# Excipient Quality

## Ethylene Glycol and Diethylene Glycol Contamination Cases
## Learnings and Regulatory Challenges

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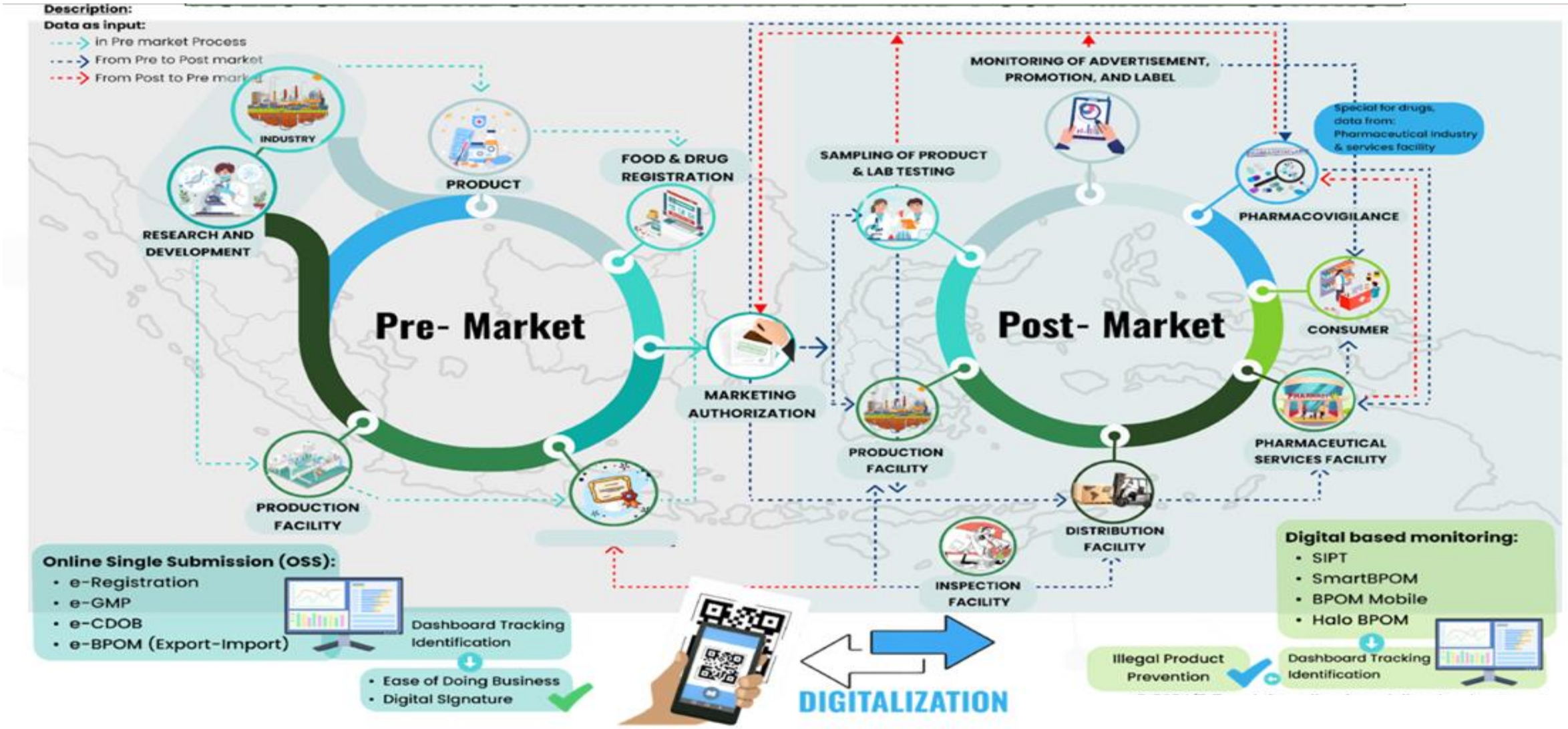
# Outline

- Regulatory Oversight of Medicines in Indonesia
- EG-DEG Contamination in Pharmaceutical Products
- Action Taken by The Indonesian FDA
- Conclusion

# Regulatory Oversight on One Life Cycle of Medicine in Indonesia



# Risk-Based Post-Market Surveillance System in Indonesian FDA

## RESOURCE AND STAFFING

- Central Office
- Provincial Offices
- Laboratory (NQCL and Provincial Office Laboratory)

Staff involved in market surveillance has been trained

## ACTIVITIES


Production, Distribution & Pharmaceutical Services Facilities Inspection

Risk-based Sampling and Testing

Advertisement, Promotion and Label Control


Importation and Exportation Control

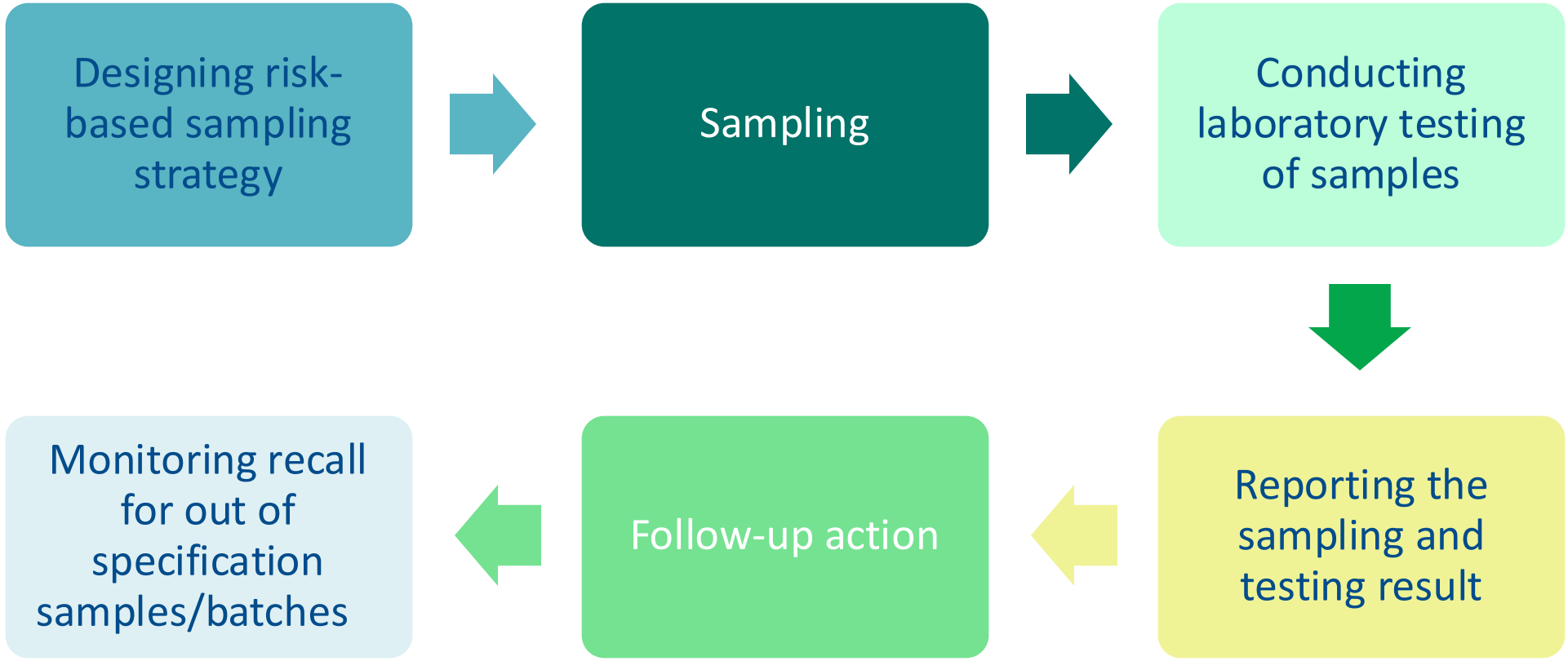
Intelligence Activities

# Risk-Based Sampling and Testing

Objective of risk-based sampling and testing

- To protect citizens from substandard and falsified medicines
- To ensure the quality of marketed medicines meet the specifications
- To detect illegal medicines, defect medicines and expired medicines
- To assure the information written on packaging and insert of marketed medicines meet the requirements
- To ensure content of nicotine and tar in tobacco products follow the regulation

# Steps of Risk-Based Sampling and Testing




- These activities are conducted by Central Office and 76 Technical Implementation Unit/Offices respectively
- Around 17.000+ samples have been collected and tested every year
- More than 96% of samples meet the specifications

# Risk-Based Sampling and Testing

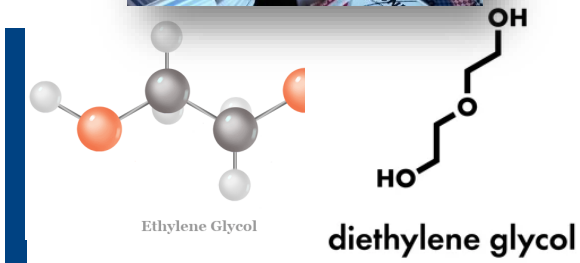

**Risk-Based Sampling**

**Conducting laboratory testing of samples**

- Both sampling and testing are conducted by regional offices based on sampling and testing guideline
- Risk-based Sampling plan must be designed beforehand by each regional office.
- Samples are collected from manufactures, wholesalers, provincial and district warehouses, healthcare facilities, pharmacies and drug stores

Testing of sample refers to Indonesian Pharmacopoeia and other Pharmacopoeias (e.g USP, BP)

# EG-DEG Contamination in Pharmaceutical Products


Ethylene Glycol

diethylene glycol

- Ethylene glycol and Diethylene Glycol (EG/DEG) are toxic chemicals (commonly used as antifreeze), not to be swallowed.
- EG DEG should not be used as an additive (added intentionally) to drug preparations
- EG DEG may be present in drugs as contaminants within certain limits.
- EG/DEG contaminant limits are required for drug substances

Class 1: Solvents to Be Avoided
Class 2: Solvents to Be Limited
Class 3: Solvents with Low Toxic Potential

Beside EG/DEG, there are other solvents whose amounts are limited in pharmaceutical preparations. This has been regulated in international guidelines such as: ICH Guideline and General Chapter USP <467> Residual Solvent

EG / DEG as contaminant may exist within certain limits in excipient **propylene glycol, polyethylene glycol, sorbitol, and glycerine** solvents

## EG-DEG Contamination Cases

- DEG contamination cases causing death in children due to acute kidney injury:
  1. In 1937 in the USA, in 1995 and early 1996 in Haiti.
  2. Between 1990 and 1998 in Argentina, Bangladesh, India, and Nigeria
  3. In 2006 in Panama
- These cases had a particularly devastating impact on children → therefore not new and is widely recognized within the global health community. ED/DEG are hazardous chemicals that have been used, both accidentally and deliberately, as cheaper substitutes for pharmaceutical-grade solvents like propylene glycol, glycerol and sorbitol in the production of liquid oral medicines.
- 2022-2024 cases: Substandard (contaminated) paediatric medicines identified in Belize, Cameroon, Cambodia, Gambia, Fiji, Indonesia, India, Iraq, Lao PDR, Lebanon, Maldives, Marshall Islands, Micronesia, Pakistan, Uzbekistan, and Yemen.

# Action Taken by The Indonesian FDA

1. Investigation and tracing of medicines used by patients (from registration databases on pre-market and post-market surveillance data)
2. In-depth investigation and tracing by inspection and tracing to the pharmaceutical industries and distributors for raw materials
3. Develop analytical method for EG DEG contamination testing on drug products
4. Intensification of product quality surveillance by risk-based sampling and testing
5. Administrative sanctions are imposed on the pharmaceutical industries and distributors for non-compliance / violation of standards and regulations
6. Reinforcing pharmacovigilance systems across all relevant stakeholders
7. Since October 2022-March 2024, Indonesian FDA has issued 23 publication/press releases to respond to the situation and as transparency to the public.
8. Strengthening the quality assurance protocols for the pharmaceutical manufacturers and distributors, including guidance and procedures for supplier qualifications.
9. Tightening requirements by revising some standards and regulations
10. Government donation to impacted patients

# Conclusion

The Indonesian FDA continuously strive to improve access to safe, efficacious, and quality-assured medicines. Ensuring the quality of excipients is paramount to safeguarding public health.

The Indonesian FDA, with its immediate and decisive response, has taken several measures to overcome the EG-DEG crisis and raise awareness on how to identify and avoid contaminated products while maintaining access to essential medicines for the public.

Collaboration with relevant stakeholders in the country, other National Regulatory Authorities, and WHO was crucial in managing the crisis and preventing similar incidents in the future. Together, we can build a secure and reliable supply chain, protecting patients worldwide from the dangers of substandard and contaminated medicines.


Thank You
BADAN POM