines contaminated with DEG/EG.

The guidance provides a list of high-risk excipients and contaminants, advising manufacturers of these excipients, as well as manufacturers of finished pharmaceutical products containing them, to implement control measures to ensure their safety, purity, and quality.

The list is dynamic and currently includes the excipients and contaminants most commonly identified in the recent incidents of contaminated oral syrup medicines including propylene glycol, glycerol (glycerine) and sorbitol. The guidelines emphasise the need to apply the principles of GMP to the manufacture and distribution of high-risk excipients.

Propylene glycol

Propylene glycol (PG) is an organic compound. It is viscous, colourless, nearly odourless liquid. It has low levels of toxicity and possesses a faintly sweet taste.

PG is manufactured in two grades, Industrial (technical grade) with a wide range of applications in the production of paints, resins, construction and automative parts and pharmaceutical grade used in foods, cosmetics and pharmaceuticals.

The pharmaceutical grade product has strict quality and regulatory requirements with specifications set out as monographs in the pharmacopoeias. The specifications required demand a high level of purity (at least 99.5%) and a very low level of impurities.

Ethylene glycol and diethylene glycol impurities can be present in the starting materials for one of PG manufacturing processes, formed as byproducts during synthesis, or result from product degradation during the manufacturing process. A pharmaceutical excipient manufacturer interviewed for this study stated their testing limits detected very low levels of DEG/EG of approximately 80ppm. Contrast this with regulatory requirements of not more than 1000ppm. Higher levels of impurities can however be seen in Industrial grade PG where less refining has taken place.

It is estimated that 4.09 million tons of PG were manufactured in 2024[47] with a global market estimated to be worth US $4.66 billion[48]. The majority is manufactured for use in the construction and transportation industries. Comparatively the market for pharmaceutical grade PG was estimated to be valued at just under US $1 billion (2024)[49].

The main manufacturing components of PG are propylene oxide, a derivative of the petrochemical industry, and glycerine a by-product of biodiesel production. The availability of these components is a major driver of the price of PG. Disruption to global supply chains during the COVID-19 pandemic pushed the cost of PG by almost 100% at the end of 2021, since that peak prices have now returned to pre pandemic levels. The cost of pharmaceutical grade PG varies depending on the country of production, but it is always significantly more expensive than industrial grade.

The specifications for pharmaceutical grade PG are set out in various national and regional pharmacopoeias.

Glycerine (Glycerol)

Glycerine is a naturally occurring colourless, odourless, sweet tasting, non-toxic, viscous liquid. It is widely used in consumer, food and pharmaceutical products. Glycerine is supplied in two main types, crude and refined. Crude glycerine is a by-product of the biodiesel industry and contains between 77%-90% glycerine. It has a number of industrial and agricultural uses.

Pharmaceutical grade glycerine is a refined version that has undergone purification to reach a level of 99.5% purity and with reduced limits of impurities. Strict quality control is necessary in the production of the pharmaceutical grade of this product and the specifications are published in the National and International pharmacopoeias. Diethylene glycol and ethylene glycol can occur as impurities during the manufacturing process of glycerine.

Purification of crude glycerine is complex and expensive. Refined glycerine is significantly more expensive than crude. The global refined glycerine market in 2024 was estimated at $4.6 billion[50] and the price of glycerine more than doubled during the COVID-19 pandemic returning to pre pandemic prices by December 2023[51].

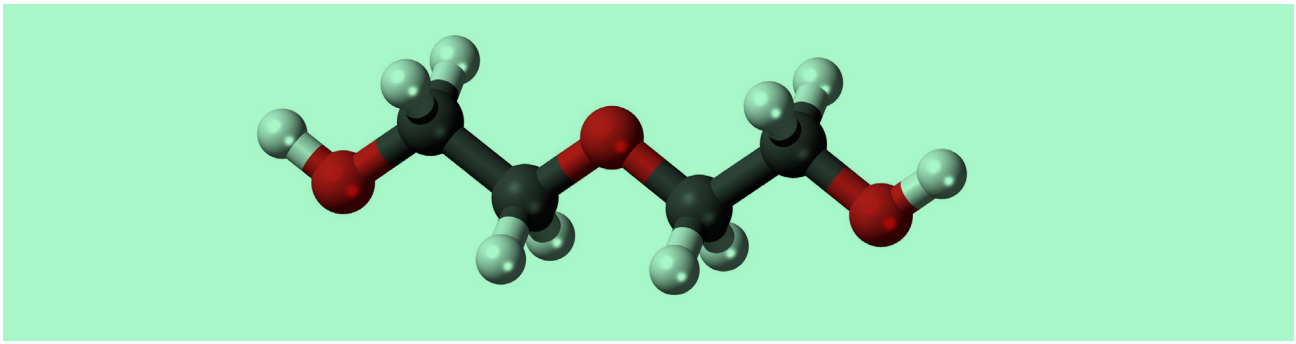
Sorbitol

Sorbitol is a sugar alcohol extracted from glucose using corn, wheat, potatoes and casava as the raw ingredients. It is manufactured in both a crystallized (granular) form and non-crystallizing (liquid) form. It is very widely used in the food, cosmetic and pharmaceutical industries. It is used in the manufacture of oral liquid medicines where it is used as a sweetener,[52] particularly in paediatric and diabetic formulations where sugar levels need to be controlled. It is estimated that 2.2 million tonnes were manufactured in 2023 with a market value of US $1.82 billion. The oral liquid form represents the bulk of the market.

EG and DEG can be present as impurities following the production of sorbitol.[53] The specification for sorbitol is set out in the national and international pharmacopoeias. One interviewee in the excipient industry stated that EG had been reported at levels of approximately 150 ppm and DEG at negligible levels. The accepted compendial limit is not more than 1000ppm (0.10%).

2.6 Contaminants in Pharmaceutical Excipients

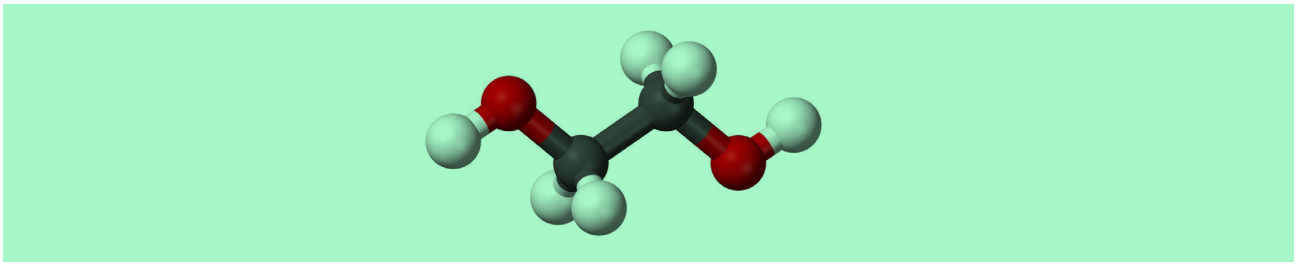
Diethylene glycol (DEG)



DEG is a colourless, odourless, sweet tasting liquid for use in industrial applications only, such as industrial solvents, coolants, brake fluids and antifreeze agents. It is not approved for use in food and pharmaceutical applications.

As of February 2025, the price of diethylene glycol is very close to pharmaceutical grade PG. Historically it was the most common contaminant in incidents of contaminated medicines, though more recently it has been replaced by EG which is at time of writing significantly less expensive.

Ethylene glycol (EG)



EG is a colourless, odourless, sweet-tasting chemical. It is mainly used in antifreeze, coolants, detergents, paints, lacquers, adhesives and cosmetics. As of February 2025, the price of ethylene glycol is significantly less than that of pharmaceutical grade PG and is more dominant as a contaminant in the most recent incidents.

Both of these contaminants may be present at trace levels as an impurity in the production of PG, glycerine and sorbitol. They are not authorised for use in the manufacture of pharmaceuticals.

Toxicity

The toxicity levels of DEG/EG in humans is not thoroughly understood. The lethal dose varies based on several factors including weight, age, dosage and length of exposure to the contaminated product. It is particularly dangerous in young children.

The clinical effects of DEG/EG[54] occur quickly once the substances have been metabolised in the liver. Symptoms typically include sickness, neurological effects and culminate in acute kidney injury (AKI) which if not treated quickly can result in death. Treatment options are limited and include administering Fomepizole, Ethanol or Dialysis[55].

Unfortunately, by the time DEG/EG poisoning is suspected, AKI has already taken hold of the patient and is difficult to treat, particularly in resource limited settings. DEG/EG poisoning in children carries a high risk of mortality or severe, lifelong morbidity. Outcomes are exceptionally poor.

For regulatory purposes the permitted level of DEG/EG in finished pharmaceutical products is most commonly restricted to not more than 0.10% (1000ppm). This limit represents a precautionary safety threshold established by regulatory bodies to minimize the risk of adverse health effects and is to ensure that even if trace amounts of DEG/EG are present, they are at levels considered to be relatively safe.

2.7. WHO Pharmaceutical starting materials certification scheme(SMACS)[56]

In 2003 WHO published guidelines on the implementation of the SMAC scheme. The purpose of the scheme was to urge Member States to establish and maintain a legal framework and regulatory approach to ensure that good practices for the trade and distribution of pharmaceutical starting materials were implemented. For the purposes of this specific guidance the term starting material includes pharmaceutical excipients. The SMACs guidelines recommend the licensing of suppliers, traders, brokers and distributors and/or a registration or notification system of suppliers, traders, brokers and distributors. It also recommends that where such arrangements are already in place the National Regulatory Authority (NRA) should inspect those engaged in the supply and distribution of pharmaceutical excipients to ensure compliance with good distribution practices.

The scheme is an administrative instrument that can be used by a Member State to officially attest to the use of a specific excipient in a finished pharmaceutical product approved for sale in its own or another country. Also, the manufacturing site in which a specific excipient is produced is subject to inspections to establish that it conforms to GMP.

The scheme can also be used by the manufacturer to attest compliance with a quality assurance system.

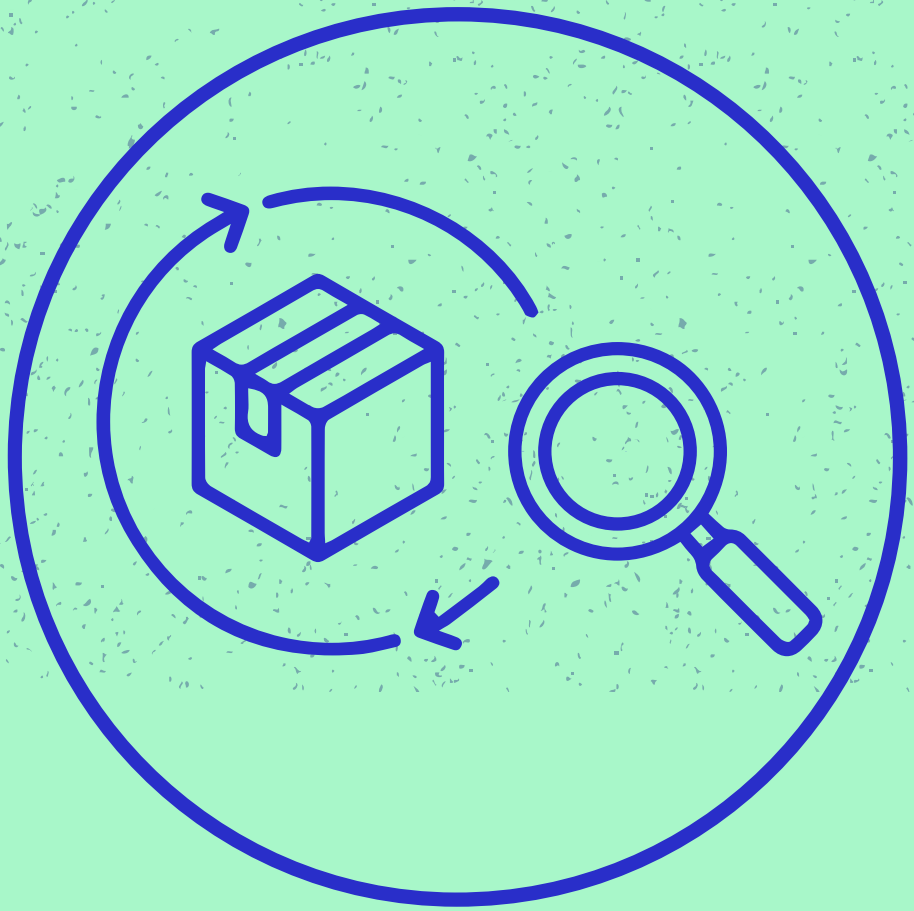
A certificate for pharmaceutical starting materials can be requested by the exporter, importer or competent authority of the importing country.

A manufacturer can issue a certificate when there is no national authority or legal framework in the exporting country that could issue a certificate and provided there is an independent certifying body or competent authority to assess compliance with a quality assurance scheme.

Despite consultation and publication of this scheme there was very little interest from Member States, and it was never fully implemented. The scheme imposes a significant burden on the NRA especially in poorly resourced settings and this may have been a contributory factor in its very limited implementation.

WHO has recently recommenced consultations with Member States to assess the viability of implementing a revised version of SMACS.

PART 2



3. International guidance for the use of pharmaceutical excipients in the manufacture of finished medical products

The WHO updated and published Good Manufacturing Practices (GMP) for pharmaceutical products main principles in 2014[57] as part of the WHO Technical Report Series. GMP comprises of a wide and complex set of guidelines the implementation of which is designed to ensure pharmaceuticals are manufactured in accordance with quality standards.

GMP guidelines emphasise that the manufacturer must assume responsibility for the quality of their pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy.[58]

The manufacturer of the finished pharmaceutical product is highly dependent on the excipient manufacturer to provide materials that are homogeneous in chemical and physical characteristics, and of the required quality.

To achieve this objective a pharmaceutical quality system (PQS) must be in place which incorporates good manufacturing practices (GMP) and quality risk management (QRM).

3.1. Pharmaceutical Quality System

The PQS amongst a wide range of other requirements include the need to ensure:

- The manufacture, supply and use of the correct starting and packaging materials.
- The selection and monitoring of suppliers and verification that each delivery is the correct material from the approved supply chain.
- All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out.
- The finished product is correctly processed and checked, according to the defined procedures.
- Pharmaceutical products are not sold or supplied before certification that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products.

Quality Risk Management

The QRM process should ensure;

- A review of starting materials and packaging materials used for the product, especially those from new sources and in particular the review of supply chain traceability of active substances.
- A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

Good manufacturing practice

GMP specific reference to starting materials:

- Starting materials (including excipients) should be purchased only from approved suppliers and, where possible, directly from the producer.
- It is also recommended that the specifications established by the manufacturer of the FFP for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.
- For each consignment, at a minimum, the containers should be checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels. Additionally, minimum tests for identity, purity and physical properties should be conducted.
- If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

Outsourcing to third parties

Finished pharmaceutical manufacturers are permitted to outsource production, analysis, and any other activity covered by GMP, but this must be carefully defined, agreed and controlled to avoid quality defects. This includes;

- The contract should permit the contract giver to audit the facilities and activities of the contract acceptor or mutually agreed subcontractors.
- Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect, or to investigating in the case of a suspected falsified product or laboratory fraud, must be accessible and specified in the procedures of the contract giver.
- The contract should describe the handling of starting materials, intermediate, bulk and finished products, if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

It is therefore permissible for a pharmaceutical manufacturer to contract a qualified third party to inspect and certify the suitability of an excipient manufacturer. Such organizations exist and are active in conducting these types of assessments to provide assurances to the pharmaceutical manufacturer that the source of their excipients is operating in compliance with applicable GMP.

The use of third-party accredited laboratories to conduct testing of excipients for the presence of DEG/EG is also permitted and acceptable in many countries.

3.2. Good storage and distribution practice

WHO good storage and distribution practices for medical products[59] sets out a number of requirements:

- Medical products should be procured from appropriately authorized suppliers.
- Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects (e.g. availability of a certificate of analysis, where applicable), at the time of receiving.
- Containers and consignments that do not meet acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.
- Repackaging and relabelling of materials and products are not recommended. Where repackaging and relabelling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.
- Procedures should be in place for the controlled disposal of original containers, to prevent re-use.
- Product, batch and container identity should be maintained at all times.
- All labels should remain legible.
- Distribution records should be sufficiently detailed to allow for a recall when required.
- Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation and marketing authorization. Written proof of such authorization, or an import permit or equivalent where there is no marketing authorization, must be obtained prior to the distribution of products to such persons or entities.

3.3. WHO Certification Scheme for the quality of pharmaceutical products moving in international commerce[60]

The scheme is a voluntary international agreement to provide assurance about the quality of FPPs moving in international commerce. The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:

- A specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
- The manufacturing site is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by the WHO in accordance with its current publication;
- The actual status of commercialization of the certified product on the market of the certifying authority, when authorized; and
- All product information submitted, including labelling, is currently authorized by the certifying authority.

Additionally, the Scheme facilitates the exchange of information related to the investigation of serious quality defects reported in the product exported.

Two documents, if available by the certifying authority, can be requested within the scope of the Scheme:

1. a certificate of a pharmaceutical product (CPP) and;
2. a batch certificate of a pharmaceutical product

Examples of the certificates and explanatory notes are included in the WHO guidance document.

A Member State or regional authority intending to become a certifying member of the scheme should possess;

- An effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products, including the responsible manufacturers and licensing of distributors.
- GMP requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of FPP are required to conform.
- Effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent medicine testing laboratory.
- A pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power to conduct or to coordinate appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples; and
- An efficient surveillance system, administrative capacity, and compliance with good regulatory practices. They must be able to issue certificates efficiently, investigate complaints, and promptly notify WHO and relevant authorities about products with serious quality defects or hazards, or publish this information on their website.

3.4. Import procedures for medical products and starting materials

WHO Guidelines on import procedures for medical product[61] stipulate the following requirements for FPP's and pharmaceutical starting materials including excipients.

- The import of medical products should be undertaken by an importer or agency authorized by the NRA as per national and regional legislation. This normally does not include medical products in transit.
- All formalities on importation of medical products should be coordinated by the relevant authorities (customs, border control, or other as appropriate), NRA and/or ministry of health, as relevant.
- The NRA should publish an updated list of authorized medical products and authorized importers permitted to import into the country for marketing. This does not include a list of exempted products and importers as per national or regional legislation. In all cases, close collaboration with the NRA is needed to verify that the product is authorized for importation and that there are no restrictions, temporary suspensions or withdrawals of marketing authorizations.

- NRAs should be empowered to take legal actions and should collaborate closely with customs, police, judiciary and others to detect substandard and falsified products and to avoid the import of such products. Efficient and confidential channels for communicating information on these products and other illicit activities should be established between all responsible official bodies.

- When considering finished medical products, the responsibility for the quality assurance of starting materials (active pharmaceutical ingredients (APIs) and excipients) used in that product is vested in the manufacturer of the finished pharmaceutical product.

- Some national and regional authorities also exercise documentary and (in some cases) quality control through laboratory testing of APIs as a prerequisite to customs clearance.

- Each imported pharmaceutical starting material (including excipients) should be accompanied by a warranty (or batch certificate) prepared by the manufacturer, for example, as recommended by the WHO pharmaceutical starting materials certification scheme (SMACS).

- Pharmaceutical starting materials purchased and imported from third party vendors should be appropriately labelled in accordance with national regulations and accompanied by a certificate of analysis from the original manufacturer.

PART 2

4. Testing and Laboratory analysis

> It is internationally recognised that a detection level of 0.10% (1000 parts per million) for DEG/EG is adequate for screening raw materials and finished pharmaceutical products from a safety perspective[62]

The methodology for testing for DEG/EG is set out as Monographs in various national and international pharmacopoeias[63]. These methods should be used by excipient manufacturers, repackagers and finished pharmaceutical manufacturers to ensure the identity, quality, purity and ascertain the presence or level of impurities, specifically DEG/EG.

4.1. Testing Excipients

GMP guidelines[64] set out the testing requirements for starting materials (including excipients).

Prior to releasing any starting or packaging material for use in finished pharmaceutical product (FPP) manufacturing, the manufacturer must verify that all excipients conform to established specifications regarding identity, purity, and specific physical properties; this necessitates conducting an identity test on a sample from each container, although a validated procedure allowing for sampling a proportion of containers is permissible when it ensures no single container is mislabelled, thus maintaining the integrity and quality of the materials used in production. Such validation should consider the following aspects:

- The nature and status of the excipient manufacturer and supplier, and their understanding of GMP requirements.
- The Quality Assurance system of the manufacturer of the excipient.
- The manufacturing conditions under which the excipient is produced and controlled.
- The nature of the excipient and the medicinal products in which it will be used.

Under such a system, a validated procedure for exemption from identity testing of each incoming container of starting material could be accepted for excipients coming:

- from a single manufacturer or plant.
- directly from a manufacturer, or in the manufacturer's sealed container, where there is a history of reliability, and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the FPP) or by an officially accredited body.

However, it is unlikely that such a procedure could be satisfactorily validated for excipients supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited.

While samples of API should be retained for at least one year beyond the expiry date of the corresponding FPP, excipients (other than solvents, gases and water) should be retained for a minimum of two years if their stability allows. These requirements ensure that manufacturers can demonstrate the quality and integrity of their products throughout their shelf life and beyond and can be crucial in defending against allegations of negligence or product defects. Retention samples of materials and products should be of a size sufficient to permit at least two full re-analysis.

4.2. Testing finished pharmaceutical product

For each batch of medicines, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

4.3. Certificates of analysis (COA)

Following consultation with stakeholders WHO updated guidelines on a model certificate of analysis[65] for use by medicine quality control laboratories (MQCL), and the trade in starting materials (including API and excipients) and FPPs. A COA should be prepared for each batch of a substance or product and include the following information:

- The name and address of the laboratory issuing the CoA.
- The identification number of the CoA and on each page.
- The page number and the total number of pages to ensure that every page is recognized as a part of the certificate.
- The name, address and contact person representing the originator of the request for analysis.
- The number assigned to the sample by the laboratory during registration upon receipt.
- The date on which the sample was received in the laboratory and the quantity of sample (number of
- units or packages).
- The name, description (for example, active ingredient, dosage form, strength, package size in the case of FPPs; grade in the case of starting materials; type and material of the primary packaging),
- Batch number (used by the original manufacturer and repacker or trader) of the sample for which the certificate is issued.
- The expiry date (or retest date, where applicable) and date of manufacture (if available).
- The name and address of the original manufacturer; in addition, if supplied by repackers or traders, the certificate should show the name and address of the repacker or trader.
- Specifications for testing and a reference to the test procedure(s) used, including the acceptance criteria (limits).
- The results of all tests performed on the sample for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits); results of tests performed by subcontractors should be identified as such.
- Any comments, observations or information on specific test conditions, where these are necessary for the interpretation of the results.
- A conclusion as to whether or not the sample was found to be within the limits of the specification
- The date and signature of the head of the laboratory or other authorized person approving the certificate.

In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities. Certificates must be originals (not photocopies) or otherwise have their authenticity assured.

4.4. Testing Pharmaceutical excipients for known impurities

A suitable and widely used analytical technique to test pharmaceutical products and excipients precisely and accurately for DEG and EG is Gas Chromatography – Mass Spectrometry (GC-MS). Whilst most medicine quality control laboratories and large pharmaceutical manufacturers will have access to this equipment, this is not always the case in resource limited settings or with medium and small pharmaceutical manufacturers.

In 2023 WHO published a screening methodology for medicine quality control laboratories using Thin Layer Chromatography (TLC)[66] which allows detection of DEG/EG concentrations down to 0.20% (above the recognised safety level of not more than 0.10%).

The method cannot distinguish between DEG and EG but can only detect the combined presence and quantity. When used by properly trained operatives the TLC method can provide an early indication of excipients containing DEG/EG. The methodology can prevent unnecessary submissions to medicine quality control laboratories of samples that tested negative for DEG/EG. In cases where the method has indicated the presence of DEG/EG quantitative testing may be required at an accredited medicine quality control laboratory.

Research is ongoing in the development of portable, reliable, faster and cheaper screening methodologies capable of deployment throughout the supply chain.

This study recommends that all batches of high-risk excipients are tested for their identity, including the presence of DEG/EG, and in cases where high risk excipients have been sourced other than directly from the manufacturer or their authorised distributor each container must be tested. Additionally in cases where suspicions are aroused as to the authenticity of a container irrespective of the source the contents should be tested.

PART 2

5. Criminal Investigation and Regulatory Enforcement

Regulatory or health laws, administered by specialized agencies, aim to ensure compliance with industry-specific standards and protect public welfare by imposing administrative penalties including fines, license suspensions, or corrective actions for violations such as regulatory non-compliance. These laws and related penal sanctions prioritize prevention and regulatory adherence, often lacking the requirement for criminal intent. In contrast, criminal laws, enforced through the judicial system, address offenses deemed harmful to society, demanding proof of criminal intent and resulting in severe penalties including imprisonment or substantial fines, with the goal of punishing offenders and deterring future criminal behaviour.

It is therefore important that both are applied effectively in dealing with Substandard and Falsified Medical Products, including contaminated medicines.

5.1. Regulatory

The principal role of regional or national medicine regulatory authorities is to safeguard public health by ensuring medicines meet the required standards of safety, quality and efficacy. A critical component of achieving that objective is ensuring the manufacture of finished pharmaceutical products are carried out in compliance with internationally recognised standards of good manufacturing and distribution practices. Non-compliance with those standards thoroughly undermines the integrity of the finished pharmaceutical product and in some cases, as has been seen in this report, result in significant and tragic consequences.

The standards are designed to be implemented through rigorous and regular inspections. Non-compliance of GMP identified during inspections is usually dealt with through the implementation of corrective and preventative actions. Whilst a regulators role is to achieve compliance of those they regulate, in cases where critical deficiencies have been identified, then the non-compliance with regulatory requirements should be enforced through the application of sanctions.

The imposition of sanctions should always be proportionate, necessary and lawful, and their application needs to be consistent, fair and transparent.

Sanctions should be designed to change behaviours and provide a menu of options to the regulator ranging from written warnings, suspensions and revocation of licences and in the most egregious cases through to criminal prosecution.

A range of sanctions provides the regulatory authority with the possibility of implementing them incrementally where appropriate, whilst maintaining the option to pursue criminal charges should circumstances dictate.

A failure to enforce the required regulatory obligations undermines their original purpose. The risk of non-compliance with regulations should be an obvious and real risk to regulated entities of the consequences of their actions or inaction.

The regulatory inspection process and enforcement of those regulations are both key elements in maintaining minimum standards.

5.2 Criminal Investigation and Prosecution

In the most serious cases there may be a need to conduct a criminal investigation resulting in a prosecution. There is a recognition that pursuing criminal investigations and prosecutions relating to intentional, reckless or negligent actions leading to the contamination of medicines requires trained and experienced personnel, which may be lacking in some resource limited settings.

As will be seen in the following case studies described later in this report, most cases are international in nature and there is a necessity to obtain admissible evidence from other jurisdictions which often entails complex legal procedures. Further challenges are found when actions that are considered a crime in one jurisdiction are not considered to be so or face a lesser penalty in another jurisdiction.

Investigators may need to have or have access to specialist knowledge of cyber investigations if the case involves online activity, digital forensics if laptops, mobile telephones or other digital devices require examination, money laundering investigation as well as detailed knowledge of the regulatory requirements of GMP and GDP.

Joint investigation teams comprising regulators, law enforcement and prosecutors, work collaboratively by combining the technical and legal skills with the investigative abilities and legal powers.

This collaboration significantly increases the chances of successful and effective outcomes in investigations and prosecutions. Ensuring that all agencies involved have agreements in place to work together and exchange information freely and efficiently, to prevent unnecessary delays and enhance effectiveness is key to success.

Incidents involving contaminated medicines are unusual and many criminal justice systems are unaccustomed to handling them. Skilled prosectors and learned judges are required, who recognise the seriousness and consequences of these types of crimes.

Courts also require a range of proportionate but dissuasive sanctions, commensurate with the seriousness of the case, that can be imposed in combination with regulatory sanctions for maximum effect.

> The economic drivers for falsifying high risk pharmaceutical excipients demands measures that not only increase the risk of a loss of one's liberty but also the financial profits of their endeavours.

Proceeds of crime legislation enabling the confiscation of assets and payment of compensation to victims should be available to courts as a further deterrent factor.


1

PART 2

6. Summary of key regulatory requirements

a comprehensive set of guidance and internationally accepted standards exist to ensure medicines are safe, high quality and efficacious.

That guidance is built on an underlying assumption, that all actors subject to them will, in the main, comply with them (or at least attempt to) and therefore they will be effective in that context. However, that effectiveness is largely, or even completely, negated in cases of wilful non-compliance or where 'the rules' are circumvented by design.

Key regulatory requirements, the application of which would avoid most contamination incidents include:

6.1. Manufacturers of Pharmaceutical Excipients

- Procure raw materials from trusted sources using appropriate qualification processes.
- Manufacture pharmaceutical excipients in accordance with GMP.
- Test pharmaceutical excipients for conformity to published pharmacopeial monographs, including for known impurities.
- Distribute to importers/distributors authorised to handle pharmaceutical excipients.

6.2. Distributors of Pharmaceutical Excipients

- Procure pharmaceutical excipients from GMP compliant manufacturers.
- Procure pharmaceutical excipients from the original manufacturer or their authorised distributor wherever possible.
- Know the identity of the original manufacturer if procuring from an authorised distributor.
- Test the pharmaceutical excipient if engaged in repackaging, relabelling or there is any doubt as to the conformity of the excipient with specifications.
- Ensure certificates of analysis are provided for the excipients they supply, clearly indicating the name of the original manufacturer and any intermediary.
- Ensure a certificate of analysis is supplied to whoever procures the excipient clearly indicating the name of the original manufacturer and all intermediaries.

6.3. Manufacturers of finished pharmaceutical products

- Ensure pharmaceutical excipients are procured from GMP compliant manufacturers or their authorised importer/distributor.
- Only procure from licensed re-packagers/relabellers if necessary having established their GMP compliance.
- Ensure certificates of analysis are supplied for each batch of excipient clearly indicating the name of the original manufacturer and all intermediaries.
- If procured from a re-packager/re-labeller ensure name of the original manufacturer and any intermediaries are identifiable.
- Test each batch of the pharmaceutical excipient for conformity to published pharmacopeial monographs, including for known impurities.
- Test the FPP to ensure conformity to required specifications.
- Distribute finished pharmaceuticals via authorised distributors.

PART 3

7. Case Studies

This report seeks to provide an analysis of cases involving the contamination of medicines with DEG and or EG.

The report highlights failures in GMP requirements as well as criminal behaviours.To do so four historical cases (since 1996) in Haiti, China, Panama and India have been examined in as much detail as possible Additionally, four more recent cases (since 2022) in The Gambia, Uzbekistan, Indonesia, and Cameroon have been reviewed.

These eight case studies have been selected based on several different characteristics relating to the production and supply of the pharmaceutical excipients and finished medicines (See Table 3). Some involve locally produced medicines or contract manufacturing, others imported medicines. Some involve imported excipients, whilst others were locally produced or falsified.

In each case efforts have been made to trace back the supply chain of either the finished medicine or the contaminated excipient to their originating source, using publicly available information and subject expert and key informant interviews.

The pharmaceutical supply chain is commonly long, complex and global. Trace-back investigations are therefore international in nature, inter jurisdictional, complex and well beyond the resources and capacities available to some Member States that have experienced these incidents.

In incidents which have involved detailed investigations, and once any subsequent prosecutions are complete, a clearer picture of the supply chain begins to emerge. Some cases are still the subject of investigations and further details may yet come to light. Some historic cases provide limited data on the origin of the contamination.

The estimated numbers of fatalities associated with each incident vary amongst official and media reports. The numbers shown are approximate and represent the latest figures reported.

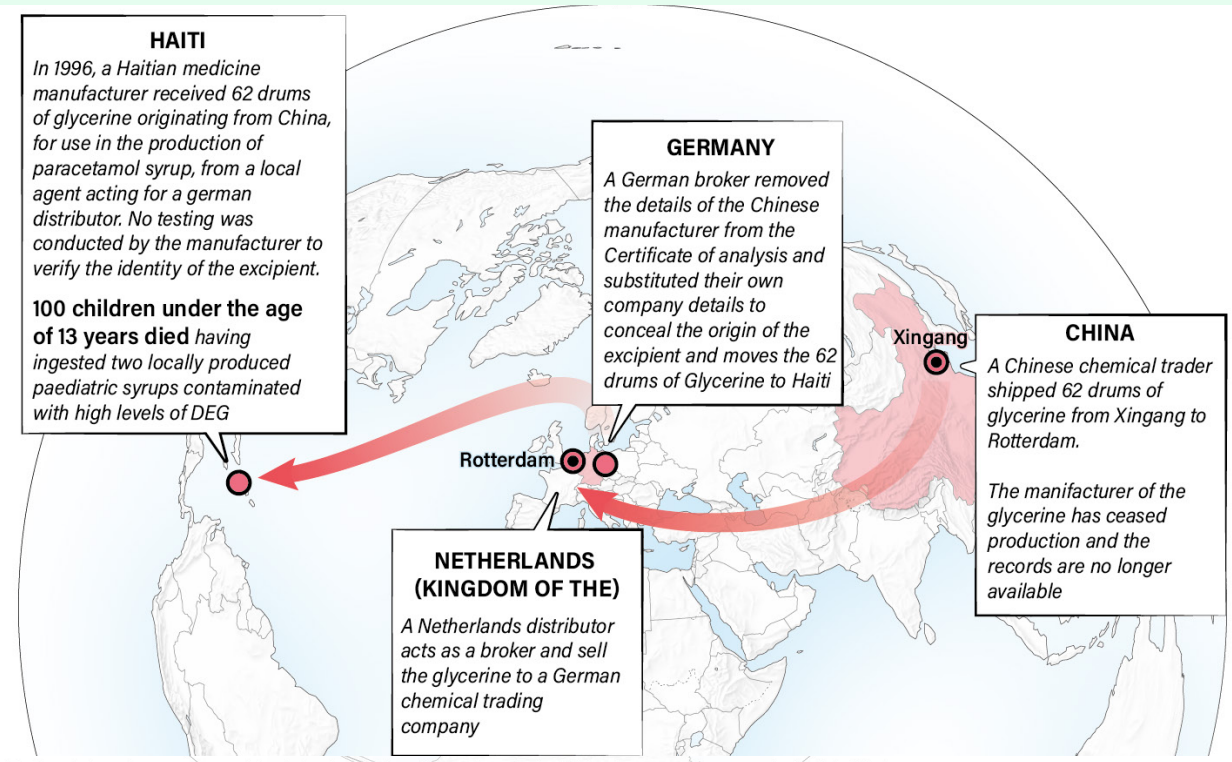
Table 3. Case studies

Country	Locally produced medicine	Imported medicine	Locally sourced excipient	Imported excipient	Fatalities	Prosecution
Haiti[67] 1996	Yes	No	No	Yes	100	No
China[68] 2006	Yes	No	Yes	No	14	Yes
Panama[69] 2006	Yes	No	No	Yes	291	Yes
India[70] 2019	Yes	No	Yes	No	12	Pending
The Gambia[71] 2022	No	Yes	Not applicable	Not applicable	66	No
Indonesia[72] 2022	Yes	No	Yes	No	200	Yes
Uzbekistan[73] 2022	No	Yes	Not applicable	Not applicable	68	Yes
Cameroon[74] 2023	No	Yes	Not applicable	Not applicable	12	Not known

7.1. Haiti 1996[75] [76]

Table 4. Haiti case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Glycerine	DEG (24%)	Paracetamol syrup	DEG 12% -20%	12-15,000 Bottles	100



Background

Between November 1995 and July 1996 approximately 100 children under the age of 13 years died having ingested two locally produced paediatric syrups contaminated with high levels of DEG. The children presented at hospitals typically displaying acute renal failure, an extremely unusual cluster of cases which triggered a multinational investigation to determine the cause. Suspicion focused on two locally manufactured paracetamol syrups which subsequently tested positive for high levels of DEG. In June 1996 the sale of the two syrups was prohibited, a public awareness campaign initiated, and a recall conducted.

Testing

The finished medicines and excipients were subjected to detailed analysis in the USA. At first suspicion fell on PG which had also been used as an excipient, as it had been associated with previous contaminations, however it was found to be within specification.

A single remaining drum of glycerine was traced at the local medicine manufacturer and tested; it was found to contain 24% DEG (240 times the permitted limit). The two paracetamol syrups consumed by patients contained between 12%-20% DEG (120-200 times the permitted limit).

Supply Chain Traceback

In June 1995 a **Haitian medicine manufacturer** received 62 drums of glycerine for use in the production of paracetamol syrup from a Haitian chemical distributor. No testing was conducted by the manufacturer to verify the identity of the excipient or the presence of impurities. Up to 15,000 bottles of two syrups were produced and distributed with the contaminated excipient.

The Haitian distributor was a local agent acting for a chemical distributor based in Germany and had received 72 drums of glycerine. The remaining 10 drums were supplied to other manufacturers and pharmacies in Haiti.

The German distributor was unable to confirm who manufactured the glycerine. They did confirm that they had received the glycerine from a chemical distributor based in the Netherlands.

The Netherlands distributor had acted as a broker and had sourced the glycerine sent to Haiti from a German chemical trading company.

The German trading company also acted as a broker, sourcing the Glycerine from a Chinese chemical trader. The German broker removed the details of the Chinese manufacturer from the Certificate of analysis and substituted their own company details to conceal the origin of the excipient.

The chemical trader in China had shipped the glycerine from Xingang, China to Rotterdam, Netherlands.

Enquiries in China revealed that the manufacturer of the glycerine had ceased production at the manufacturing site and records were no longer available.

ACTORS:

1 x
Chemical manufacturer

5 x
Intermediaries

1 x
Pharmaceutical manufacturer

4 x
Jurisdictions

ACTIONS:

1 x
Alteration to Certificate of analysis

0 x
Testing of excipients by any intermediaries or end user

In addition samples of glycerine sourced by the Netherlands broker via the same supply route and stored in Rotterdam were sampled and tested. They revealed the same level of contamination as the Haiti glycerine. Their identification prevented further cases of contamination.

7.2. China 2006[77][78]

Table 5. China case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Propylene Glycol	DEG 100%	Armillarisin A	% unknown	3,600 Injections	14

Background

In April 2006 a university hospital in Guangzhou, China administered an injectable antibiotic known as Armillarisin A to treat patients for gall bladder disease. Over 60 patients were injected, 15 of whom experienced acute kidney injury, and 14 later died.

A specialist team established that the Armillarisin A, was the common denominator. The adverse events in patients were reported to the Chinese regulatory authorities who notified all hospitals to cease using Armillarisin A injection and issued a notice to the manufacturer to cease production and distribution.

Further testing of the medicine was conducted which established the presence of diethylene glycol.

Supply Chain Traceback

In September 2005 a **local GMP certified pharmaceutical manufacturer** ordered 1 ton of pharmaceutical grade propylene glycol for use as an excipient in the production of Armillarisin A

↓

The Propylene glycol was supplied by a fake chemical distributor using forged documentation who advertised the excipient at a low price on an e commerce platform.

↓

The manufacturer conducted a basic test on the excipient and although showing inconsistencies in its specifications failed to investigate further and issued a falsified COA passing the excipient for use, allegedly to meet manufacturing schedules

↓

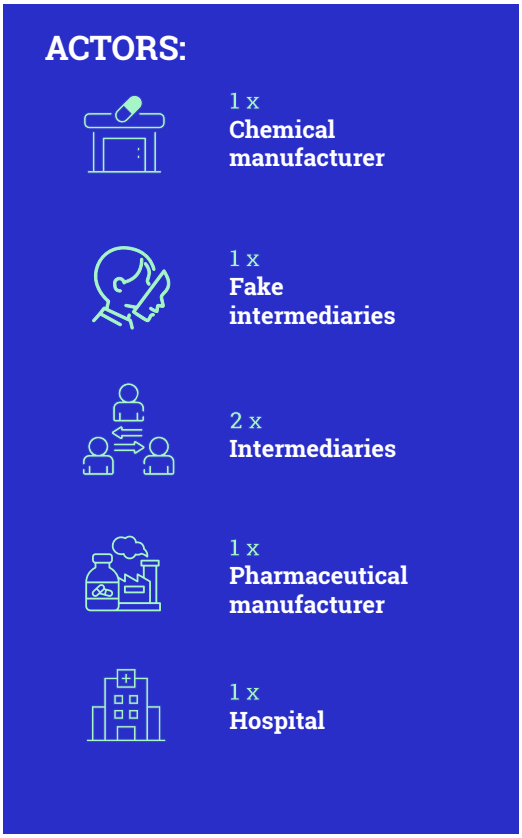
The local manufacturer then used the excipient to produce Armillarisin A and sold 3600 injections to a local distributor.

↓

That distributor sold them to a second distributor, who supplied them to a local hospital.

↓

In April 2006 the hospital administered them to patients, 14 of whom later died.



ACTIONS:

1 x Fraudulently supplying pharmaceutical excipients

1 x Falsely labelling drums

1 x Use of forged documents

1 x Failure to investigate inconsistent test results

1 x Falsified Certificate of Analysis

INVESTIGATION

Excipient Supplier

The fraudulent company who supplied the excipient was operated by an unqualified local businessman and trader who used falsified documents including a medicine manufacturing licence, business licence and medicine registration certificate in the name of a false chemical plant. He had received an online order for 1 ton of pharmaceutical grade PG from a local medicine manufacturer. To fulfil the order the trader instead purchased 1 ton of DEG, at the time DEG was half the price of PG.

The trader then knowingly supplied it to the medicine manufacturer purporting it to be pharmaceutical grade PG. The medicine manufacturer subsequently used it to manufacture the Armillarisin A which led to the death of 14 persons. At the criminal trial medical evidence was presented proving that causality was established between the deceased and intoxication with DEG.

The trader was convicted of endangering public security, selling fake and substandard products and falsely declaring registered capital. He was sentenced to life imprisonment, a sentence later upheld on appeal. During the investigation it was established that he also supplied fake labels to the pharmaceutical manufacturer to attach to the drums of excipient stating it was pharmaceutical grade PG. It was also established that he had supplied a further 30 tons of chemicals misrepresenting the contents including 2.25 tons of DEG purporting it to be PG.

Pharmaceutical Manufacturer

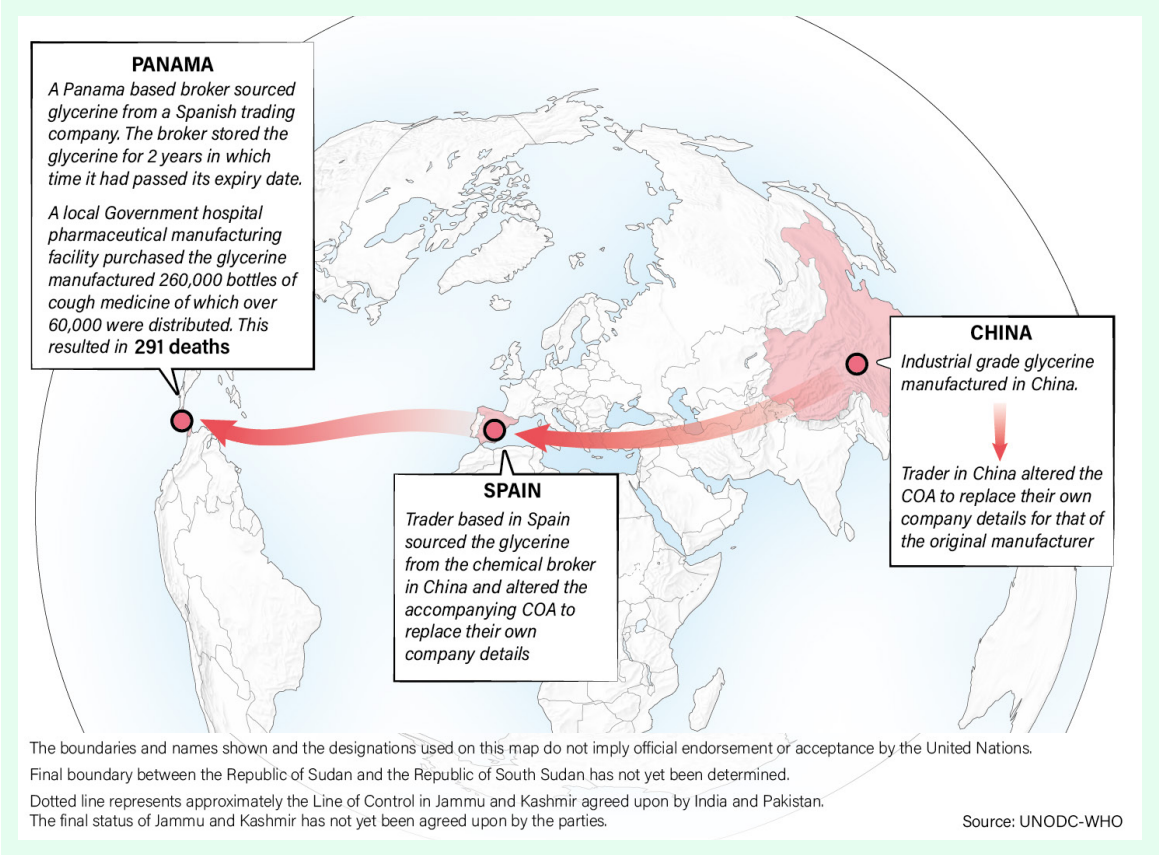
In 2008 a further prosecution was successfully concluded of 5 executives from the pharmaceutical manufacturer for negligently causing a serious accident. They included 3 general managers, the purchaser and the laboratory supervisor. They were sentenced to between 4-7 years imprisonment.

One of the executives alleged corruption with local officials claiming he purchased his companies GMP certificate for $12,000.

7.3. Panama 2006[79 80 81 82]

Table 6. Panama case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Glycerine	DEG 20%	Cough Syrups	DEG 8%	60,000 bottles	291



Background

In July 2006 patients began presenting at public hospitals in Panama displaying a range of symptoms including AKI.

Detailed investigations discovered that many of the patients had been taking a medicine called Lisinopril used to treat high blood pressure and heart failure. It was at first thought that Lisinopril may have been responsible, but it was later identified that one of the common side effects of Lisinopril is a dry tickly cough for which locally produced cough syrups were prescribed.

Subsequently it was later reported that 291 persons (died and a further 111 survived having ingested cough syrups contaminated with DEG. It is suspected that the true figures are higher.

Investigation

Initial suspicion fell on the blood pressure medicine prescribed to a number of the affected patients. Laboratory testing revealed the medicine to be within specification. It was only when it was realised that a common side effect of the medicine was a dry cough for which a cough medicine was prescribed that the focus of the investigation switched to the cough medicine. Analysis of the cough medicine revealed contamination with approximately 8% DEG, which is 80 times the permitted level. The cough medicine had been manufactured by a government hospital manufacturing facility and widely distributed by the government social security fund. Samples of the excipients used in the production of the medicine were

obtained and tested. The glycerine was found to be contaminated with 22% DEG, which is 220 times the permitted level.

Supply Chain Traceback Investigation

A local Government hospital pharmaceutical manufacturing facility purchased 46 drums of Glycerine labelled as pharmaceutical grade from a locally based chemical broker. It was used to manufacture 260,000 bottles of cough medicine of which over 60,000 were distributed. The manufacturing facility did not conduct any testing of the glycerine for identity or impurities.

The Panama based broker sourced the glycerine from a Spanish based trading company. The broker stored the glycerine for 2 years in which time it had passed its expiry date. The broker extended the expiry date without conducting any testing.

The trader based in Spain sourced the glycerine from a chemical broker based in China. The Spanish broker altered the accompanying COA to replace their own company details for that of the Chinese trader. They also stated they did not know the glycerine was intended for human consumption.

The trader in China sourced the glycerine from a local glycerine manufacturer. The trader in China altered the COA to replace their own company details for that of the original manufacturer.

The glycerine manufacturer in China stated they only manufactured industrial grade glycerine did not manufacture pharmaceutical grade glycerine and were not authorised to do so. However, the COA accompanying the glycerine declared it had a purity level of 99.5%.

ACTORS:

- 1 x **Chemical manufacturer**
- 3 x **Brokers**
- 1 x **Pharmaceutical manufacturer**
- 3 x **Jurisdictions**

ACTIONS:

- **2x Changes to COA**
- **1 x Relabelling of drums**
- **1 x Extension of expiry date**
- **0 x Testing by intermediaries or end user of excipients for impurities**

Prosecution

In 2016 following protracted legal proceedings five persons were convicted and imprisoned. The Panamanian broker who received the glycerine was found guilty of altering the certificate of analysis and was sentenced to five years imprisonment. The head of the Social Security Fund quality control laboratory who signed off the glycerine for use and the storekeeper who also certified the use of the glycerine were sentenced to 12 months imprisonment. Two persons who headed the administrative body responsible for the supervision of the quality control laboratory were also sentenced to 12 months imprisonment.

The Spanish broker was investigated but the case was dismissed. Panama referred Spain to the European Court of Human Rights.

The health regulatory authorities in China concluded that they had no power to prosecute the manufacturer or the distributor of the glycerine as neither were authorised to manufacture or trade in pharmaceutical products.

7.4. India 2019 [83] [84] [85]

Table 7. India case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Propylene Glycol	DEG (% not available)	Cough and cold Syrups	DEG (34%)	5500 bottles	12

Background

In November 2019 over 20 children began presenting at hospitals in Ramnagar, Jammu and Kashmir. The children were suffering from coughs and colds, vomiting and eventually AKI. Some of the children survived but with permanent disabilities, 12 died of kidney failure.[86]

Investigation

Doctors began a wide and thorough investigation to establish the cause of the illness. This included testing all of the medicines that the children had consumed. One of the medicines, a cough syrup, tested positive for high levels of DEG. Confirmatory testing was conducted at an accredited Government medicine quality control laboratory, that confirmed the presence of DEG at levels of 34-36% (340-360 times permitted levels).

By February 2020 widespread media coverage was reporting the incident. In March 2020 a special investigation team was established to examine the case. Later in 2020 another child was identified in a neighbouring State with similar symptoms who later died of AKI. The investigation revealed that after the initial incident, the manufacturer rebranded the syrup and continued sales through a sister company in a neighbouring State. That rebranded medicine was tested and found to also contain high levels of DEG. The Indian regulatory authorities banned the distribution and sale of the syrup.

Both the original medicine manufacturer and its sister company had received at least 16 warnings from the State drug regulators about substandard medicines prior to the Jammu case[87]. Testing of the identity and purity of the excipient used by the manufacturer was apparently not conducted as is required by Indian legislation. The medicine manufacturer was shut down for a period, but manufacturing was reinstated for products not containing PG. It is not known if the contaminated medicines were exported to other countries.

The medicine manufacturer denies any responsibility for the contamination.

Supply Chain Traceback

The contaminated batch of cough syrup was produced by the medicine manufacturer in September 2019.

The manufacturer stated that the pharmaceutical grade PG was sourced from a local supplier. The supplier states they only supply industrial grade PG not pharmaceutical grade.

The local excipient supplier states they procured the PG from a large local petrochemical manufacturer. The petrochemical manufacturer deny doing any business with the medicine manufacturer or the local excipient supplier.

ACTORS:

1 x **Chemical manufacturer**

1 x **Intermediary**

1 x **Pharmaceutical manufacturer**

ACTIONS:

1 x History of non-compliance with GMP

0 x Testing by intermediaries or end user of the excipients for impurities.

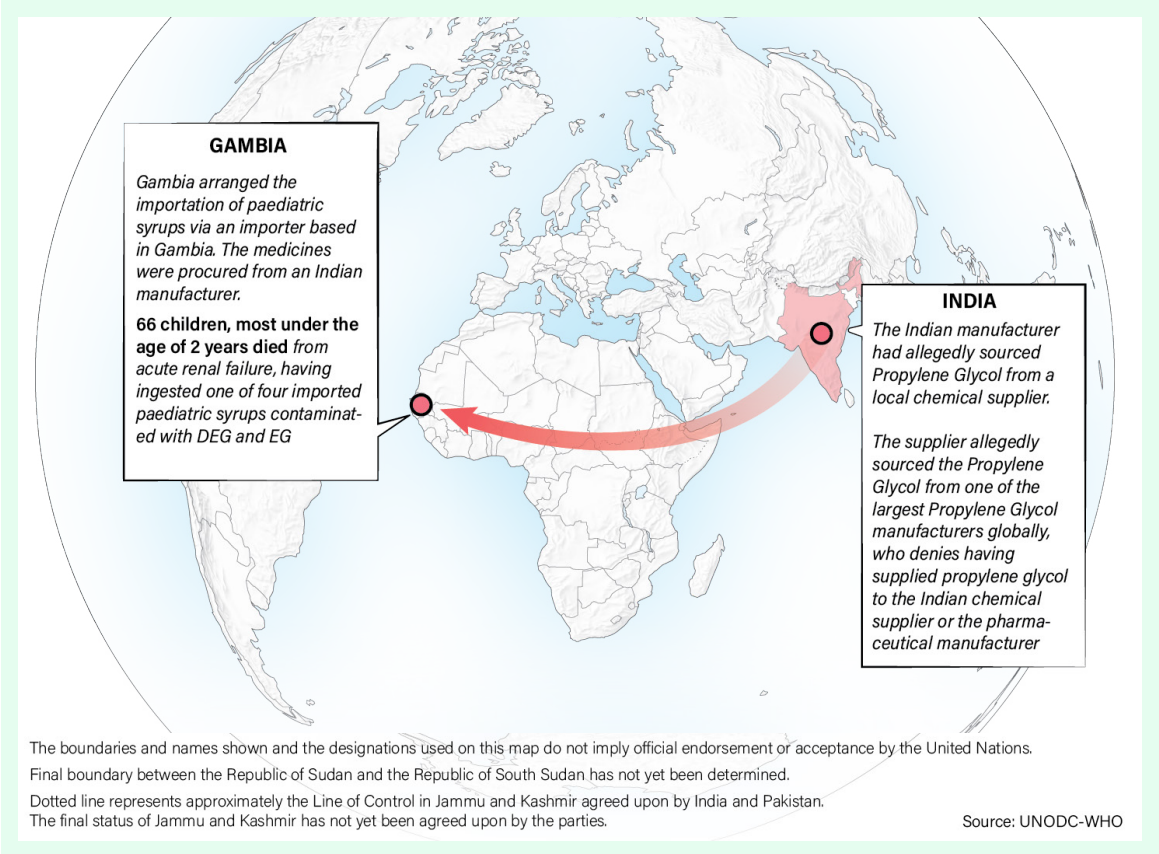
Prosecution

Charges have been filed against the 3 owners of the original medicine manufacturer for culpable homicide not amounting to murder, drug adulteration with a noxious substance and voluntarily causing a grievous hurt. The distributor supplying the medicine and the pharmacist selling them were charged with drug adulteration and causing grievous hurt.[88] The current status of the case is unknown.

7.5. The Gambia 2022[89 90 91]

Table 8. The Gambia case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Propylene Glycol	Unknown	Paediatric Cough Syrups	DEG 1-21.3% and EG 0.3 - 5.9%	50,000 bottles	66



Background

Between July and September 2022, The Gambia confirmed that 66 children, most under the age of 2 years died from acute renal failure having ingested one of four imported paediatric syrups contaminated with DEG and EG.

Doctors at a local teaching hospital had noticed an unusual upsurge in young patients suffering from renal failure.

In September 2022 the Government advised the public to suspend the use of all paracetamol syrups, and following testing by 3 independent laboratories identified four over the counter paediatric syrups contaminated with EG/DEG.

The syrups had been manufactured in December 2021 and imported to Gambia from India directly from the manufacturer.

In October 2022 the government suspended all importations from that manufacturer. The WHO then issued a global medical product alert concerning the four medicines.

The Government supported by other external agencies carried out a house to house recall of all cough syrups and paracetamol, as well as a wide publicity and awareness campaign utilising the media and places of worship.

Reports of further casualties significantly decreased and completely ceased following the recall.

Some of the medicines subject of the recall were later seized by Customs officials in Senegal having been smuggled out of Gambia presumably to avoid the financial loss incurred by a recall of the products. This is a behaviour seen in other countries following the recall of medicines.

The Indian regulatory authorities were notified and requested to take appropriate action.

Investigation

The pharmaceutical manufacturer was ordered to stop production of the syrups following an inspection by the Indian regulator which uncovered multiple violations of GMP. The manufacturer had a history of non-compliance and regulatory breaches, and the two owners of the company were sentenced to two years 6 months imprisonment in connection with another medicine quality related issue concerning medicines exported to Vietnam[92].

The syrups in this case were manufactured in India for export only. They were not licensed to be placed on the market in India. Regulatory oversight of these medicines is light compared to medicines authorised for use in India. This is a common practice and not restricted to India.

India has now implemented testing of all syrups destined for export and publishes recall notices on the National Regulators website.

The Gambia do not manufacture any pharmaceuticals. They rely on imports for all pharmaceuticals used in the Country. There is a national medicine regulatory authority, but no medicine quality control laboratory or ability to test the products being imported. There are limited resources available to visit manufacturers in exporting countries to assess the level of compliance with GMP.

In response to this case The Gambia have also initiated quality testing at third party laboratories of all medicines of all dosage forms destined for importation to The Gambia. A medicine quality control laboratory is now planned and an increase of staff to the Medicine Control Agency.

Supply Chain Traceback

The Gambia arranged the importation of paediatric syrups via an importer based in The Gambia.

The medicines were procured from an Indian manufacturer who had been supplying other medicines to The Gambia.

The Indian manufacturer had allegedly sourced Propylene Glycol from a local chemical supplier.

The Indian supplier allegedly sourced the Propylene Glycol from one of the largest Propylene Glycol manufacturers globally.

The Propylene glycol manufacturer denies having supplied propylene glycol to the Indian chemical supplier or the pharmaceutical manufacturer.

Image source: WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

ACTORS:

1 x **Chemical manufacturer**

1 x **Intermediary**

1 x **Pharmaceutical manufacturer**

2 x **Jurisdictions**

ACTIONS:

1x History of non-compliance with GMP

0 x Testing by intermediaries or end user of excipients for impurities

7.6. Indonesia 2022

Table 9. Indonesia case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Propylene Glycol	Up to 99% EG	Paediatric Cough Syrups	EG	60,000 bottles	Approx 150[93]

Background

Over 300 children experienced severe health conditions and multiple fatalities after consuming oral liquid medicines later found to contain EG and DEG.

These cases coincided with a rise in reports of AKI in children, initially observed in early 2022, with a notable increase in October of the same year.

Indonesian authorities and experts conducted an investigation to determine the cause of the incident. Upon reviewing the WHO Medical Product Alert and publicity surrounding the recent Gambian case they engaged in communication with WHO and clinicians in The Gambia.

Subsequent to the cases in The Gambia and Indonesia, WHO has further issued a seven medical product alerts[94] relating to finished products and pharmaceutical excipients containing unsafe levels of EG/DEG some of which have also been linked to fatalities.

Samples of the oral liquid medicines from Indonesian patients were submitted to local Regulatory and Police forensic laboratories where harmful levels of DEG/EG were identified.

Subsequent laboratory analysis of samples of paediatric oral liquids containing high risk excipients confirmed the presence of high levels of EG. National alerts were issued and there followed an investigation to establish the supply chain. In November 2022, WHO issued a Medical Products Alert concerning eight oral liquids produced by four local manufacturers.

Investigations ultimately identified six local manufacturers that had used contaminated excipients in the production of some oral liquid products[95]. These manufacturers were sanctioned for non-compliance with applicable regulations including the revocation of their GMP certificates and distribution permits. Furthermore, local Regulatory has also revoked 116 marketing authorizations of oral liquids that had used contaminated excipients or had an impact of revocation of GMP Certificates.

However, there is no correlation between the cases of oral liquid product contamination and the contaminated excipient supply chain incidents in the Gambia and Indonesia.

In 2020 the Indonesian Ministry of Health issued guidelines stipulating a maximum limit of 0.10% for DEG/EG in pharmaceutical products. Subsequently, in 2022, the Indonesian Food and Drug Authority (BPOM) issued similar guidance setting maximum limits for DEG/EG in food additives, applicable to both registration and importation purposes.

Supply Chain Traceback

Details of the origin and distribution of the contaminated excipients has been obtained from open sources reporting the details of the outcome of the prosecution against the distributors and manufacturers involved in this case[9697].

A local had knowingly supplied EG and DEG purporting it to be pharmaceutical grade propylene glycol. He had downloaded the logo of a multi-national chemical manufacturer of pharmaceutical grade PG , and attached them to the drums.

The drums were passed to a distributor who created false COA's claiming the chemicals were safe to be used in pharmaceuticals, not having tested the contents

They were then passed to a second distributor, and on to six local manufacturers of paediatric syrups.

The local manufacturers produced large quantities of syrups with the falsely labelled PG and distributed them throughout Indonesia.

Following further investigation, a total of 103 syrups were identified produced by six I companies which were then sanctioned for non-compliance with regulations.

Image source: WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

ACTORS:

- 1 x **Excipient supplier**
- 2 x **Intermediary**
- 6 x **Pharmaceutical manufacturers**

ACTIONS:

- **1 x Fraudulently supplying pharmaceutical excipients**
- **1 x Falsely labelling drums**
- **1 x Falsification of Certificate of analysis**
- **0 x Testing by intermediaries or end user of excipients for impurities**

Prosecution

Supplier 1

A local businessman whose business was struggling during the COVID-19 pandemic began to supply drums of industrial grade EG relabelled as pharmaceutical grade PG.

The supplier downloaded the logo of a global chemical manufacturer and applied it to the drums of falsely labelled ethylene glycol to add credibility and deceive subsequent users that the product had originated from a reputable manufacturing plant in Thailand.

The supplier then continued to supply drums of similarly falsely labelled excipients for several months to a local chemical distributor.

The owner and a second individual were convicted and sentenced to 10 years imprisonment.

Supplier 2

The second distributor issued certificates of analysis claiming the excipients were of a quality to be used in the manufacture of medicines without testing it. He then supplied it to another local chemical supplier.

Two individuals from the company were convicted and sentenced to 10 years imprisonment

Supplier 3

This supplier purchased the falsely labelled excipients from supplier 2 in good faith and supplied them to a regular client who was a medicine manufacturer.

Medicine manufacturer

The manufacturer used the falsely labelled excipients to produce 70 batches of paediatric cough oral liquids.

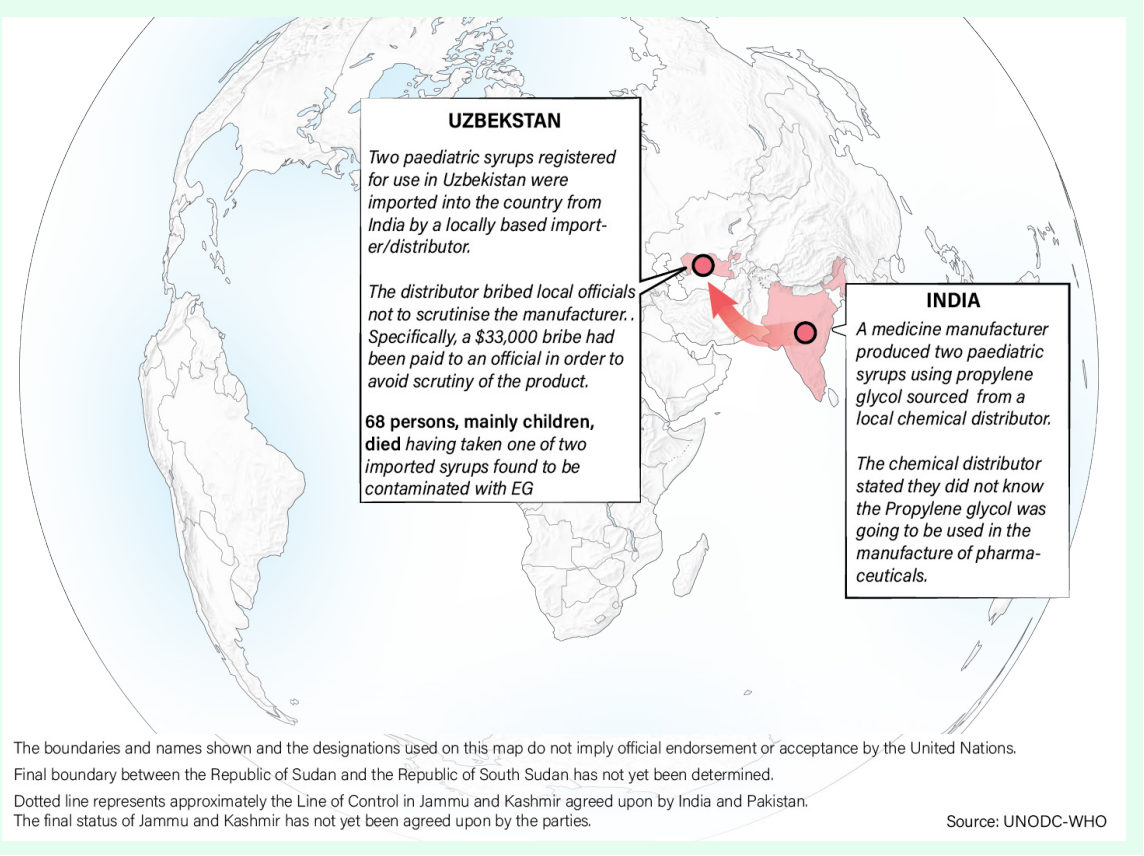
The Chief Executive and three other company executives/staff were convicted for failing to test the falsely labelled excipients and sentenced to 2 years imprisonment following a contested trial.

Image source: WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

7.7. Uzbekistan 2022 [98] [99] [100] [101] [102] [103] [104] [105]

Table 10. Uzbekistan case summary

Excipient	Excipient Contaminant	Medicine	Level of contamination	Quantity	Fatalities
Propylene Glycol	DEG/EG	Paracetamol Syrups	17-31% DEG/EG	Unknown	68



Background

Samarkand in Uzbekistan first started to see young patients presenting at hospitals displaying symptoms of acute renal failure in late 2022. Doctors were suspicious of the sudden upsurge in cases and raised the alarm. The government suspended sale of the medicines and submitted samples for laboratory analysis.

Subsequently 68 persons, mainly children, died having taken one of two imported syrups found to be contaminated with EG.

Testing revealed the two medicines to contain either DEG or EG to levels of between 17% - 31%.

In January 2023 WHO issued a medical product alert concerning 21 batches of two medicines[106] circulating in Uzbekistan and contaminated with high levels of DEG/EG.

Investigation

The Uzbekistan authorities launched a major investigation into the cause of the contamination and those responsible. They discovered that the importer/distributor acting for the medicine manufacturer had been bribing regulatory officials and healthcare workers to accelerate, promote and increase the sales of these medicines in the country. Specifically, a $33,000 bribe had been paid to an official in order to avoid scrutiny of the product.

The Uzbek authorities also called on counterparts in India to investigate the manufacturer who had produced the medicines and take appropriate action. India subsequently suspended the manufacturers licence[107]. Indian authorities also issued a warning against the use of PG supplied by the distributor of the contaminated excipient.

Laboratory testing revealed that one of the syrups contained more than 300 times the permitted level of DEG/EG.

The two owners of the Indian manufacturer fled India and an INTERPOL warrant was issued for their arrest[108], they were later arrested in the United Arab Emirates but subsequently released and remain at large.

In India charges have been brought (2024) against the medicine manufacturer and the supplier of the PG for the manufacture and sale of substandard medicines that could pose serious harm or be fatal under the Drugs and Cosmetics Act. The current status of the case is unknown.

Prosecution

In Uzbekistan following a six month trial 23 persons were found guilty of a range of offences including the production and sale of substandard medicines, bribery, tax evasion, malpractice and abuse of power[109].

The director of the importer/distributor of the medicines received 20 years imprisonment for giving a bribe and tax evasion. The company chief accountant, registration manager and sales director were imprisoned for between 4-10 years. They were charged with a range of offences including tax evasion and forgery. It was alleged the distributor was engaged in making large payments to healthcare professionals to maximise prescribing and sales of the medicines.

Nineteen government officials involved in the regulation, registration and testing of medicines, ranging from directors and deputy directors through to heads of departments, laboratories and chairs of regulatory committees, were convicted of complicity in a range of crimes under the Uzbekistan criminal code.

Offences committed included tax evasion, mediating and accepting bribes, complicity in the production, manufacturing, acquisition, storage, transportation for the purpose of sale of substandard or counterfeit medicines, abuse of power, negligence and forgery.

They received sentences ranging between 2-18 years imprisonment, fines and orders to pay compensation to families of victims, and return monies received through bribes.

Supply Chain Traceback

Two paediatric syrups registered for use in Uzbekistan were imported into the country by a locally based importer/distributor. The distributor bribed local officials not to scrutinise the manufacturer.

Both medicines had been produced by the same Indian manufacturer.

The manufacturer sourced propylene glycol from a local chemical distributor.

The chemical distributor stated they did not know the propylene glycol was going to be used in the manufacture of pharmaceuticals.

ACTORS:

1 x **Chemical manufacturer**

1 x **Intermediary**

1 x **Pharmaceutical manufacturer**

2 x **Jurisdictions**

ACTIONS:

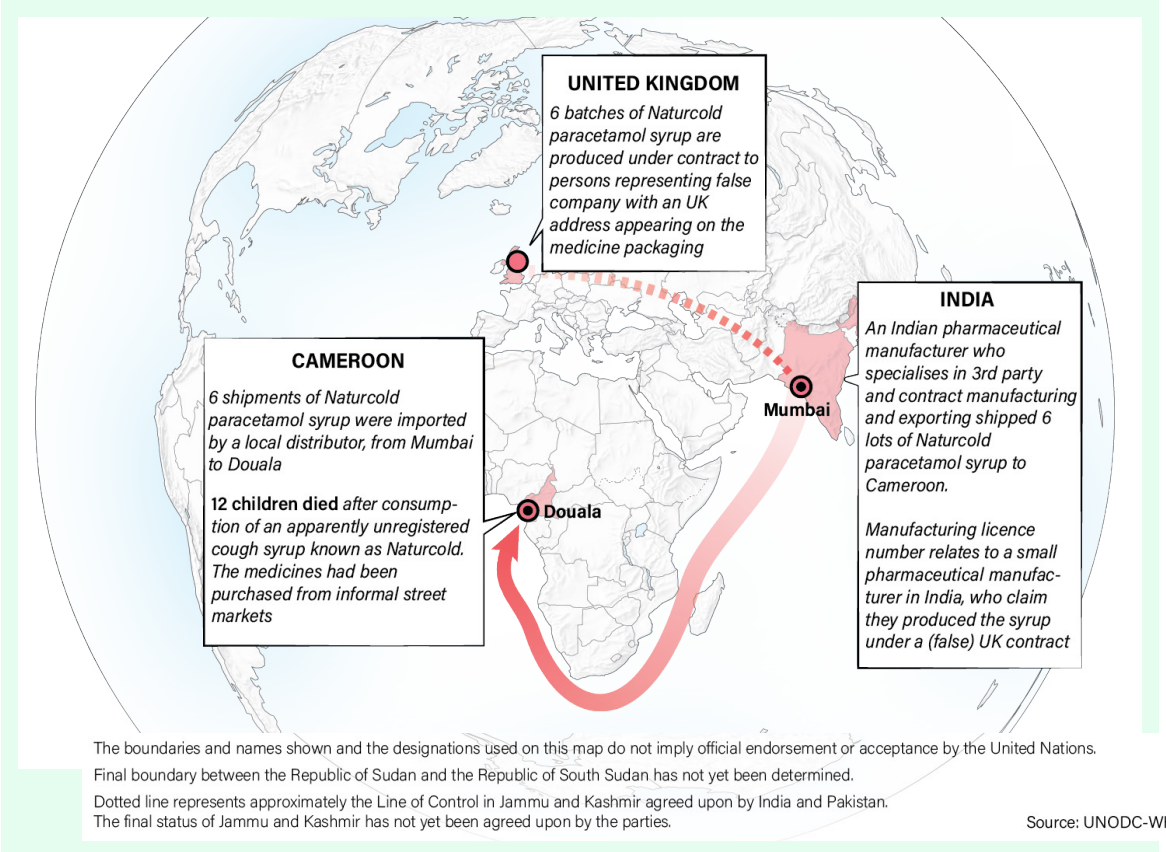
1x History of non-compliance with GMP

0 x Testing by intermediaries or end user of excipients for impurities

7.8. Cameroon 2022 [110]

Table 11. Cameroon case summary

Excipient	Excipient Contaminant	Medicine	Level of Contamination	Quantity	Fatalities
Unknown	DEG	Cough Syrup	24.4-27.9 DEG	Unknown	12



Background

In March 2023 the WHO became aware of media reports emerging from Cameroon of a public communication warning of the risks to children following the deaths of 3 infants having ingested a cough syrup.

Between March and June 2023, a further 9 deaths were recorded from various parts of Cameroon of children who had consumed an apparently unregistered cough syrup known as Naturcold. The medicines had been purchased from informal street markets.

The children had experienced symptoms consistent with past cases of contamination involving DEG/EG resulting in respiratory failure, and acute kidney injury.

Testing

A non-governmental organization (NGO) operating in Cameroon secured samples of Naturcold from the market and following negotiations with the Ministry of Health the samples were forwarded via WHO to an accredited medicine quality control laboratory for analysis. The laboratory tested 3 samples, two of which were open and obtained from patients, and one that was unopened. All three tested positive for the presence of Diethylene glycol of between 24.45-27.9% (240-270 times the permitted level).

Investigation

The labelling on the syrup claimed that the medicine was marketed by a company with an address in the United Kingdom. Investigations by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK revealed that no manufacturer or company existed under that name in the UK and the address was a residential premises. Neither had any licenses been issued to the named company. The MHRA stated that UK addresses were sometimes used on medicines made in other countries. This was done to suggest to the buyer and patients that the medicine had originated in the UK when in fact they had not.

Publicly available records detailing products imported into Cameroon revealed that six shipments of Naturcold had arrived between 2022-2023, the most recent of which was in March 2023.

Supply Chain Traceback

The Gambia arranged the importation of paediatric syrups via an importer based in The Gambia.

↓

The medicines were procured from an Indian manufacturer who had been supplying other medicines to The Gambia.

↓

The Indian manufacturer had allegedly sourced Propylene Glycol from a local chemical supplier.

↓

The Indian supplier allegedly sourced the Propylene Glycol from one of the largest Propylene Glycol manufacturers globally.

↓

The Propylene glycol manufacturer denies having supplied propylene glycol to the Indian chemical supplier or the pharmaceutical manufacturer.

Image source: WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

ACTORS:

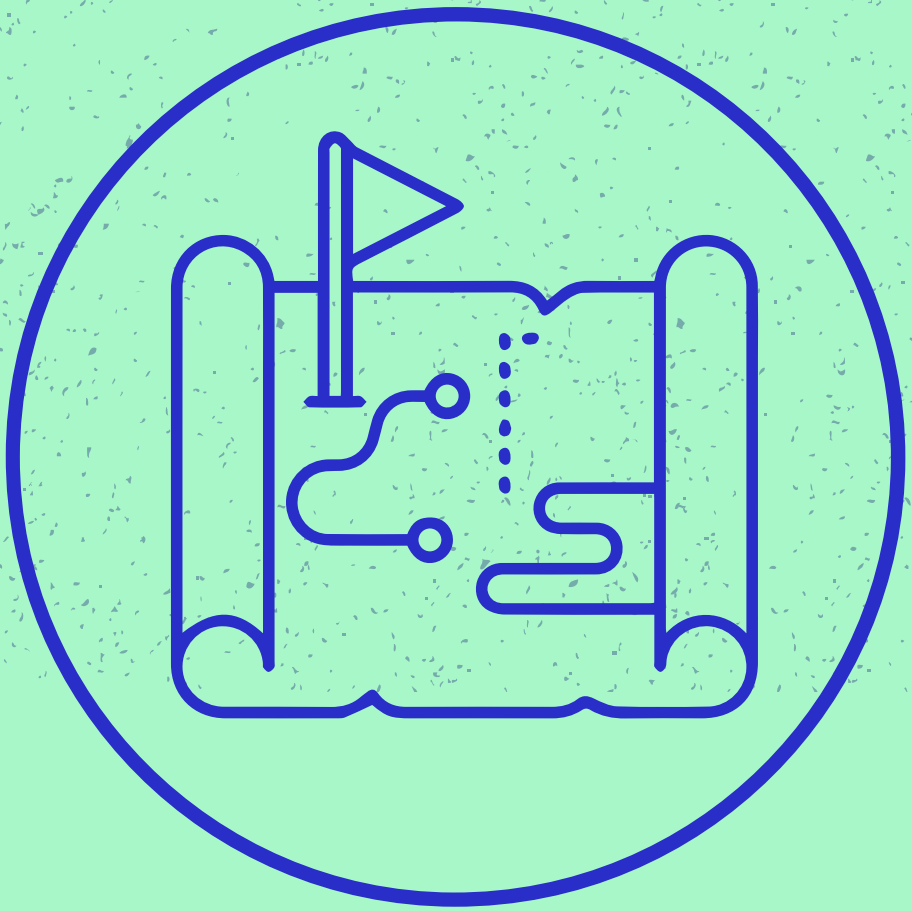
- 1 x **False company**
- 1 x **Contract manufacturer**
- 1 x **Exporter**
- 1 x **Importer**
- 2 x **Jurisdictions**

ACTIONS:

- **1 x Use of false company details**
- **1 x Contract manufacturer failing to confirm bona fides of client**
- **1 x Export/import of unregistered medicine**
- **1 x Distribution in informal street markets**
- **1 x Failure to test excipients for impurities**

The manufacturer whose licence number is displayed on the packaging claims that the products must be falsified and denies producing contaminated medicines. The current status of the case is unknown.

PART 3



8. Field Study [111] [112]

8.1. Background

Pakistan is a federal republic comprising 4 provinces, 1 Capital Territory and 2 Pakistan administered areas. It has a population of approximately 250 million. The pharmaceutical industry in Pakistan is worth about $3.5 billion and contributes 1% to Gross Domestic Product (GDP) annually. There are currently approximately 650 pharmaceutical manufacturers in Pakistan of which 80 account for almost 96% of market share. Pakistan exports $235million of pharmaceuticals (2024) to Afghanistan, Southeast Asia, Central Asia, Central America, Pacific Islands and Africa. Pakistan has published an ambitious strategy to significantly increase their export market[113] [114].

In 2011 Pakistan suffered a serious case of contamination of a locally manufactured medicine to treat heart failure resulting in over 200 deaths. The case did not involve contamination with DEG/EG. That case contributed to the formation of the Drug Regulatory Authority of Pakistan and huge investment in the upgrading of existing medicine quality control laboratories. Pakistan currently has access to 5 laboratories which have been pre-qualified by the WHO, and a further two currently undergoing pre-qualification.

Pharmaceuticals are regulated by the Drug Regulatory Authority of Pakistan (DRAP), which was established by the DRAP Act 2012. The Federal Government (DRAP) are responsible for manufacturing, licensing, registration, inspection, pricing, import/export, lot release, controlled drugs, clinical trials, quality assurance, post market surveillance, laboratory testing and pharmacovigilance[115]. Responsibility is devolved to Provincial Governments for oversight of the sale, storage, distribution, post market surveillance, laboratory testing and pharmacovigilance.

If regulatory oversight uncovers criminal activity those matters are reported to the Federal Investigation Agency or the police.

Pakistan was assessed as a key country in which to conduct a field visit due to several factors as set out below:

- Contaminated oral liquid medicines manufactured in Pakistan were discovered during market surveillance in The Gambia and the Maldives.
- These incidents triggered investigations by the Drug Regulatory Authority of Pakistan (DRAP).
- DRAP issued instructions to all medicines manufacturers to test for DEG/EG impurities in Propylene Glycol, Glycerine and Sorbitol prior to use in the manufacture of medicines.
- Recognising that small and medium sized manufacturers were unlikely to have the equipment required to test for these impurities, Pakistan established a system where samples of excipients could be submitted for testing to the Central Drugs Laboratory before use. Manufacturers were also reminded of the availability of third party accredited laboratories that could conduct the testing.
- DRAP then published detailed rapid alerts on excipients that failed to meet specifications during testing and recall notices for medicines that failed to meet specifications during testing.
- Social media platforms were being used to advertise and sell falsely labelled high risk excipients (i.e. uncontrolled informal market).
- DRAP focal points engage with the WHO Global Surveillance and Monitoring system and have pro-actively reported several incidents that have led to in medical product WHO Medical Product Alerts showing their commitment to global cooperation.
- The level of commitment and transparency demonstrated by DRAP in addressing the risks was apparent.

It is worth noting that at the time of writing there have been no recorded incidents of adverse events (including fatalities) attributed to contaminated syrups manufactured in Pakistan, either in Pakistan or to any countries to which medicines have been exported.

The field visit was conducted in February 2025. It focused specifically on 10 rapid alerts of pharmaceutical excipients issued by DRAP in 2024, and the export of locally produced oral liquid medicines. The visit conducted over 2 weeks involved a number of interviews and visits to government institutions, drug regulatory authorities, law enforcement, international organizations, excipient manufacturers, medicine manufacturers and excipient distributors. The opportunity to visit and interview manufacturers who had sourced falsified excipients was of great benefit in understanding the drivers that lead to contaminated medicines. The visit also presented an opportunity to examine in much greater depth the online sale of falsified excipients and disposal of used excipient drums.

8.2. Contaminated Medicines

Following the 2022 incident of contaminated medicines in The Gambia (See case study) risk-based post market surveillance on all imports of oral liquid medicines was commenced. It identified a suspect cough syrup that had been manufactured and imported from Pakistan. The suspicious syrup was sent to an accredited medicine quality control laboratory in Ghana where testing confirmed the medicine to be contaminated with 1.86% EG, beyond the accepted level of 0.10%.

In April 2023 WHO and the Drug Regulatory Authority of Pakistan (DRAP) were informed of the test results. DRAP inspected the manufacturer and suspended its production of oral liquid medicines. Suspicion fell upon the glycerine used in the production of the syrup and a recall was issued for the product discovered in The Gambia and three other syrups that had been produced with the same batch of glycerine. Some of these medicines had been exported to Tajikistan, whose competent authorities were notified by WHO.

In November 2023, more contaminated oral syrup medicines were detected in the Maldives. As a result of the 2022 incident in The Gambia, and having recently been trained in the use of newly developed screening techniques, the National Regulatory Authority of the Maldives conducted risk based post market surveillance and screening of imported oral liquid medicines. Five batches of a syrup produced and imported from Pakistan failed the screening tests. Samples of the product were sent to the Australian Therapeutic Goods Administration (TGA) for confirmatory testing where it was determined that the product was contaminated with ethylene glycol at concentrations between 0.62-0.82%.

WHO notified DRAP who conducted an inspection of the manufacturer and suspended its production of oral liquid medicines. DRAP discovered 8900 bottles of an affected batch had been distributed in Pakistan and also exported to Fiji, Lao PDR, Belize and the Maldives. All affected countries were notified by WHO. As a precautionary measure DRAP issued alerts in respect of 4 other oral liquid medicines produced with the same batch of excipients. In December 2023 WHO issued a Medical Product Alert concerning all five medicines recalled by Pakistan.

In neither of these cases were there any reports of adverse events in patients.

Small and medium sized manufacturers in Pakistan are unlikely to have the equipment to test for DG/EG impurities in starting materials and excipients which requires gas chromatography and mass spectrometry (GC-MS) equipment. In February 2024 DRAP issued a warning to all medicine manufacturers to test for DEG/EG impurities in high risk excipients. Additionally, DRAP implemented a system where manufacturers could submit a sample from each batch of high risk excipients (PG, glycerine and sorbitol) for testing at the Central Drugs Laboratory in Karachi at a reasonable cost and timescale. Manufacturers may also use accredited third party laboratories to conduct the necessary testing.

As a result of these initiatives, DRAP recorded an increase in the detection of DEG/EG in excipients. Regulatory inspectors also conducted sampling of oral liquids, which again revealed the presence of DEG/EG in finished medicines.

Between January 2023 and January 2025 DRAP have issued 11 recalls or alerts for medicines containing levels of DEG/EG exceeding permissible limits. These alerts and recalls listed multiple batches of 47 medicines produced by 19 local manufacturers. It is not currently known where all of the excipients originated, but in cases that have undergone investigation it appears that excipients have been supplied by intermediaries in the supply chain rather than from the excipient manufacturer or their designated official distributors. Scant documentation exists detailing the identity or addresses of the intermediaries or of the transactions. Where invoices do exist, they fail to identify the batch numbers of the excipients supplied making traceability impossible.

8.3. Contaminated Excipients

From January 2024 to February 2025 DRAP significantly increased vigilance and testing on high risk pharmaceutical excipients. During that period DRAP issued 12 rapid alerts concerning drums of contaminated pharmaceutical grade glycerin, sorbitol and PG.

The alerts cover multiple samples representing 16 different batches labelled and purporting to originate from 6 chemical manufacturers based in 6 countries.

So far at least 12 of the batches are confirmed as bearing falsified labelling. Some have genuine batch numbers, some are false. The expiry dates shown on some of the batches do not correspond to the shelf life of the genuine excipient and have been extended.

Some of the labels demonstrate a serious attempt to closely replicate the genuine labelling and bar codes of global chemical manufacturers, but they also reveal small differences in colour tones, measurements and fonts. Some have grammatical or spelling errors.

The condition of the steel 215kg/200l litre steel drums containing the excipients are sometimes poor, rusty and dented, others are in good condition. The largest chemical manufacturers supplying pharmaceutical grade excipients supply the chemicals in new, clean, steel drums, often bearing seals and barcodes. These drums are usually no-returnable.

Testing of 15 of the batches showed contamination with EG or DEG or both to varying levels exceeding the acceptable 0.10% permissible limit.

Table 12. DRAP Alerts of contaminated excipients 2024-25

Date of Alert	Excipient	Status	Test Results	DRAP Alert[116]	WHO Alert
11 Jan 2024	1 batch Propylene Glycol	Falsified		N0 I/S/01-24-02	1/2024
1 Feb 2024	I batch of Glycerine	Not known	EG 0.16%	N0 I/S/02-24-03	
13 Feb 2024	1 batch Propylene Glycol	Falsified	EG 44.47%. DEG 0.32%	N0 I/S/02-24-06	
7 Mar 2024	2 Batches Propylene Glycol	Falsified	EG 0.7%-78.78%	N0 I/S/02-24-11	1/2024
8 Mar 2024	1 batch Propylene Glycol	Not Known	EG 0.46%	N0 I/S/03-24-12	
8 Mar 2024	2 batches of Propylene Glycol	Falsified	EG 20.09%-34.68% DEG 7.3%	N0 I/S/03-24-14	1/2024
15 May 2024	1 batch of Sorbitol	Falsified	EG 0.6341%	N0 II/S/04-24-19	
22 Aug 2024	3 batches of Propylene Glycol	Falsified	EG 0.76%	N0 II/S/08-24-29	4/2024

25 Oct 2024	1 batch Propylene Glycol	Falsified	EG 2.37%	N0 I/S/10-24-38	
12 Dec 2024	1 batch Propylene Glycol	Falsified	EG 1.19%	N0 I/S/12-24-52	
25 Feb 2025	I batch Propylene Glycol	Falsified	EG 91.4%	N0 I/S/02-25-23	
15 Mar 2025	1 batch Propylene Glycol	Falsified	EG 0.19%	N0 I/S/03-25-32	

8.4. Excipient Supply Chain

E commerce and social media platforms

E commerce and social media platforms hosting chemical trading groups are being used to trade industrial quantities of chemicals including pharmaceutical excipients in Pakistan. This is not a practice restricted to Pakistan and similar practices exist in several other countries. Some of these platforms are open to the public, whilst others require a rudimentary registration process with no need to validate your identity. Some of the groups boast thousands of members.

Traders, brokers and other intermediaries operating in these groups offer a wide range of chemicals to all industries including the food, cosmetic and pharmaceutical sectors which all require the purest and most expensive grade of excipients.

Traders will usually post photographs of the products in the groups. Investigations conducted by one of the genuine pharmaceutical excipient manufacturers observed falsely labelled versions of their pharmaceutical grade PG being offered with the labels showing slight printing, font, and layout differences, some which also refer to false batch numbers and false product expiry dates.

The traders will provide a mobile telephone number and encourage any customer to contact them by WhatsApp which is an end-to-end encrypted messaging service offering greater privacy rather than continue negotiations on a public platform.

In April 2025 DRAP issued an advisory to pharmaceutical manufacturers not to source high risk excipients from unofficial channels including e commerce and social media platforms and warned of obligations under existing regulations, non-compliance of which may result in sanctions[117].

Investigation

During this field study one such trader was advertising photographs of falsely labelled PG from two excipient manufacturers who had previously seen contaminated and falsely labelled versions of their products used to manufacture medicines in Pakistan. In both cases they had been subject to previous alerts issued by DRAP.

DRAP contacted the trader and negotiated the purchase and delivery of two 215 kg drums of pharmaceutical grade PG. The following day a vehicle arrived with the two drums and the driver was questioned. He claimed to be merely the delivery person and revealed the location of a storge facility where a further 4 drums of PG were recovered. A total of 1290 kgs of falsely labelled pharmaceutical grade excipient was seized. The batch number of the PG was one that had previously been established as falsified and subject of a rapid alert in Pakistan.

The location was a sub store where chemicals would be delivered for onward delivery to the customer. This way the location of the main store would remain unknown to the delivery person. An order book was

recovered that was written in code to conceal the identity of the customers. It appeared the deliveries had been taking place for about a year. Samples of the PG were submitted for testing and found to contain EG at a contaminated of 91% (910 times higher than permitted levels). This case is still under investigation.

The criminals engaged in this process were exhibiting behaviours to:

- Replicate the labels of global chemical companies purporting to be pharmaceutical grade excipients and attach them to drums of chemicals containing extremely toxic levels of impurities.
- Advertise the falsely labelled product on social media platforms in specialist chemical trading forums.
- Negotiate sales through using mobile phones and encrypted chat platforms.
- Conceal the location of their main storage facility by using sub stores.
- Insist on delivering the product by a third party to avoid disclosing the location of the sub store.
- Retain a delivery ledger which concealed the identity of the customer.

The trader was unconcerned if their customers were from the food, cosmetics or pharmaceutical industries. The product when tested was highly contaminated suggesting this was EG falsely labelled as pharmaceutical grade PG. Currently EG is approximately 50% cheaper than Pharmaceutical grade PG.

As explained in Part 2 of this report manufacturers of pharmaceutical products are required to source their starting materials, including excipients from reliable and proven sources, operating to GMP standards. The supply of excipients from online traders, often with no declared physical address, with either a complete lack or cursory record of invoicing and no certificates of analysis represents a major risk to the supply chain. When this is combined with a lack of testing by the end user then the result can be catastrophic.

Used chemical drums

During this field study visits were conducted to glycerine and sorbitol manufacturing factories. No PG is manufactured in Pakistan and all PG is imported. Discussions have been held with PG manufacturers who are exporting to Pakistan and to their authorised distributors in Pakistan.

PG, Glycerine and Sorbitol are commonly supplied in 215kg steel or plastic drums. In most cases there is no recycling or returns of the drums to the manufacturers as it is not economically viable. It is up to the end user to dispose of the drums. As previously mentioned in Part 2 of this report pharmaceutical manufacturers are expected to deface the labels on empty drums before disposing of them. However, one manufacturer of Glycerine that was visited during the field study actually prints its label directly on to the plastic drum which makes removal very difficult if not impossible. In relation to the Glycerine manufacturer the name of their company is embossed onto the plastic drum.

Steel and plastic excipient drums are disposed of by the end user and sold on to traders. A very active market in the sale of used steel and plastic drums exists and is also conducted on e-commerce and social media platforms. On examining photographs of empty chemical drums advertised on these platforms many can be seen still bearing original labels. The existence of empty drums of genuine pharmaceutical excipients still bearing the original and genuine labels again represents the risk that they can be refilled with another chemical and sold back into the market for use in the food, cosmetic or pharmaceutical industries.

Authorised Distributors of excipients

During this field study an authorised distributor for a global manufacturer of PG was visited and interviewed. The distributor was the sole authorised importer/distributor for that manufacturer. The manufacturer conducted thorough due diligence and an audit of the distributor before engaging them. A contract was signed restricting the distributor to only supplying end users of the excipient. No sale to intermediaries, relabelling or repackaging entities was permitted and compliance with the contract is also subject to regular audit. The excipient manufacturer applies seals to the 215kg drums of PG together with a QR code which is scanned at each step of the distribution chain and monitored.

PART 4

9. Analysis

The selected case studies and the field study discussed in Part 3 are the principal sources of material used to identify recurrent themes in cases involving medicines contaminated with DEG/EG over the past 30 years. The characteristics emerging from those studies have been cross referenced with the interviews conducted with representatives from the various stakeholders and existing published material identified during the literature review.

As can be seen in all of the case studies there has been, to various degrees, a disregard for the measures and safeguards set out in the guidelines, regulatory requirements, and legislation surrounding the manufacturing, distribution and use of pharmaceutical excipients and finished pharmaceutical products.

For ease of reference the emerging themes have been divided into the following categories and sub-categories.

9.1. Motivators

Economic

The market in pharmaceutical excipients is exposed to the same volatility as many other commodities. Geopolitical factors, armed conflicts, political unrest, natural disasters and pandemics have a significant impact on the availability and in turn the price of pharmaceutical excipients. Shortages in the availability of raw materials required to produce excipients leads to delays, high demand and increased prices.

From limited publicly available market data for PG, glycerine and sorbitol it can clearly be seen that during the COVID-19 pandemic prices suddenly rose to at least 3 times higher than pre pandemic prices. Manufacturing facilities were temporarily closed and supply chains severely disrupted. The pharmaceutical industry, keen to maintain their manufacturing continuity and volumes throughout the pandemic led to a surge in ordering not normally seen in the market.

Although price fluctuations and availability of pharmaceutical excipients may be a contributory factor in the more recent incidents of DEG/EG contaminated medicines, it fails to explain the fact that there have been contamination incidents over the past 90 years where no obvious factor influencing the market can be identified.

Regulatory requirements demand pharmaceutical manufacturers to use excipients of the purest quality in the production of medicines. Tolerance levels for known impurities in pharmaceutical excipients are stringent, meaning production costs are substantially higher than in industrial grade versions of the same substance, which is then reflected in their price.

In the drive to produce low cost medicines some manufacturers may resort to high-risk cost saving behaviours, which compromise the quality of the FPP.

The price differential has motivated some excipient traders and distributors to supply non-pharmaceutical grade excipients misbranded or mislabelled as pharmaceutical grade for the sake of profit.

Also, some manufacturers may have chosen to replace pharmaceutical grade excipients with cheaper industrial grade versions . When these products are used to manufacture medicines, they contain levels of impurities beyond those permitted. There have been cases in which this has resulted in significant harm.

Risk v Benefit

Global, extended and complicated supply chains can significantly impact the ability to trace the source of contaminated excipients. The risk to perpetrators of being identified and prosecuted for either the falsification or intentional, negligent or reckless use of substandard or falsified excipients remains low and the financial benefit sufficiently persuasive.

Weak regulatory oversight both in the country of manufacture and the importing country contributes to reducing the risk of sanction. If a FPP is produced for export only (not authorised for placing on the market in the country of manufacture), regulatory oversight may frequently be even less stringent. Exports are often to low and lower middle-income countries where regulatory requirements are less stringent, some with very weak regulatory oversight and sanctions, and others with no facilities to submit the medicines for laboratory analysis. In these cases, risks to a pharmaceutical manufacturer of being identified as responsible for the production of a substandard medicine are low.

Criminal and regulatory sanctions should adequately reflect the serious consequences of stepping outside of the recognized international standards applied to the manufacturing, distribution and supply of medicines.

By failing to proportionately and consistently sanction serious regulatory breaches a clear message is sent that there is no deterrent to those who have criminal intent, or just wish to cut corners to save costs. The financial benefit of non-compliance to those individuals and entities historically and currently outweighs the risk of being held to account.

The recent WHO Medical Product Alerts have contributed greatly to increased awareness, more post market surveillance and testing and a need for importing countries to demand quality and implement measures to ensure that is the case. It is this that helps to alter the risk/benefit balance to the manufacturer, but these efforts need to be sustained.

9.2. Methods

Substitution

Intentionally substituting pharmaceutical grade PG with industrial grade PG which contains higher levels of DEG/EG impurities is a way of cutting manufacturing costs. Levels of DEG/EG impurities will differ, but some of the case studies (see case studies of Panama and India) demonstrate that use of industrial grade PG will lead to casualties, especially amongst children, through exposure to DEG/EG.

In some of the case studies PG has been completely and intentionally substituted with falsely labelled EG motivated by profit.

Dilution

Laboratory results have demonstrated a wide variance of the levels of DEG/EG contamination. Most are well beyond the levels that could be attributed to the use of contaminated equipment or packaging and suggest intentional contamination.

Excipient manufacturers produce and supply industrial quantities of chemicals ranging from consignments involving tonnes through to 1000 litre (1 metric tonne) containers known as topes, and commonly 200 litre (215kg) barrels or drums. Smaller FPP manufacturers may not require such large quantities and having sourced a drum may only use part of it. There is a risk that part used drums of pharmaceutical grade excipient are topped up with a similar chemical including DEG/EG and resold in the original labelled drums.

Mislabelling

As previously stated, the pharmaceutical excipient supply chain can be long and complex, involving multiple agents, brokers, re-packagers, re-labellers, wholesalers, distributors and importers. Some take physical possession of the excipient; some may repackage or relabel, and some will merely broker the sale and not take physical possession of the chemicals at any stage.

Several of the case studies have involved the intentional mislabelling of drums of excipients as pharmaceutical grade PG or glycerine at some point along the supply chain, in one case on multiple occasions. Intentionally falsified labels claiming to originate from multinational chemical companies have been produced and used intentionally to add credibility to the drums and their contents. Global chemical company logos have been downloaded and reproduced from websites and affixed to drums of excipients to convince end users of their authenticity and contents.

Document Manipulation

A certificate of analysis is a document expected when receiving excipients from a manufacturer or distributor. Guidance states the level of detail required in a COA including the full details of the original manufacturer of the excipient, and when licensed repackaging or relabelling has taken place, full traceability back to the original manufacturer should be possible. However, it is common practice to alter the certificate of analysis and accompanying documentation to remove the details of the last entity in the supply chain and the origin of the excipient to protect the interests of the intermediary and deter the customer from obtaining the excipient direct from the source.

Due to the often global nature of the supply chain this makes traceability difficult and, in some cases, impossible and often beyond the capacity of resource limited settings. In some cases, completely falsified certificates of analysis have been produced and in one case study testing highlighted anomalies which were ignored due to production timescales and a false COA produced declaring the excipient of standard quality. A second case study demonstrated the unauthorised extension of the expiry date of a high risk excipient by a number of years.

Reuse of Packaging Materials

Pharmaceutical excipients are supplied in a range of containers, but frequently these include 200 litre (215kg) steel or plastic drums. These drums have labels firmly affixed declaring the grade and purity of the contents. Once these drums are delivered and used by the FPP manufacturer they are sold or discarded. In most cases there is no return or recycling programmes provided by multinational chemical suppliers as it is economically unviable to arrange for the transport, industrial cleansing and reuse of the containers. Empty drums, bearing labels declaring they contain pharmaceutical grade excipients are then available for reuse. Secondary markets exist for such drums, which appear on specialist e commerce and social media platforms. These drums are then vulnerable to refilling with any chemical but still bearing labels declaring the contents as pharmaceutical grade ingredients.

Discarded packaging is a vulnerability already exploited by those engaged in the falsification of high value medicines. A similar vulnerability exists for high-risk excipients.

Absence of Testing

> "A pharmaceutical manufacturer who cannot guarantee the quality of their starting materials (including excipients) effectively undermines all of the guidance, regulation and legislation designed to safeguard the quality, safety and efficacy of the medicines they produce." National Medicine Regulator

As previously stated, responsibility for testing the finished medicine falls squarely with the manufacturer of that medicine. An absence of testing for known impurities in high-risk medicines that have been manufactured with high risk excipients is a highly dangerous omission and a critical failure in their core responsibilities under GMP.

The testing of high-risk excipients for impurities requires access to either expensive equipment, reference standards, or third party accredited laboratories. All involves expense and sometimes delay, adding to production costs and reducing profits.

Manufacturers of pharmaceuticals who lack the equipment, skills or desire to ensure the starting materials they use and finished pharmaceuticals products they produce are of the required quality are endangering public health, sometimes with disastrous results.

The case studies subject of this report shows a repeated absence of testing for impurities, sometimes exacerbated by the falsification of certificates of analysis, extension of expiry dates or mislabeling which have repeatedly led to the avoidable deaths of patients.

9.3. Enablers

Weak Procurement Systems

In many of the case studies described in this report there has been little, or no steps taken. There have been few by pharmaceutical manufacturers to authenticate the source or origin of the excipient, conduct vendor assurance or comply with GMP.

Decisions to purchase excipients had been based on price and availability. During this research invoices from intermediaries supplying pharmaceutical grade excipients have been examined and relate to fictitious addresses, rented offices, or mobile telephone numbers that when rung are not answered. In some cases, certificates of analysis have been provided by these intermediaries which are falsified or historic and are photocopies or scans relating to excipients provided previously by authorised distributors.

GMP requires finished pharmaceutical manufacturers to assure that those from whom they source starting materials (including excipients) are producing those materials in accordance with GMP and are supplied with an authentic certificate of analysis relating to the batch supplied.

Weak Regulatory Oversight

In Part 2 of this report a summary of Internationally recognised good practice relating to pharmaceutical excipients and their use in FPPs is set out. Much of this good practice has been adopted but not necessarily fully implemented or consistently applied by Member States.

The burden on regulators to oversee the implementation of the guidelines is both high and critical. In 2022 WHO identified 70%[118]of regulatory systems were below the minimum desired maturity level of a stable, well-functioning and integrated regulatory systems. The main challenges for this were identified as a lack of national policy and long-term strategy, insufficient commitment and engagement from a political level, inadequate resources to establish and sustain regulatory oversight, and bad regulatory practices.

Currently only 34 Member States are designated as WHO listed authorities (WLA)[119] for medicines, (their regulatory decisions may be used for regulatory reliance by other countries), and a further 9 as Maturity level 3 or 4 (well-functioning or advanced regulatory systems) for medicines under the WHO Global benchmarkingtool .[120]

A lack of medicine quality testing laboratories or screening technologies to detect DEG/EG has also hampered efforts to quickly identify the cause of adverse events in patients and recall products from the market. Some Member States have had to arrange testing in third countries which causes significant delays in taking steps to protect public health.

Regulators should first and foremost be focused on achieving compliance of those they regulate. Where breaches of regulatory requirements have been identified and are deemed critical to the protection of public health then the proportionate enforcement of the regulations and consistent application of sanctions should be considered. An incremental approach to applying sanctions may be appropriate, or in the most serious cases immediate resort to criminal proceedings may be required.

In a number of the case studies the companies involved in manufacturing the finished medical product have a history of serious non-compliance and in some cases convictions. A history of this nature should be considered when procuring medicines, as well as prioritising risk-based inspections and risk-based post market surveillance. Careful consideration of the suitability of that individual or entity to engage in future licensed activities should be carefully weighed.

Due to the global nature of the supply chain in pharmaceutical excipients and FPPs National Regulatory Authorities are not only responsible for the quality of products circulating in their own market, but also to the markets to which their products are exported. They are regulators of the global community as well as their own population.

While the finished pharmaceutical manufacturer bears ultimate responsibility for ensuring the identity and purity of excipients and the correct specification of the final product, the exporting country must also share some responsibility. It is reasonable to expect that the exported medicine meets the same requirements as if it were intended for their own domestic market. Exporting substandard products to third countries reflects badly on the exporting country and can have a detrimental effect on their reputation and wider export market.

Complexity of the Supply Chain

The case studies demonstrate the international and complex supply chain for pharmaceutical excipients. Manufacturers in one part of the world advertising their products through e commerce platforms and websites to intermediaries and customers globally poses significant challenges for the traceability of products. Some of the intermediaries take physical possession of the product and may make authorised changes to the packaging for onward supply, others broker the product virtually. As mentioned above document manipulation as part of protecting business interests has proved to be an aggravating factor in achieving traceability back to the original manufacture in an already complicated market.

Supply chains can be long and protracted with operators in different jurisdictions, operating in different languages. Some intermediaries may not be specialists in trading chemicals and unresponsive to enquiries from other countries. Regulators may not have the resources to trace back the origin of the contaminated product. The risk to other countries from the same batch of contaminated excipient or FPP is amplified if no traceback investigation is undertaken.

Online trading and social media platforms are now being used to trade chemicals including pharmaceutical excipients, in some jurisdictions. Drums of chemicals claiming to be pharmaceutical grade propylene glycol bearing falsified labels have been confirmed by a major chemical manufacturer and discovered during the field study conducted during this research, and have led to the issuance of WHO global medical product alerts and stimulated investigations.

In most of the case studies no confirmatory screening or testing of the identity or purity of the excipient was conducted, and testing of DEG/EG was either not conducted or not required in the FPP. The medicines are then distributed locally or in a number of cases exported leading to adverse events in patients and widespread risk to patients.

The consequences are obvious but far removed from the person using discarded barrels, falsified labels and advertising their product on a social media platform in one country, to it reaching the hands of a medicine manufacturer to produce a syrup, and eventually to the end user of the medicine in another country dispensing it to their infant.

Ecommerce and Social Media Platforms

The advertising, sale and supply of high risk excipients on ecommerce and social media platforms has become common practice in recent years. Photographs of products and their labelling is often posted. Excipient manufacturers have observed falsely labelled versions of their labels affixed to steel drums purporting to contain pharmaceutical grade high risk excipients. An example is discussed in Part 3 of this report.

Attempting to regulate this type of market poses significant challenges to all regulators. Risk based monitoring for high risk excipients using new technologies may be necessary combined with better oversight by excipient manufacturers of high risk markets and enforcement of their IPR rights where applicable.

A number of recommendations are suggested at the end of this report, including vendor assurance processes, testing, and greater focus during regulatory inspections on the procurement and testing of high risk excipients, it is also important that law enforcement and NMRA's have established relationships, MOU's or agreements with the ecommerce and social media platforms in order to request the take down of postings advertising falsified high risk excipients that represent a serious threat to public health.

Weak Awareness and Reporting Systems

A combination of a lack of awareness and poor reporting systems combine to hamper the early diagnosis of cases of Acute Kidney Injury and detection of DEG/EG contamination. Most countries have pharmacovigilance systems in place to monitor adverse events in patients, however reporting levels can be low. Appropriate case definition and the early diagnosis of cases of AKI especially amongst children is important in helping to establish the root cause quickly and taking remedial action.

Most reported incidents follow a cluster of cases involving AKI especially amongst young children and infants, usually over a short period of time and in close geographic proximity. Only once numbers have become sufficiently high to raise attention are the cases investigated, and sometime later suspicion and testing focuses upon a medicine that had been consumed. By which time there may be multiple casualties.

As has previously been stated pharmaceutical grade PG, glycerine and sorbitol are used in cosmetics, food and pharmaceuticals. Many countries have national poison centres that may have picked up a signal or suspicious reporting caused by the use of, or consumption of those types of products. This can provide an early warning that contaminated excipients may be in circulation and also represent a risk to the pharmaceutical sector. This can trigger increased risk based communication, inspection and post market surveillance of pharmaceuticals prior to the emergence of widespread adverse events in patients. A case definition relating to poisoning by DEG/EG should be agreed. Whilst this may present some difficulties to develop, there are preliminary steps that could be taken to assist in identifying cases of potential mass poisoning by DEG/EG. To identify potential mass poisoning by DEG/EG, it is recommended to implement enhanced surveillance and reporting, targeted clinical and laboratory protocols, coordinated interagency response, antidote availability, and sample retention and analysis. See Annex 2.

Whilst recognizing that this will not cover every eventuality, analysis of past cases suggests it may lead to the early identification of the circulation of contaminated medicine and help prevent further casualties.

The cases described usually involve at least one batch of contaminated medicine, a batch size can vary widely but often involves several thousand units. Once a contaminated batch is in circulation the early identification of suspected cases will greatly improve the ability to prevent mass casualties.

Engaging healthcare professionals and specifically paediatric specialists in raising awareness of DEG / EG poisoning, and the steps to take in the early identification and reporting of suspicious cases is critical in managing outbreaks of mass poisonings.

Providing user-friendly and accessible reporting mechanisms that have been promoted amongst healthcare professionals and the public is essential. Ensuring timely follow up from the authority to whom the report is submitted is also key to increasing reporting levels.

The WHO Global Surveillance and Monitoring system for substandard and falsified medical products is the platform to which Member States and other stakeholders are encouraged to report cases of confirmed or suspected SFMP's, including cases of medicines or excipients contaminated with DEG/EG. Where necessary the WHO will issue Medical Product Alerts particularly when it is likely that the SFMP is available in a wide geographic region. The publication of such risk communications allows WHO to better coordinate information sharing and provide technical support to impacted countries.

Additionally, the International Health Regulations (IHR) are a set of legally binding instruments signed by 194 WHO Member States which defines Countries' rights and obligations in handling public health emergencies that have the potential to cross borders. Whilst originally focusing on outbreaks of epidemics the regulations now extend to public health emergencies of international concern. This should include cases of SFMP. There remains an under reporting of cases generally and some countries have failed to recognize or report cases involving DEG/EG contamination to either system.

Weak Border Controls

Some of the Member States adversely affected by contaminated medicines or excipients, whether substandard or falsified suffer from porous borders. Whilst designated ports of entry for medical products together with a joint Customs and Medicine regulatory presence at those ports is encouraged this is not always possible and does not account for the numerous informal border crossings that exist in many countries.

In countries that rely on high volumes of imported medical products sheer volumes make it impossible to inspect every batch of every product. Risk based approaches to oversight are encouraged focusing finite resources on medicines and excipients that represent the highest risk. Fast and efficient processes between Customs and NMRA's in ensuring only those products that are authorised for import are cleared for entry. Global high risk excipient manufacturers should establish relationships and training programmes with National Customs, Regulatory authorities and border control on how to identify suspicious consignments, documentation or trade routes and on what action to take.

The analysis of import data and the thorough investigation of cases involving contamination can lead to the development of profiles of suspicious consignments from finished medicines to excipients or their packaging which assist in targeting resources.

Following a recall of a medicine from the market there may be an attempt by unscrupulous traders to smuggle the recalled product to another country to minimise any financial loss. This has been seen in one of the more recent case studies and led to the seizure of contaminated paediatric syrups. It is a behaviour previously seen in relation to recalled falsified medicines.

Ultimately the existence of porous borders means it is even more important to exercise control of the market in pharmaceuticals within the country. Whilst challenging, particularly in resource limited settings, using all available intelligence, from multiple agencies to assess risk and adopt risk based post market surveillance systems is key to focusing finite resources on the locations, entities and products that represent the greatest risk.

Legal and Regulatory Framework

Prosecutions concerning contaminated medicines are relatively rare, usually complex, international in nature, and are likely to involve complicated indictments relating to other crimes. These may include differing degrees of homicide, money laundering, fraud, forgery, drug trafficking, corruption, tax evasion, combined with regulatory breaches, confiscation of assets and compensation hearings.

Formal investigations by authorities seeking evidence from different jurisdictions usually have to rely on pre-existing bi-lateral legal agreements (mutual legal assistance treaties), involving complex procedures between countries which often are not in place. Prosecutors familiar with and trained in these procedures are important.

In some cases, evidence involving websites, social media and electronic payments will involve investigators and prosecutors with a knowledge of cyber investigations and in some cases crypto currencies. The digital examination of computers and mobile phones is likely to be necessary in most cases and the source of key evidence. Investigators, prosecutors and judges experienced in these procedures are necessary to ensure admissibility in court proceedings. Evidence concerning the laboratory analysis of medicines, substances and toxicity, and their regulatory oversight is required in all of these cases. Access to experts and the necessary equipment is critical.

The skills required to investigate pharmaceutical related crime draw on expertise from Police, Medicine regulators and sometimes Customs. Information sharing, coordination and collaboration are key prerequisites. A joint law enforcement, regulatory, border control agency approach is not always possible due to barriers in information exchange and trust, and will hinder investigations and prosecutions.

Cases can be lengthy, expensive and hotly contested. Well trained and well resourced investigators, specialist prosecutors and judges with an awareness of pharmaceutical crimes under the umbrella of a legal framework and well functioning criminal justice system are critical and likely to be beyond some resource limited settings.

Prosecutions are more likely to occur where deaths have occurred, and public interest is high, attracting the interest of the media and politicians. Cases that involve more traditional forms of criminality (drug trafficking or money laundering) that have become associated with pharmaceutical crime may also reach the Courts. But cases that solely feature egregious breaches of medicines regulation which pose a serious threat to public health but have been identified before causing harm are less likely to be prosecuted. Criminal courts are less used to dealing with these types of cases, but by addressing them a clear message can be transmitted to others in the supply chain that there are consequences for such actions.

Sentences for serious breaches of medicine legislation, substandard and falsified medicines, and knowingly or negligently supplying or using substandard or falsified pharmaceutical excipients should clearly reflect the risk posed to public health and be commensurate to the specific facts of the case. Sentences should be designed to change behaviours and act as a deterrent to offending. Those tempted to offend should be aware of the serious consequences of their actions not only to the public but to themselves.

The factors listed above reduce the risk of investigation and prosecution to those acting with criminal intent and operating internationally. But it is through the detailed and thorough investigations conducted by professional well trained personnel provide a rare opportunity of obtaining the deepest understanding of the motivators, methods and enablers of these types of cases. It is that depth of understanding that facilitates the development of policy, procedure and practices to effectively prevent, detect and respond to these types of cases in the future.

Corruption

Several of the case studies feature allegations of corruption. In two cases the conviction of Government employees for receiving bribes and in one case businessmen offering and facilitating bribes to government officials. Other cases involve the conviction of public officials, regulators, laboratory managers and those responsible for registration for negligence of their duties. This report does not examine the causes of corruption but does identify that corruption has featured and been proved in a court of law in cases of medicines contaminated with DEG/EG which have led to deaths.

In other cases, unproved allegations have been reported against Government officials. The corrupt registration of medicines, procurement, facilitation of import licences, GMP certification of manufacturers and falsification of test results all completely undermine the raft of legislation, regulation and guidance that underpin the safety, efficacy and quality of the medicines available to the public. It thoroughly damages trust in governments and medicines on the market.

Sanctions for those engaged in the offering, negotiating, providing and accepting bribes to undermine regulatory or judicial processes relating to the licensing, manufacturing, distribution, importation, sale and supply of medicines should reflect the potential consequences of those actions.

9.4. Criminality

A wide range of very serious crime is illustrated in the case studies included in this report. Many of the cases have led to a widespread loss of life and represent the very most serious forms of criminality, others constitute offences such as fraud, corruption, tax evasion and forgery, which are prosecutable under both national criminal codes and international legal frameworks, including the United Nations Convention against Corruption. The sentences imposed in those cases that resulted in successful prosecutions clearly show extended terms of imprisonment, and in one case life imprisonment.

The United Nations Convention against Transnational Organised Crime (UNTOC)

The United Nations Convention against Transnational Organised Crime (UNTOC) [121]was adopted in 2000 and now has 193 parties and 147 signatories[122]. It is the main international instrument in the fight against transnational organized crime.

Member States that ratify this instrument commit themselves to taking a series of measures against transnational organized crime, including the creation of domestic criminal offences (participation in an organized criminal group, money laundering, corruption and obstruction of justice); the adoption of new and sweeping frameworks for extradition, mutual legal assistance and law enforcement cooperation; and the promotion of training and technical assistance for building or upgrading the necessary capacity of national authorities.

It defines an organised crime group as:

A structured group of three or more persons, existing for a period of time and acting in concert with the aim of committing one or more serious crimes or offences established in accordance with this Convention, in order to obtain, directly or indirectly, a financial or other material benefit.

Serious crime is defined as:

Conduct constituting an offence punishable by a maximum deprivation of liberty of at least four years or a more serious penalty.

The involvement of organised crime groups in some large cases of falsified medicines is well evidenced, with structured groups operating internationally, generating vast profits and utilising complex international money laundering techniques. While there is limited evidence confirming the involvement of structured criminal organizations in the supply of falsified excipients, certain networks demonstrate features—such as coordination, profit motivation, and repeated offending—that may warrant further assessment against the criteria established by UNTOC."

Criminal Actors

The case studies reveal a combination of actions and behaviours by separate parties which together conspire to result in devastating consequences. Those actions ranging from deliberate criminal intent to gross negligence or reckless disregard for regulatory compliance, all of which may constitute criminal liability depending on national legal thresholds.

The genesis of these cases emerges from the action of those who intentionally misrepresent excipients as pharmaceutical grade when they are not. This may be carried out through intentional mislabelling, dilution or substitution. There is a lack of evidence to suggest that organised crime groups are engaged in this activity.

However, there is evidence to suggest that some effort is expended on attempting to replicate the labels of internationally recognised leading brands of genuine excipients with the clear intention of deceiving others that it is the genuine product. This constitutes a breach of intellectual property rights which in some jurisdictions is one of the triggers to launch proceeds of crime and confiscation proceedings.

Some traders or distributors supplying falsely labelled excipients may be doing so unknowingly or unintentionally. As previously stated there may be multiple intermediaries in the form of traders, distributors and wholesalers involved in the supply chain. Obtaining compelling evidence to determine which had criminal intent can prove challenging to investigators and will often requiring international cooperation, lawful access mechanisms (e.g. MLATs), and adherence to digital forensic standards for admissibility in court.

Some of those intermediaries engage in the common business practice of altering documentation, including certificates of analysis, to conceal the previous actor in the supply chain and the originator of the excipient. This contributes to difficulties in tracing the excipient back to the originator or establishing at which point false labelling, substitution or dilution had taken place.

Some traders are advertising the falsely labelled excipients in specialist chemical trading groups on social media platforms attracting some pharmaceutical manufacturers wishing to source slightly less expensive product.

All manufacturers including those tempted to purchase pharmaceutical grade excipients from unauthorised and untried sources are knowingly in breach of regulation and are aware of the potential serious consequences of untested excipients from untrusted sources.

On the basis of the case studies from China and Indonesia and the field study from Pakistan the criminality appears to be being carried out by individual actors or business owners operating outside of regulatory frameworks and motivated by profit. That is not to say that if the profits from this form of criminality were to increase further organised crime groups may diversify their activities as has been seen more broadly with falsified medicines.

Some cases have highlighted corrupt practices involving government officials or pharmaceutical company representatives that have undermined the processes and procedures for oversight of the pharmaceutical supply chain. Another case resulted in the prosecution of government officials for negligence leading to contaminated medicines reaching patients.

Corruption can often lead to long term damage and mistrust in government authorities, healthcare professionals and medicines. Specialist trained investigators are required to deal with public sector corruption which would constitute serious crime under UNTOC.

The absence of evidence of the involvement of organised crime groups does not detract from the serious consequences arising from those that are involved in the supply of falsified pharmaceutical excipients. Indeed, while these crimes may be committed by individuals, rather than organised crime groups, the harm caused to vulnerable populations by these individual actions is disproportionately severe. These types of incidents demand detailed investigations, advanced investigative techniques, specialist laboratories and regulatory expertise. Speed in taking proportionate actions to protect public health needs to be combined with a rapid investigative response to preserve and obtain compelling and admissible evidence against offenders and minimise the threat.

The complexity of these criminal dynamics reinforces the need for joint action by regulatory authorities, law enforcement, prosecutors, and international partners. Enhancing capacity in digital forensics, financial investigations, and international legal cooperation will be key to dismantling these criminal supply chains and ensuring accountability.

9.5. Responses

The nature of these types of incidents rightly attracts intense international public, press and political attention. Scrutiny is quickly focused on the timely response from the authorities responsible for oversight. Any failures in the prevention, detection and response to such cases is subject to public forensic examination.

Countries which have experienced recent patient adverse events resulting from DEG/EG contamination of medicines, and those in which these medicines were manufactured have responded to the incidents in a range of different ways, examples of which are listed below:

Regulation

- Changes to regulation concerning the oversight of the importation and distribution of high risk excipients.
- Increased cooperation agreements with cargo companies, couriers, post and logistic providers responsible for supervising shipped goods.
- Greater responsibility on pharmaceutical manufacturers to evaluate and if necessary, audit excipient suppliers.
- Increased regulation on traceability of import of excipients.
- Increased regulation on the management of drug poisoning cases.
- Increased risk based inspections of pharmaceutical manufacturers of high risk syrups.
- Risk based post market surveillance of high risk syrups.
- More transparent publication of recall and rapid alert notices.

Testing

- Pre export testing of syrup medicines for export purposes.
- Access for pharmaceutical manufacturers to Government laboratories for testing High risk excipients prior to use.
- Increased Revisions to pharmacopeial monographs on testing for impurities.
  screening of syrup medicines on importation prior to distribution.
- Development of and publication of screening methodology for detection of DEG/EG.
- Development of portable screening technology for detection or DEG/EG.

Reporting and Awareness

- Training programmes for pharmaceutical manufacturers on GMP.
- Increased proactive reporting to WHO GSMS.

Investigation and Prosecution

- Reactive and proactive investigations into the sale and use of contaminated excipients.

Funding

- Increased funding for National Regulatory Authority.
- Increased funding for establishment of National medicine quality control laboratory.

Some of the responses have required external funding and support from international and non-governmental organizations which will require future assessment as to their sustainability and proportionality.

PART 4

10. Recommendations

10.1. Overarching recommendation

Member States and International Organizations are urged to recognize that further unnecessary loss of life and disability, due to medicines contaminated with DEG/EG will reoccur unless additional measures are urgently taken to mitigate the risk.

Key Recommendations		
Prevention	**Education and Awareness**	Engage healthcare professionals, regulatory authorities, law enforcement and customs, industry, civil society, patient and consumer organizations: Raising awareness about substandard and falsified medical products and specifically contaminated medicines and high-risk excipients, through campaigns, workshops, and collaborations with various organizations. Educating the public and encouraging reporting of suspicious products.
	Comprehensive Legal Framework	Policy and legislation: Ensuring regulation and legislation provides adequate powers for law enforcement, customs and regulatory authorities to investigate, detain, examine, sample, test, and where necessary quarantine, seize and destroy medical products and high-risk excipients suspected or established to be substandard of falsified.
	Multi-Stakeholder Engagement	Collaborate in the investigation of contaminated medicines. Joint investigation teams should be established in the investigation of cases involving SF medical products and specifically cases involving contamination. These teams should be comprised of specialists and include representatives from the medicine regulator, law enforcement, Customs and the Judicial system and other specialists as required. Information sharing agreements should be established to facilitate effective working.
	Supply Chain Integrity	Improved compliance and increased regulatory oversight: Focusing on the sourcing, distribution, supply, documentation, use and disposal of packaging of high-risk excipients by pharmaceutical manufacturers in compliance with GMP and GDP.
Detection	**Access to laboratories and screening technologies**	Training and equipping national medicine quality control laboratories: Ensuring that laboratories have the necessary tools and expertise to screen and test for contaminants like DEG/EG in pharmaceutical products. Including use of advanced screening technologies and training of personnel.
	Risk-Based Inspection and Surveillance	Developing risk-based inspection programs: Focusing inspections on manufacturers that produce medicines with high-risk excipients by prioritizing resources and efforts based on the level of risk associated with different products and manufacturers. Developing risk based post market surveillance programmes focused on high-risk oral liquid finished medical products.
	Reporting Systems	Streamlining the process for reporting cases of contaminated medicines locally and to international systems like WHO GSMS and IHR focusing on timely and accurate reporting, facilitating global monitoring and response.

	Border Control	Assigning trained personnel at key entry points to oversee the import and export of high-risk pharmaceutical excipients.
Response	**Alerts and Recalls**	Establishing efficient systems for issuing alerts and recalls when contaminated excipients or medicines are detected. This includes mandatory reporting to WHO GSMS and/or IHR to ensure swift action.
	Regulatory Strengthening	Creating training programs for regulatory authorities on how to respond to incidents involving contaminated medicines. This includes early diagnosis, reporting, investigation techniques, working with stakeholders and communication strategies.
	Transparent Legal Process	Applying adequate legislation with dissuasive sanctions by enacting laws that impose severe penalties for the intentional, reckless, or negligent supply or use of high-risk excipients.
	Evidence-Based Policy and Procedure	Use formal, evidence-based designation and review of high-risk excipients through regular reviews of excipients to identify those that pose high risks, through expert-led assessments and dissemination of findings to stakeholders.

Responsible Parties

- National Regulatory Authorities (NRA): Responsible for regulatory oversight, inspections, and enforcement of compliance.
- Pharmaceutical Manufacturers: Responsible for adhering to GMP standards and ensuring the integrity of their supply chains.
- WHO: Provide support, convening, training, and global monitoring systems.
- Customs and Border Control: Oversee the import and export of high-risk excipients.
- Healthcare Professionals: Engage in training and awareness programs.
- Civil Society Organizations: Collaborate in awareness campaigns and reporting systems.
- Law Enforcement Agencies: Conduct investigations and enforce legal sanctions.
- Judicial System: Implement legal processes and sanctions.

Annex 1. Full set of recommendations

Regulatory and public health recommendations

Recommendations for WHO	
1	Conduct formal, evidence based, expert led designation and regular review of the list of high-risk excipients, for publication and dissemination to all Member States and stakeholders.
2	A review and consultation of the existing WHO starting material and certification scheme should be conducted, with a focus on simplification of the system using new technologies, and the clear inclusion of high-risk pharmaceutical excipients.
3	Simplified reporting to the global surveillance and monitoring system for all cases involving suspected and confirmed contaminated medicines, and substandard and falsified versions of high-risk excipients by Member States, manufacturers and distributors.
4	Promote reporting via IHR focal points of all cases involving medicines or high-risk excipients that represent an international risk to public health.
5	Provide support to Member States in the development and Implementation of National action plans for SF medical products.
6	Develop and deliver a training module focused on the public health aspects of immediate response, investigation, and communication related to incidents involving contaminated medicines.

Recommendations for National Regulatory Authorities	
Regulatory Legal Framework	
1	Financial and other incentives for pharmaceutical manufacturers demonstrating a consistent history of compliance with GMP should be developed to encourage a sustained culture of compliance.
2	High-risk pharmaceutical excipients as designated by WHO that are being advertised, sold or supplied and are purporting to be of pharmaceutical grade should be brought within the oversight of the National Medicine Regulatory Authority, with the requisite powers to investigate and sanction or recommend prosecution.
3	Implement policy and legislation to address conflicts of interest of government officials engaged in the regulation of pharmaceuticals.
4	An adequate range of dissuasive sanctions are needed for critical findings of non-compliance with good manufacturing and distribution practices discovered during regulatory inspections, investigations and post market surveillance programmes for high-risk excipients or finished medical products made with high-risk excipients. Sanctions should include cautions, warnings, suspensions and revocation of licences.

Inspection -Manufacturing	
1	High-risk pharmaceutical excipients as defined by the WHO should be regulated and prioritised during inspections to the same degree as active pharmaceutical ingredients.
2	Medicines at risk of contamination from DEG/EG and those that manufacture them on an 'export only' basis should be subject to the same degree of regulation and oversight as those medicines destined for placing on the market in the country of manufacture.
3	Risk based inspection programmes should be developed in relation to manufacturers engaged in the production of medicines containing high-risk excipients.
4	GMP inspections should prioritise high-risk pharmaceutical excipients during the inspection process, specifically in relation to their procurement, documentation, testing, storage and use.
5	Special attention should be given to the defacement of labels and method of disposal of high-risk excipient packaging (e.g. empty drums and barrels) during regulatory inspections.
6	Special attention should be given to the authenticity and provenance of certificates of analysis, invoices and documentation relating to high- risk excipients, ensuring the original manufacturer of the excipient and all intermediaries involved in its supply are clearly identified.
7	A failure to test a high-risk excipient for DEG/EG impurities and a failure to carry out vendor assurance checks and due diligence of suppliers of starting materials (including excipients) should be regarded as a critical or equivalent finding of non-compliance with GMP/GDP and attract a commensurate sanction.
Inspection – Distribution	
1	Those entities engaged in the importation, distribution, brokering, trade, relabelling and repackaging of high-risk pharmaceutical excipients should be subject to regulation, including licensing and regular inspections.
2	Those engaged in the repackaging or relabelling of high-risk excipients should be subject of licensing and regulatory oversight including inspection, and any non-compliance with GMP/GDP concerning the testing or integrity of the material should be regarded as a critical or equivalent deficiency and attract a commensurate sanction.
3	Risk based post market surveillance programmes should consider specific targeting of high-risk categories of medicines vulnerable to DEG/EG contamination for regular sampling and testing throughout the domestic market at all levels of the formal and informal supply chain.
4	Use of technology to monitor risks to supply chains, shortages, stock outs and price fluctuations of high risk pharmaceutical excipients should be explored and implemented to provide an early warning of possible increased risks.
5	Recall and Alert systems should be reviewed to ensure recall procedures are established and are effective, and alerts are disseminated in a timely and appropriate way to reach the relevant audience.

Testing	
1	All NRA medicine quality control laboratories should be trained and equipped in testing for the presence of DEG /EG in finished pharmaceutical products and excipients.
2	Reliable screening methods for the detection of DEG/EG should be available to all NRA's and training supplied in its use.
3	Portable, reliable, robust and affordable screening devices should be developed and deployed at strategic points in the supply chain including ports of entry and during regulatory inspections or enforcement actions to detect levels of DEG/EG exceeding the limit of 0.10%.
4	Closer coordination should be established between medicine quality control laboratories and Police Forensic laboratories for exchange of information, expertise and trend analysis.
Pharmacovigilance	
1	A case definition should be developed for cases of DEG/EG poisoning to assist in the early identification, treatment, linking and reporting of cases.
2	Raise awareness amongst healthcare professionals of the case definition, adverse effects of medicines contaminated with DEG/EG and pharmacovigilance reporting mechanisms.
3	National pharmacovigilance systems should enhance communication and links to National Poison centres for the identification of cases and trends in the food and cosmetic sectors of DEG/EG poisoning, which may provide an early warning of potential risks to the pharmaceutical sector.
Import/Export	
1	Regulatory personnel should be permanently deployed at designated ports of entry and include in their duties risk based oversight of the import and export of high-risk pharmaceutical excipients or high-risk medicines vulnerable to DEG/EG contamination.
2	Export data for oral liquids should be monitored to help inform risk based inspection of manufacturers and risk based surveillance and testing.
Enforcement	
1	A publicly available enforcement policy including available sanctions should be published specifically in relation to cases involving a failure to test excipients for their identity and purity, specifically for the presence of DEG/EG.
2	Information exchange between NRA's Police, Customs and any other relevant Govt departments should be subject of formalised agreements to ensure the rapid and efficient exchange of information, and timely investigation relating to SF medical products and specifically cases of contaminations.
3	Joint investigation teams should be established in the investigation of cases involving SF medical products and specifically cases involving contamination. These teams should be comprised of specialists and include representatives from the medicine regulator, law enforcement, Customs, Judicial system and other specialists as required.

Reporting	
1	NRAs must report all incidents of suspected/confirmed DEG/EG contamination to the WHO GSMS and or IHR systems.
2	NRAs should as a priority contact any countries to which a contaminated or suspected contaminated medicines or batch of excipient has been exported and inform those countries and the WHO GSMS/ IHR for appropriate action as soon as is practicable.
3	Third party accredited laboratories should be legally compelled to disclose to National Regulatory Authorities any contamination of high-risk pharmaceutical excipients or medicines discovered whilst performing testing on behalf of clients.
4	Increase and maintain awareness amongst all stakeholders and the public of the existence of reporting mechanisms.
5	FPP manufacturers should be required to report incidents of supply of substandard or falsified excipients.
Public Outreach	
1	**Prevention:** Engage civil society, patient and consumer organizations to raise awareness of the existence of SF medical products including contaminated medicines, carefully balancing the need to raise awareness whilst avoiding unnecessary alarm.
2	**Detection:** Ensure civil society and the public are aware of when and how to report suspicions of SFMP and specifically medicines contaminated with DEG/EG to the authorities
3	**Response:** Engage civil society, consumer groups and faith based organizations to assist in the timely and widespread dissemination of official recalls and alerts particularly to 'hard to reach' communities.

Healthcare professionals	
1	Provide professional training curriculums for healthcare professionals on substandard and falsified medical products including: · How to identify and report SF medical products · How to identify suspected cases of medicines contaminated with DEG/EG · How to identify potential adverse effects caused by medicines contaminated DEG/EG · How to report to pharmacovigilance centres and/or National Medicine Regulatory Authorities
2	Engage specialist professional organizations and bodies relevant to the most at risk patient groups (e.g. Paediatric associations), to raise awareness amongst the healthcare professional community of the risks of oral liquid medicines contaminated with DEG/EG.
Pharmaceutical excipient manufacturers, distributors and medicine manufacturers	
High-risk excipient manufacturers	
1	Source and test raw materials from approved vendors.
2	Only distribute high risk pharmaceutical excipients to approved and designated importers/ distributors.
3	Restrict approved distributors to only supply to the end user or their approved agent.
4	Audit approved distributors regularly and respond to negative findings.
5	Increase awareness of importers/ distributors and customs authorities on identifying suspicious labelling and consignments.
6	Consider use of tamper proof seals and track and trace technology on drums of high risk excipients.
7	Explore possibility of supplying high-risk excipients in a range of smaller quantities to reduce the need for repackaging and relabelling.
8	Explore viability of reuse, recycling and return programmes for used containers.
9	Collaborate with trade organizations representing high-risk excipient manufacturers in trends of excipient falsification.
10	Report cases of falsification to the WHO global surveillance and monitoring system (GSMS).
11	Enforce IPR rights relating to High-risk excipients.
High-risk excipient Importers, distributors, re-packagers and re-labellers	
1	Procure high-risk excipients from the original manufacturer or exceptionally from their designated and authorised distributor.
2	Ensure Certificates of analysis clearly indicate the original manufacturer of the excipient, and all intermediaries involved in its supply.
3	Ensure all certificates of analysis are supplied if multiple testing has been conducted.
4	Only supply to end user of high-risk excipients or their designated agent.
5	Report cases of falsification to the National Medicine Regulatory Authority or the WHO global surveillance and monitoring system (GSMS).

Finished Pharmaceutical product manufacturers	
1	Prioritise the sourcing of high-risk pharmaceutical grade excipients from approved vendors acting for the original manufacturer of the excipient.
2	Enter into a contractual agreement stipulating the source and specification of the excipient.
3	Conduct thorough vendor assurance and due diligence.
4	Audit the vendor on a regular basis and respond to negative findings.
5	Avoid repackaged or relabelled high-risk excipients where possible.
6	Avoid sourcing excipients from unauthorised or unknown intermediaries.
7	Avoid sourcing excipients from unknown websites, or social media platforms.
8	Always test high risk excipients for compliance with specifications and for the presence of known impurities, specifically DEG/EG before use.
9	If sourcing high-risk pharmaceutical excipients other than from the manufacturer or their designated distributor then test each container of that excipient. If sourcing directly from the manufacturer or their designated distributor and vendor assurance has been carried out, quality agreements are in place, and there has been no history of quality issues, then test on batch only basis.
10	Dispose of empty drums of high-risk excipients responsibly having carefully removed or completely defaced the labelling and retain evidence of having done so. Retain details of whom packaging has been resold to.
11	Report substandard or falsified versions of high-risk pharmaceutical excipients to the National Medicine Regulatory Authority or WHO GSMS

Criminal Justice and Investigation recommendations

UNODC	
1	Together with INTERPOL the development and delivery of a training curriculum for investigators, regulators and prosecutors in the investigation and prosecution of pharmaceutical crime, including; · Evidence gathering, · Forensics (digital and non-digital) · Accessing evidence in other jurisdictions, · Money laundering, (online payment systems and crypto currencies) · Online investigation, · Case presentation.

2	Together with the World Customs Organization, develop a training programme for customs and border protection personnel on substandard and falsified medical products including high risk pharmaceutical excipients.
3	Together with the World Customs Organization conduct an analysis of the profiling of suspicious consignments of pharmaceutical grade excipients to inform risk based interventions including. · Trade volumes, · Trade routes, · Involvement of freezones, · Smuggling methodologies.
4	Development of an awareness raising programme and case forums for Judges and prosecutors with responsibility for the oversight of complex international criminal proceedings involving pharmaceutical crime and specifically cases of contaminated medicines.

Criminal Justice System	
1	Adequate legislation is enacted including dissuasive sanctions covering the intentional, reckless or negligent manufacture, distribution, export, sale, supply or use of substandard and falsified high risk excipients. With aggravated sanctions where significant harm or risk has been caused to patients.
2	Adequate powers for Customs, law enforcement and National medicine regulatory authorities are available to detain, inspect, sample, test, quarantine, seize and destroy suspected or confirmed substandard or falsified high risk pharmaceutical excipients regardless of intended us e or medical products manufactured with such products.
3	Enactment of proceeds of crime legislation to permit the tracing, seizure and confiscation of assets accrued from pharmaceutical related crime, and reinvestment of those assets to support the prevention, detection and response to substandard and falsified medical products.
4	Legislation with commensurate criminal sanctions for offering, negotiating, paying and accepting bribes or inducements by or for Government officials is enacted and implemented, with aggravated penalties in cases resulting in harm or risk to public health.

Law Enforcement Agencies	
1	Information exchange between NRA's Police, Customs and any other relevant government departments should be subject of formalised agreements to ensure the rapid and efficient exchange of information relating to SF medical products and specifically cases of contaminations. Barriers to timely and effective communication should be identified and removed.

2	Specialist officers should be recruited and trained in pharmaceutical crime and associated criminality including money laundering, drug trafficking and conducting international investigations. Particular attention should be given to cyber investigations and digital forensics.
3	Participation in national, regional and global networks of stakeholders engaged in the prevention, detection and response to pharmaceutical crime should be encouraged to maximise information exchange, cooperation and collaboration.
4	Linkages and regular liaison should be established between Police forensic laboratories and medicine quality control laboratories for the faster identification of trends and sharing of intelligence and expertise.
5	Joint investigation teams should be established in the investigation of cases involving SF medical products and specifically cases involving contamination. These teams should be comprised of specialists from the regulatory authority, law enforcement, Customs, Judicial system and other specialists as required.

Customs and Border Control	
1	Specialist officers at ports of entry should be trained in pharmaceutical crime, identification of suspicious documentation, smuggling methods, suspicious methods of freight, routes and consignments.
2	Information exchange between NRA's Police, Customs and any other relevant Govt departments should be subject of formalised agreements to ensure the rapid and efficient exchange of information relating to SF medical products and specifically cases of contaminations.
3	A review of import procedures for high-risk excipients and medicines at risk of contamination from DEG/EG should be conducted.
4	A legal framework including for the inspection, detention, testing, seizure and destruction of SF medical products and specifically contaminated pharmaceutical excipients should be in place and implemented.
5	Risk based vigilance programmes should be established for the importation of high risk pharmaceutical excipients and medicines at risk of contamination from DEG/EG should be developed and implemented.
6	Profiles should be developed for suspicious consignments, including smuggling methods, to facilitate risk based oversight.
7	Screening technology and training in its use should be provided to Customs officers at designated ports of entry.
8	Joint investigation teams should be established in the investigation of cases involving SF medical products and specifically cases involving contamination These teams should be comprised of specialists from the health, law enforcement, Customs and Judicial system and other specialists as required.

Annex 2. Early Identification, diagnosis and reporting.

Enhanced Surveillance and reporting:	
1	Implement real-time syndromic surveillance across emergency departments and poison control centres, focusing on clusters of AKI, metabolic acidosis, and neurological symptoms.
2	Establish rapid communication channels to disseminate alerts to healthcare providers, pharmacies, and the public about potential contamination.
Targeted Clinical and Laboratory Protocols:	
3	Develop standardized case definitions for DEG/EG poisoning, including specific clinical and laboratory criteria.
4	Prioritize and expedite laboratory testing for serum creatinine, electrolytes, acid-base balance, and, if possible, EG/DEG levels.
5	Raise awareness of clinicians and healthcare workers on the signs and symptoms of DEG/EG poisoning, including metabolic acidosis, renal failure, and neurological symptoms.
6	Ensure meticulous patient history collection, particularly regarding medication use and shared sources.
Coordinated Interagency Response:	
7	Establish clear lines of communication and information sharing between poison control centres, hospitals, laboratories, and public health agencies.
8	Implement a coordinated public communication strategy to inform the population about potential risks and symptoms.
9	Begin tracing the supply chain of suspect medication immediately.
Antidote Availability:	
10	Stock antidotes like fomepizole or ethanol, which can inhibit the metabolism of DEG/EG, and ensure they are readily available in healthcare facilities.
11	Provide training on the administration of these antidotes.
Sample Retention and Analysis	
12	Instruct healthcare facilities to retrieve and retain samples of suspected contaminated medications for subsequent analysis.
13	Establish protocols for secure storage and timely analysis of these samples.

Annex 3. Regulatory Risk assessment tool

	Key high-risk identifiers for medicines contaminated with DEG/EG	Key indicators for risk-based inspection of manufacturers	Key focus areas for inspection
1	Price of Propylene Glycol has increased or shortages in the market	Disruption in production, availability of raw material, or distribution.	Risk of replacement with less expensive DEG/ EG increases.
2	Manufacturer obtains high risk excipients from unsafe sources	Manufacturer obtains high risk excipients from brokers, traders or intermediaries rather than directly from excipient manufacturer or their authorised importer/ distributor	1. Has a formalized risk assessment been conducted on the use and source of the high-risk excipient[1][2] 2. Check source of high risk excipients. 3. Establish if source is excipient manufacturer or their designated agent or an intermediary. 4. Examine invoices for batch numbers and names of excipients. 5. Establish if supplier has a genuine physical address and is traceable. 6. Check other products supplied form the same supplier, and for how long. 7. Check if manufacturer has carried out vendor enquiries, due diligence and has quality agreement in place. 8. Check if certificate of analysis was provided and corresponds to the batches supplied, clearly identifying the original manufacturer of the excipient. 9. Examine documents carefully for photocopies, scans, alterations and grammatical errors. 10. Check condition of barrels and drums. 11. Check labels for spelling mistakes, grammatical errors and shelf life consistent with genuine product.

[1] European Union Directive (2015/C95/02 dated 19 March 2015) Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XC0321(02)

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3	Manufacturer fails to test purity of excipient for DEG/EG prior to use.	Manufacturer has no GC-MS capability for testing DEG/EG impurity levels in excipients or screening methods.	1. Does the manufacturer have access to GC-MS or screening technology to test for DEG/EG impurities in excipients. 2. Is the manufacturer using accredited third party laboratories for testing for DEG/EG Impurities in excipients 3. Check each batch and container of high-risk excipients used in the manufacture of oral liquids has been tested for DEG/EG impurities using a validated test method. 4. Check test results for DEG/EG impurities
4	Manufacturer produces contaminated medicine.	Manufacturer produces inexpensive non-prescription oral liquid medicines using high risk excipients.	1. Check if manufacturer is actively producing medicines commonly at risk of DEG/EG contamination.
5	Manufacturer engages in contract manufacturing of high risk, inexpensive oral liquids.	Manufacturer performs third party contract manufacturing of non-prescription oral liquid medicines using high risk excipients.	1. Check if manufacturer has conducted due diligence on contract giver. 2. Establish bona fides of entitles and examine all associated documentation. 3 Establish the registration status of the medicine to be manufactured in the country of manufacture and the intended export market.
6	Contaminated medicine distributed on the domestic market.	Manufacturer has had to recall out of specification medicines from the market in previous 3 years	1. Check if all registered oral liquids have been placed on the market in the Country of manufacture or have only been exported.
7	Contaminated medicines exported to other countries.	Manufacturer has had to recall out of specification medicines from the export market in previous 3 years	1. Check export data on names of medicines, volumes, regularity and to whom exported.
8	Manufacturer engages in contract manufacture of high-risk medicines.	Manufacturer fails to establish bona fides of clients.	1.Check agreements with contract giver and establish due diligence had been conducted and intended market of the medicine is clearly identified. 2. Check if manufacturer arranging export of the medicine or using a third party.
9	Adverse events in patients.	Medical products from same manufacturer have previously caused adverse events in patients.	1. Cross check against regulatory and recalls and alerts.
10	Manufacturer unsafely disposes of used packaging of high-risk excipients.	Manufacturer resells empty high risk excipient packaging to traders.	1. Check how used drums and barrels are disposed of and their condition. 2. Request evidence that all labels have been removed or defaced from all drums before disposal, with details of batch numbers 3. If resold establish details of purchaser, when sold and details of name of high risk excipient, manufacturer and batch numbers.
11	Manufacturer has a history of non-compliance with GMP	Manufacturer has a history of GMP non-compliance in previous 3 years.	1. Check regulatory records for history of non-compliance.
13	Is the manufacturer required to perform a formalized risk assessment.		1. Evidence of a formalized risk assessment should be requested and reviewed.

Annex 4. Research Methodology

This report was produced in compliance with UNODC research quality standards. Ethical implications have been considered throughout. The research utilised a mixed methods approach incorporating a literature review, case studies, key informant interviews, field research and data analysis. An examination of existing guidance, good practice and regulation was conducted and compared against case studies to identify weaknesses and vulnerabilities in the pharmaceutical excipient supply chain.

Some incidents involving the contamination of medicines with DEG/EG are subject of published peer reviewed academic papers. Others have been widely reported in the media or subject of public rapid alerts and medicine recalls by National Medicine Regulatory Authorities or International Organizations. As such material that is already in the public domain has been assessed as to its content and reliability, seeking corroboration wherever possible with references provided.

Literature Review

A narrative review was conducted utilising a keyword search concerning medicine contamination attributed to the presence of DEG/EG utilising PubMed, Google Scholar and the Medicine Quality Monitoring Globe[123]. The search has been updated throughout the research. The literature review was conducted in English language only. Additionally lay media articles, regulatory and international organization alerts, recalls, and grey literature were searched. This search was further refined to focus specifically on the supply chain of high-risk excipients used in the production of medicines confirmed to have been contaminated following laboratory testing and analysis.

The academic and grey literature published concerning DEG/EG contamination is mainly focused on the early diagnosis and treatment of DEG/EG poisoning and the subsequent laboratory testing methods available. Very few examine in detail the pharmaceutical excipient supply chain, which is the principal focus of this research.

Just over 90 articles were identified and included as of some relevance based on their topicality, currency, authority and availability. With a few notable exceptions there was a lack of academic literature or reporting concerning detailed investigations into the supply chains of contaminated excipients. Articles were excluded if there was a lack of corroborative evidence, or the primary source of the information or data was absent. Three cases did reveal in some detail the chain of custody of excipients later revealed to contain toxic levels of impurities and they have been included as case studies in this report.

Case Studies

This research has focused on eight case studies involving mass poisonings attributed to medicines contaminated with DEG/EG. Those case studies feature four historical cases and four more recent cases. All involved fatalities. The reasons for the selection of these particular cases are explained in detail in Part 4 of this report. The information is drawn from several sources including published peer reviewed papers, formal reports to WHO or the NRA, media reporting and other publicly available documents. Interviews with persons involved in the investigation or management of these cases has been conducted where possible.

Legal proceedings are pending in relation to some of the cases, therefore not all the evidence is yet in the public domain.

Key Informant Interviews

Careful consideration has been given to the principles of privacy, confidentiality and informed consent of all those persons interviewed in accordance with UNODC research quality standards.

Interviewees were offered anonymity and where requested; this has been respected. Interviewees were selected based on their direct experience with the matters subject of this report or are recognised experts in relevant fields related to this research.

Semi structured interviews have been conducted with key informants from different stakeholder groups within both the private and public sectors. Interviews were tailored to the wide range of stakeholders involved and their differing roles. Different sets of questions and supplementary questions were prepared for the interviews specific to their role and responsibilities. Interviews were carried out either in person or online.

The framework of the interviews featured tailored questions specific to the interviewee concerning awareness, current practice, regulatory requirements, regulatory oversight, weaknesses and vulnerabilities, market intelligence and recommendations.

Table 13. List of subject matter expert interviews

Organizations	Departments/Roles	Comments
World Health Organization	Inspection Services	Online
	Laboratory Networks and Services	Online
	Incidents, Substandard and Falsified Medical Products	Online
	Quality Assurance Norms and Standards	Online
	Regulatory Convergence and Networks	Online
	WHO Country Office Pakistan	In person
World Customs Organization	IPR Health and Safety	Online
INTERPOL	Illicit Goods and Global Health	Online
	National Control Bureau, Pakistan	In person
UNODC	UNODC Country Office, Pakistan	In person
Anti-Narcotics Control Force, Pakistan	Leadership team	In person
Ministry of National Health Services, Regulation and Coordination, Pakistan	Chief Secretary Special Secretary	In person

Drug Regulatory Authority, Pakistan	CEO, Deputy CEO Directors- ➜ Quality assurance and laboratory testing, ➜ Pharmaceutical evaluation and registration ➜ Quality ➜ Pharmacy Services Additionally; ➜ Import/Export teams ➜ SF focal points ➜ Pharmacovigilance ➜ Inspectorate	In person
USFDA	Office of compliance	Online
Medicine Control Agency, The Gambia	Operations Directorate	Online
Provincial Drug Inspectorates, Islamabad, Lahore and Karachi	3 x Inspectorates	In person
Drug Testing Laboratory	Head of Laboratory	In person
Central Drug Testing Laboratory	Head of Laboratory	In person
Sorbitol Manufacturer	Senior Management and Quality assurance	In person
Propylene Glycol Manufacturer	Product Director	Online
Glycerine Manufacturer	Senior Management and Quality assurance	In person
3 x Oral liquid Manufacturers	Senior Management and Quality assurance team	In person
Propylene Glycol Distributor	CEO	In Person
Propylene Glycol Distributor	Market Manager	Online
Propylene Glycol Distributor/ Repackager	Regulatory Affairs	Online
International Pharmaceutical Excipients Council (Trade Association)	IPEC members x 3	Online
Excipient Freight Carrier	Vice President	Online
Pharmaceutical Security Institute	CEO	Online

This research study approached 45 entities or individuals of which 2 declined, 2 failed to respond 1 responded by questionnaire and 40 were interviewed, some of whom have also participated in supplementary interviews.

A number of Member States with experience of recent contaminations, International Organizations and Industry bodies were approached for interviews. Several declined for various reasons including ongoing court proceedings, others failed to respond to requests. An option to contribute by questionnaire was offered and accepted by one Member State who had experienced a recent case of contaminated medicines.

Some institutions were unfamiliar with the incidents of contamination, the risks associated with falsification of pharmaceutical grade excipients or had no information relevant to the research.

Field Study

Pakistan was assessed as a key country in which to conduct a field visit due to several factors as set out in detail in section 9 of the main report.

Analysis

A wide range of publicly available and open source information has been accessed during this research. Wherever possible corroboration has been sought through key informant interviews, and cross referencing through publicly available documents.

Access to data sets held by the WHO have been provided in relation to this research, specifically reports to the WHO Global Surveillance and Monitoring System for substandard and falsified medical products.

Publicly available excipient market information, although limited, was accessed.

A plethora of guidance, regulation and good practice has been published by International and trade organizations with the purpose of assuring the quality, safety and efficacy of medicines. The implementation and effectiveness of these practices has been tested against the case studies to identify the areas of vulnerability and weakness that still exist. Full details of the guidance accessed during this research is included in the bibliography.

The analysis has provided more detail of the motivators, methods, enablers and responses to the contamination of medicines with DEG/EG resulting in a set of recommendations for further consideration.

Limitations

This research study has benefited greatly from the participation of some Member states that have experienced contamination incidents, together with a wide range of subject matter experts. However, some Member States and other stakeholders have decided not to participate in this study or have not responded to invitations to participate. In those cases, the study has primarily relied on WHO Medical Product Alerts and freely available public information. Some of the more recent incidents are subject of ongoing criminal or civil legal proceedings and as such access to the full details and evidence is not yet possible.

Incidents of mass poisonings attributed to medicines contaminated with DEG/EG attract wide publicity. Older incidents benefit from published peer reviewed academic literature or grey literature. More recent cases have been widely reported in lay press reports. Where references have been made to grey literature or lay press articles efforts have been made to ascertain the reliability of the primary source of the information reported and the accuracy of the content. These sources have been used where no information has been provided by the Member States or entities involved and may provide an incomplete summary of the incident.

With a few exceptions information identifying the precise point of relabelling, falsification or contamination of the excipient is unknown, unavailable or has not been subject of detailed investigation.

Detailed and freely available historical data on price fluctuations of the pharmaceutical excipients market is not readily available.

The numbers of fatalities and hospitalizations resulting from incidents of DEG/EG contaminations vary. The number invariably increases as the incident investigation proceeds. Whenever numbers have been quoted during prosecutions those figures have been used.

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