Detecting and Managing Excipient Quality Issues: Singapore's Post-Market Experience

USP-MHLW/PMDA Joint Workshop

Session 2: Excipient Quality

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Scope

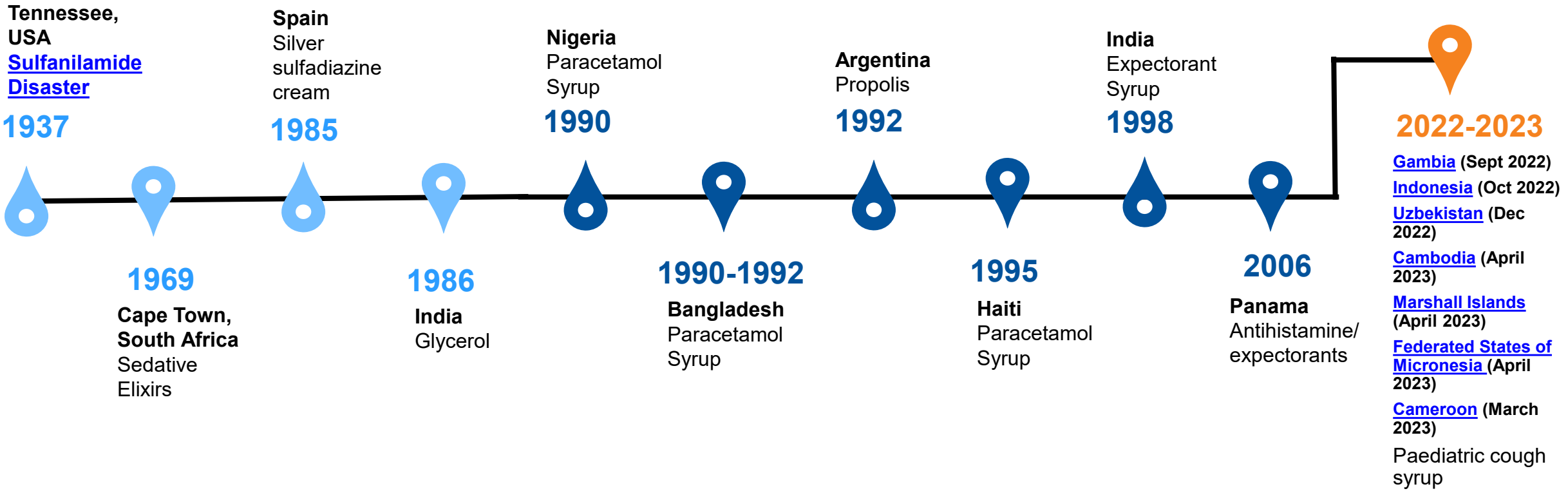
Poisoning of Diethylene Glycol and Ethylene Glycol

Singapore's post-market surveillance framework

- Environment scanning
- Product quality surveillance
- Product defect reporting and recall

Importance of risk communication and regulatory guidance

Poisoning by Diethylene Glycol (DEG) and Ethylene Glycol (EG)



Ref: https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_139.pdf

Post-Market Surveillance and Communication

Detection

- Environment scanning
- Product quality surveillance
- Product defect reporting and recall
- GMP inspection
- Adverse event reporting

Assessment

- Risk assessment
  Risk mitigation plans

Communication

- Dear Healthcare Professional Letter
- Press Release
- HSA ADR News Bulletin
- Other communication channels

Engagement

- Industry engagement
- Educational outreach

Environmental Scanning

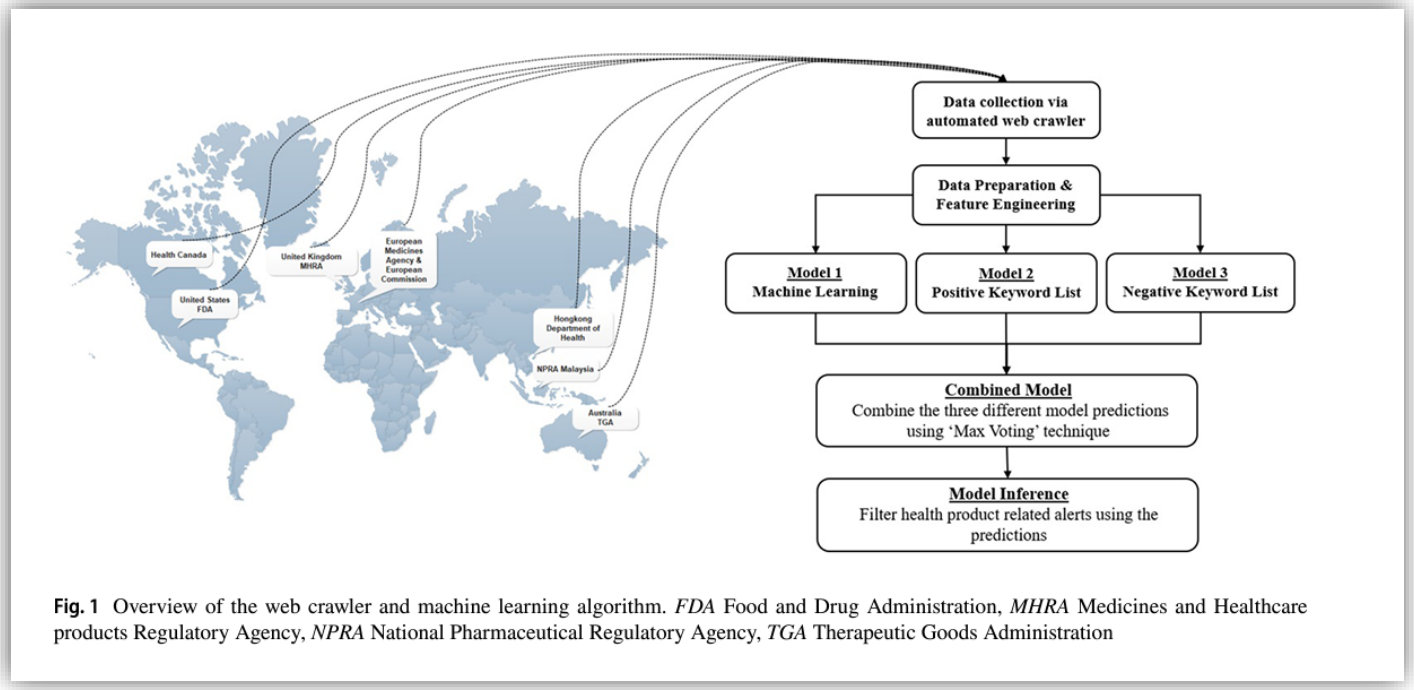


Fig. 1 Overview of the web crawler and machine learning algorithm. *FDA* Food and Drug Administration, *MHRA* Medicines and Healthcare products Regulatory Agency, *NPRA* National Pharmaceutical Regulatory Agency, *TGA* Therapeutic Goods Administration

Purpose

- Global supply chain requires vigilance of global quality/safety issues
- Automated web crawler to support active surveillance of global quality/safety issues
- Exploration of machine learning algorithm to identify quality/safety issues ahead

Ref: https://doi.org/10.1007/s40264-021-01084-w

Product Quality Surveillance (PQS)

Objective

- Monitor the quality of the health products available in the market
- Detect unwholesome, adulterated or substandard products and take prompt and appropriate regulatory actions to address any potential risks

Regulation

- Regulation 65 of the Health Products (Therapeutic Products) Regulations

Risk-based approach

- Regular review
- Selection criteria
- Intended use
- Testing history
- Sales volume
- Alerts received or published

https://www.hsa.gov.sg/therapeutic-products/medicines-quality-and-compliance-monitoring/product-quality-surveillance-for-therapeutic-products

PQS: What do we test?

Testing labs

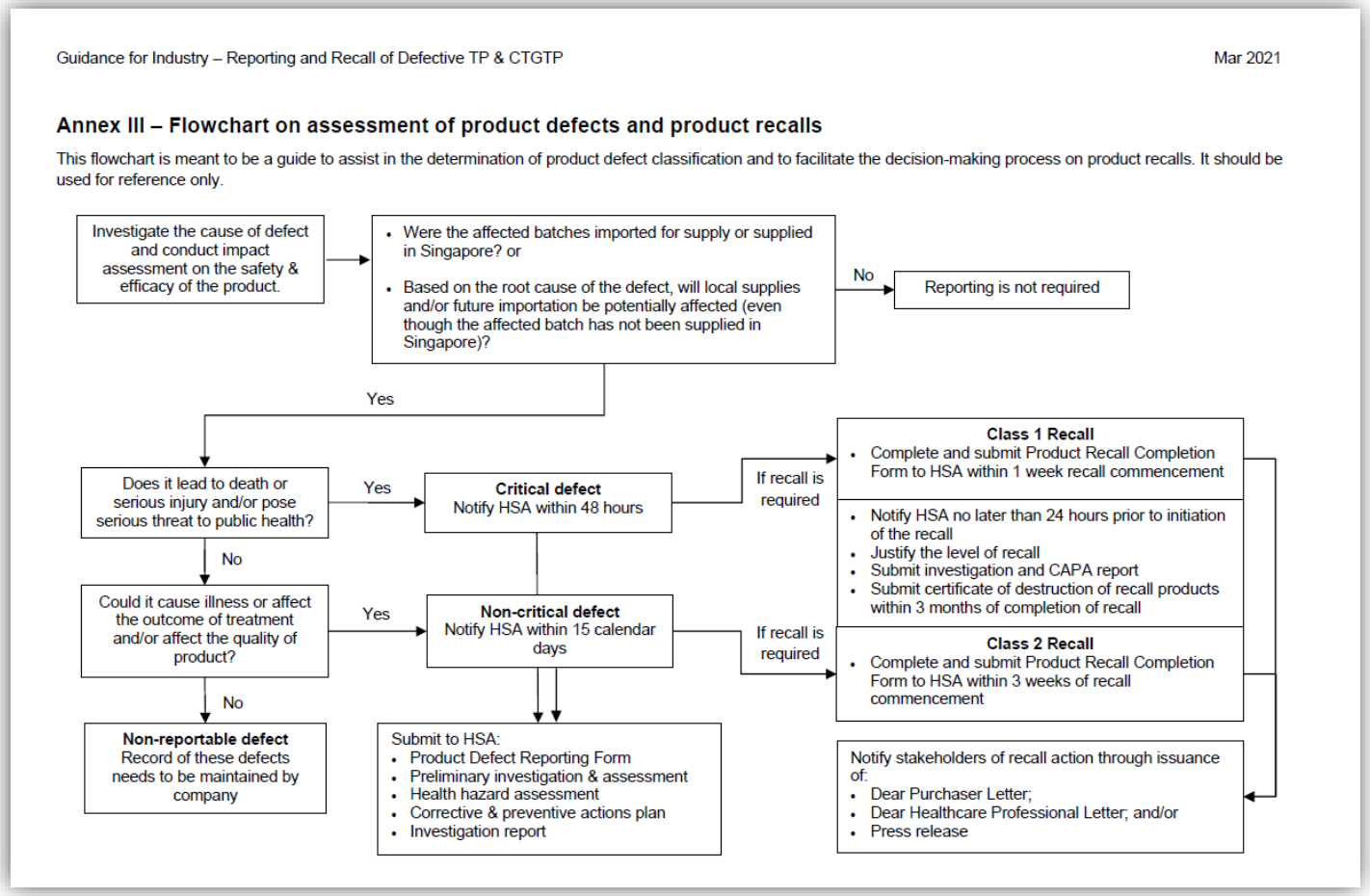
- Health Sciences Authority's Pharmaceutical Laboratory, a WHO Collaborating Centre of Medicines Quality Assurance since 1993
- Other accredited laboratories

Test conducted

- Different test may be conducted, dependent on the reason of testing
- Identity
- Assay
- Disintegration/dissolution
- Related substance/chromatographic purity

Ref: https://www.hsa.gov.sg/therapeutic-products/medicines-quality-and-compliance-monitoring/product-quality-surveillance-for-therapeutic-products, https://www.hsa.gov.sg/about-us/applied-sciences/pharmaceuticals/analysis

Product Defect Reporting



Guidance for Industry – Reporting and Recall of Defective TP & CTGTP Mar 2021

Annex III – Flowchart on assessment of product defects and product recalls

This flowchart is meant to be a guide to assist in the determination of product defect classification and to facilitate the decision-making process on product recalls. It should be used for reference only.

Regulatory Oversight

- Clear guidance on assessment of products defects and type of recall facilitates early withdrawal of products with excipient quality issues
- Regulatory oversight ensures completion of recall process and communication to stakeholders

Ref: https://www.hsa.gov.sg/docs/default-source/hprg-vcb/product-defect-and-recall/guidance_defect-and-recall-reporting_1mar2021.pdf

Published Information on Product Recall

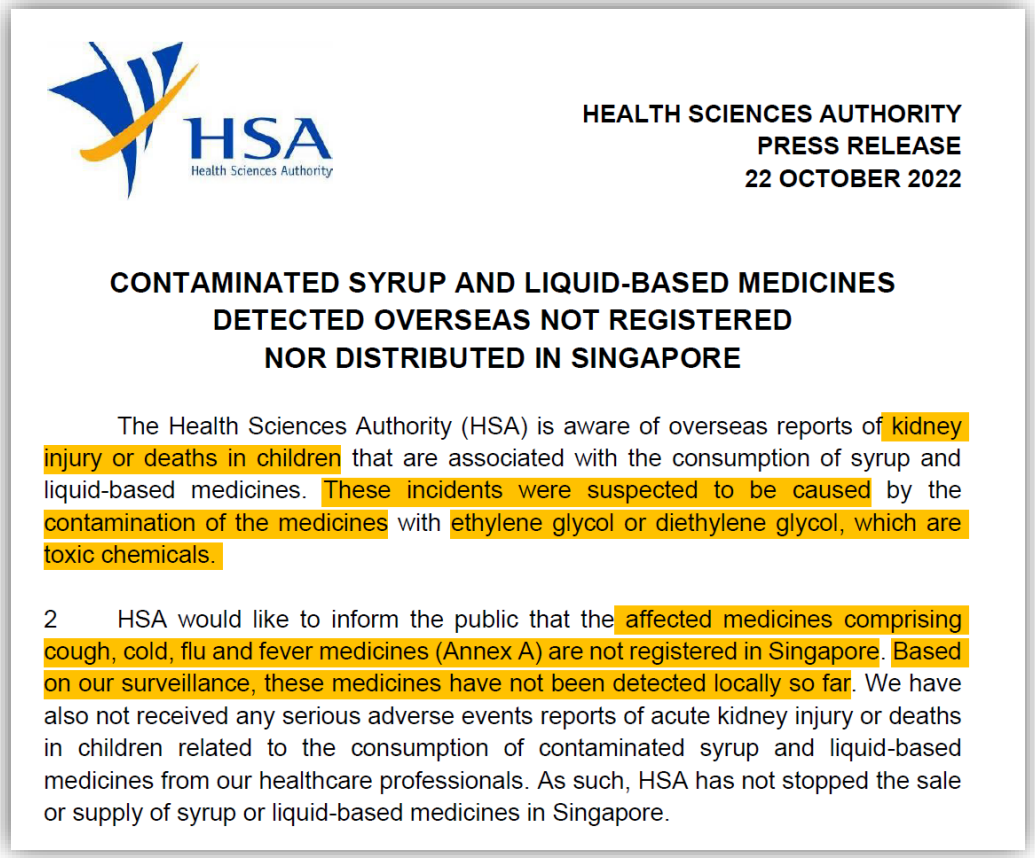
Recall of [redacted] 5mg Tablet

Retail-level recall of one batch of [redacted] 5mg Tablet due to an out-of-specification test result for assay.

Date of recall:	23 May 2024
Product:	[redacted] 5mg Tablet
Active Ingredient:	[redacted]
Product Category:	Therapeutic Product
Batch No.:	638/22001
Class of Recall:	2
Level of Recall:	Retail
Local Company:	[redacted]
Description of Issue:	The affected batch was recalled due to an out-of-specification result for assay test.
Recall Instructions:	Hospitals, clinics and pharmacies: Stop supplying the affected batch and return the remaining stocks to the company.

Ref: https://www.hsa.gov.sg/announcements?contenttype=Product%20Recalls

Risk Communication



HSA
Health Sciences Authority

HEALTH SCIENCES AUTHORITY
PRESS RELEASE
22 OCTOBER 2022

CONTAMINATED SYRUP AND LIQUID-BASED MEDICINES DETECTED OVERSEAS NOT REGISTERED NOR DISTRIBUTED IN SINGAPORE

The Health Sciences Authority (HSA) is aware of overseas reports of kidney injury or deaths in children that are associated with the consumption of syrup and liquid-based medicines. These incidents were suspected to be caused by the contamination of the medicines with ethylene glycol or diethylene glycol, which are toxic chemicals.

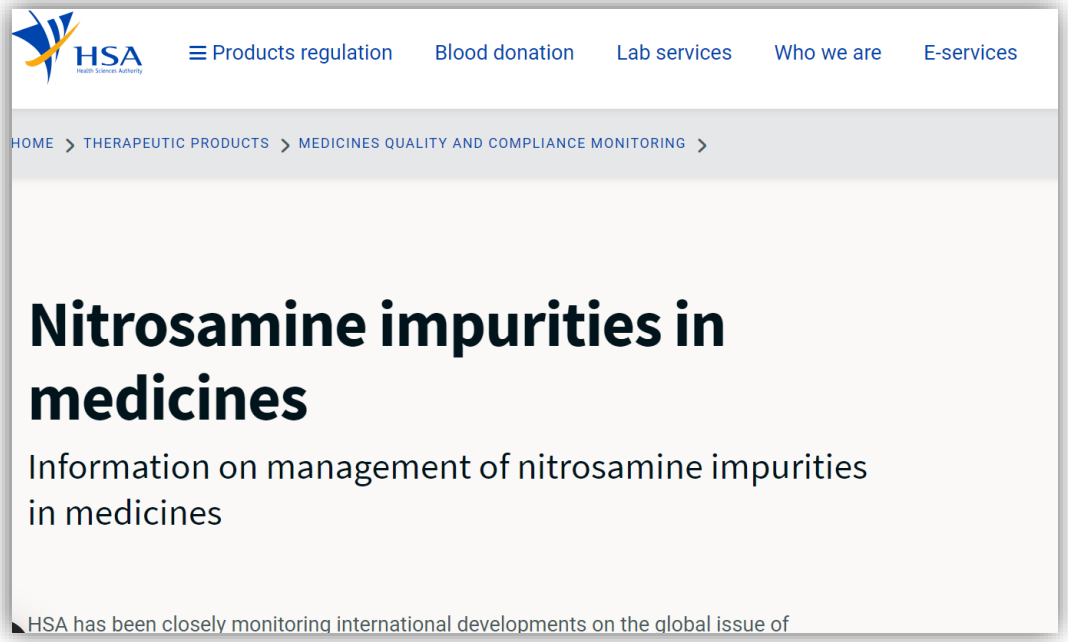
2 HSA would like to inform the public that the affected medicines comprising cough, cold, flu and fever medicines (Annex A) are not registered in Singapore. Based on our surveillance, these medicines have not been detected locally so far. We have also not received any serious adverse events reports of acute kidney injury or deaths in children related to the consumption of contaminated syrup and liquid-based medicines from our healthcare professionals. As such, HSA has not stopped the sale or supply of syrup or liquid-based medicines in Singapore.

Raise Awareness

- Adverse events
- Causality and evidence to-date
- Contamination
- Contaminants
- Name of products

Ref: https://www.hsa.gov.sg/announcements/press-release/contaminated-syrup-liquid-medicines-detected-overseas

Risk Communication



Audience

- Public
- Healthcare professionals
- Industry

Channels of communication

- Dear healthcare professional letter
- Press release
- Hotline
- Service touchpoints
- Industry stakeholder dialogue
- Webpage

Highlight

- Background
- What are nitrosamines?
- What we are and others doing?
- List of impacted medicines
- Guidance for product registrants
- Test method

Ref: https://www.hsa.gov.sg/therapeutic-products/medicines-quality-and-compliance-monitoring/nitrosamine-impurities-in-medicines

Regulatory Guidance on Nitrosamine

Stakeholder Communication

March 2020
Communicate regulatory requirements to stakeholders

Risk Assessment

By 1st Sept 2021
Perform risk assessments of all therapeutic products containing chemically synthesised drug substances using the quality risk management principles described in the ICH Q9 guideline

Risk Control

By 30 June 2023
Detailed assessment, product testing and corrective action and preventive action (CAPA) plan

By 31 Dec 2023
Submission of variation application to implement CAPA

Risk Review

For all new applications
of products containing chemically synthesised drug substance

- new drug applications (NDAs)
- new generic drug applications (GDAs)

A nitrosamine risk assessment is required and should be submitted as part of the Chemistry, Manufacturing and Controls (CMC) dossier.

Public Attention on Regulatory System and Managing Excipient Quality Issues

Parliamentary Questions (Qn no. 2777, 8 May 2019)

To ask the Minister for Health

(a) how rigorous is medication tested by the Health Sciences Authority before the drugs enter Singapore;

(b) whether the testing is in line with international testing standards;

(c) whether there are public concerns with generic use of medications in Singapore; and

(d) what are the steps and considerations taken by the Ministry compared to other countries' handling of the same worldwide concern, particularly with the Losartan recall.

Ref: https://www.moh.gov.sg/news-highlights/details/medicines-quality-and-losartan-recall

Summary

Dire consequence of quality excipients issues

- Excipient quality issues can have dire consequences to global health and can erode trust in regulatory system

Pharmacopoeial harmonisation

- Harmonised pharmacopoeias, regulations and post-market surveillance will facilitate information exchange and actions on excipients quality issues

Continuous regulatory strengthening and capacity building

- Regulatory system strengthening in quality management system, post-market surveillance and risk communication are essential for detecting and communicating excipient quality issues

Multi-disciplinary collaboration

- Collaboration among regulators, industry, healthcare system and pharmacopeial organisations is critical in managing excipient quality issues

Thank You