Indonesia's Adoption of Annex 1

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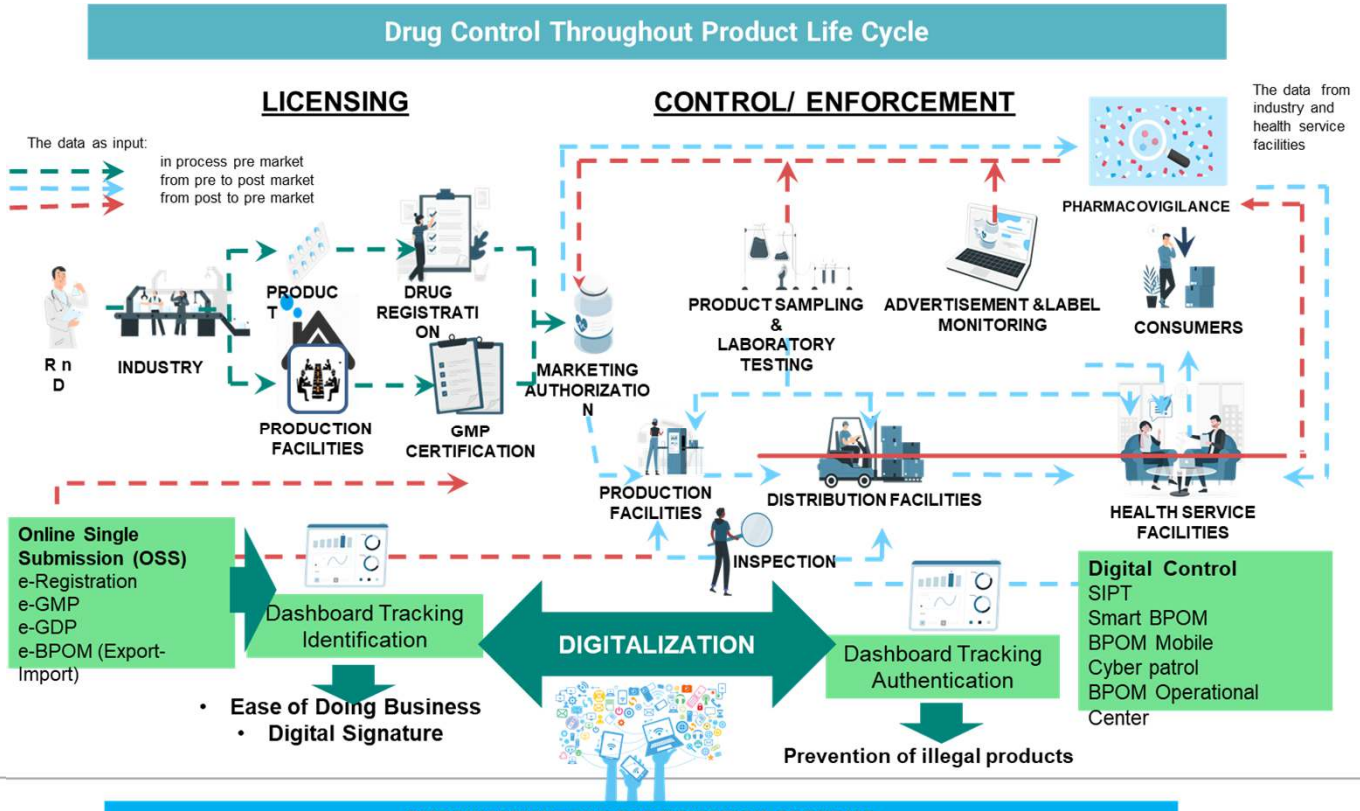
PDA Implementation of CCS & PUPSIT Workshop 2024

Introduction

DRUG AND VACCINES REGULATORY FRAMEWORK



PHARMACEUTICAL INDUSTRY PROFILE IN INDONESIA

215
Pharmaceutical Industries (PI)

204 Chemicals

5 Biosimilar, New Compound

3 Vaccines

4 Stem Cells

1 Radiopharmaceutical

19
Pharmaceutical Raw Material Industries (PMI)

12 chemical

2 biological

2 vaccines

3 capsule shell

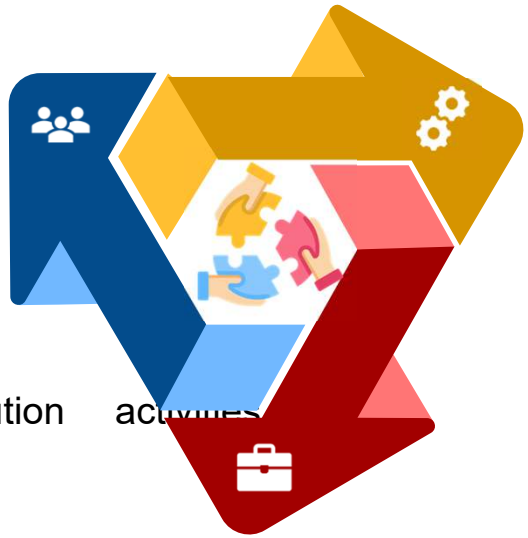
plasma

19 GMP CERTIFIED BLOOD ESTABLISHMENTS

Triple Helix Drug Control

Public/Communities

- Check the product's quality before used/bought
- Monitor and report post market products that expired, illegal or falsified.



Government

- Preparation of policies, regulations, requirements, criteria and guidelines (regulators)
- Conducting pre-market and post-market food and drug control
- Enterprises empowerment
- Ease enterprises/bussines
- Educate the Consumers/Public/Communities

Stake Holder (manufacturer/distributor)

- Conduct production and/or distribution activities according to the GXP
- Monitor the product's quality
- Conduct the pharmacovigilance activity
- Educate the consumers

Legal Framework of GMP Implementation

GOVERNMENT:
Empowering, Organizing, Controlling and Supervising Production, Procurement, Storage, Promotion and Distribution of Pharmaceutical Products

Law No. 17 of 2023 on Health

Pre-Market and Post-Market Drug Control

Article 138 Section (1)
Fulfill the Safety, Efficacy and Quality Pharmaceutical Product Requirements. Affordable and fulfill the Halal Product Assurance

Pharmaceutical Products including: Drug, Starting Materials, Traditional Medicines, including Traditional Medicines Starting Materials, Cosmetics, Health Supplements and Quasi Product

Article 138 Section (4)
Procurement, production, storage, promotion, distribution and pharmaceutical care/service should comply with the Standar/Regulations

Article 413 Section (1)
Every person who produces and/or distributes pharmaceutical products, medical devices and household health supplies should comply with business licensing based on norms, standards, procedures and criteria in accordance with the provisions of the regulations.

Regulation of Government No. 28 of 2024 on Implementing Law of Republic of Indonesia No. 17 of 2023 on Health

Aticle 413
Business/Enterprises Licensing

Pharmaceutical products, medical devices, and/or household health products can only be produced by licensed facilities

Licensing does not apply to facilities producing products for special use

The production of pharmaceutical products must comply with GMP requirements as stipulated by the regulations

Regulation of Government No. 5 of 2021 on Implementing Risk-Based Licensed Enterprises

Article 129 dan 283
Norms dan Criteria & Control

Every individual who produces medicines and medicinal substances must adhere to good manufacturing practices

Oversight of business licensing in the pharmaceutical and food subsector is conducted by the head of the institution responsible for drug and food oversight, governors, regents/mayors, Special Economic Zone Administrators, or heads of the BPBPB (Special Economic Zone Development Agency), each within their respective authorities based on this Government Regulation and other applicable laws

Norms, Standard, Procedure and Criteria to Our GMP (CPOB)

Revision of Indonesian GMP GL

- Chapter 1 - Pharmaceutical Quality System
- Chapter 2 - Personnel
- Chapter 5 - Production
- Chapter 6 - Good Storage and Dispatch Practices
- Chapter 7 - Quality Control
- Chapter 11 - Outsourced Activities

Annex 14 Management of Narcotics, Psychotropics, and Pharmaceutical Precursors

- Annex 2 → Annex 2A: Production of Advanced Therapeutic Products, Annex 2B: Production of Biological Drug Substances and Biological Products.
- Annex 6 Manufacture of Investigational Medicinal Products
- Annex 8 GMP for API
- Annex 9 Manufacture of Radiopharmaceuticals

Revision of Good Manufacturing Practice Guidelines 2018 (CPOB 2018) refers to:

PIC/S GMP PE 009-16, 1 February 2022
WHO TRS 981 Tahun 2013 Annex 2,
WHO TRS 986 Tahun 2014 Annex 5,
WHO TRS 992 Tahun 2015 Annex 3 dan Annex 5
WHO TRS 996 Tahun 2016 Annex 5,
WHO TRS 999 Tahun 2016 Annex 2, dan
WHO TRS 1025 Tahun 2020 Annex 2
,

CPOB 2024

- CPOB / cGMP that written on BPOM Regulation No 7 of 2024, need to be adjusted with science and technology developments, so that they are always harmonized with international standards.
- There are several adjustment/revision on Annex 1 *PIC/S GMP Guide on the manufacture of sterile products and Annex 1 Manufacture of Sterile Medicinal Products on EU Guidelines for GMP for Medicinal Products* at 2022.

Revised *Annex 1 PIC/S GMP* dan *EU guideline GMP including*:

Contamination Control Strategy **(CCS) Implementation as part of integrated activity on drug manufacturing**

The powerful aspects such as Quality Risk Management and Quality System should be emphasized during Implementation of CCS

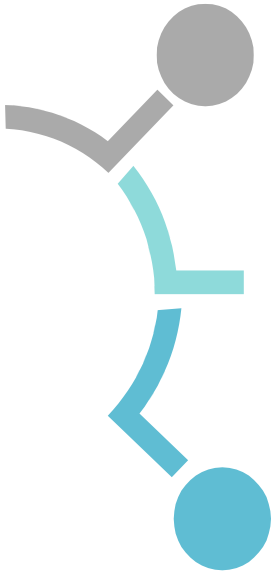
CCS as a holistic program in order to ensure all of the critical points and their interactions controlling activity

CPOB Annex 1 revision plan regarding on Manufacturing Sterile Product

Revised Annex 1 was entry into force on 25 August 2023, except for point 8.123 which is postponed until 25 August 2024. The date of entry into operation for PIC/S is aligned with that of the revised EU Annex 1, which is identical to PIC/S Annex 1 (with some very minor editorial differences)

Indonesia GMP GL Rev on Annex 1 is now in the finalisation process expected entry into force by the end of this year

Key Changes in Annex 1 PIC/S



1.

- Expands on contamination control and facility design.
- Adds guidelines for Aseptic Process Simulation (APS), Barrier Technology, and Monitoring Systems

Enhanced Clarity and New Guidelines

2.

Higher requirements for personnel training, equipment maintenance, and risk-based approaches.

Increased Complexity

What are the main changes in annex 1?

- Annex 1 & Risks
- Equipment Handling
- Barrier Technology and Decontamination
- Personnel
- Preparation
- In-Process Control
- Monitoring Systems

Critical Concepts in Annex 1 for Sterile Manufacturing

However, several principles or guidelines, such as contamination control strategy, building and facility design, clean room classification, qualification, and personnel gowning, can be applied to support the production of non-sterile products like liquids, creams, ointments, and low bioburden biological intermediates, where controlling and reducing microbial, particulate, and pyrogen contamination is considered important.

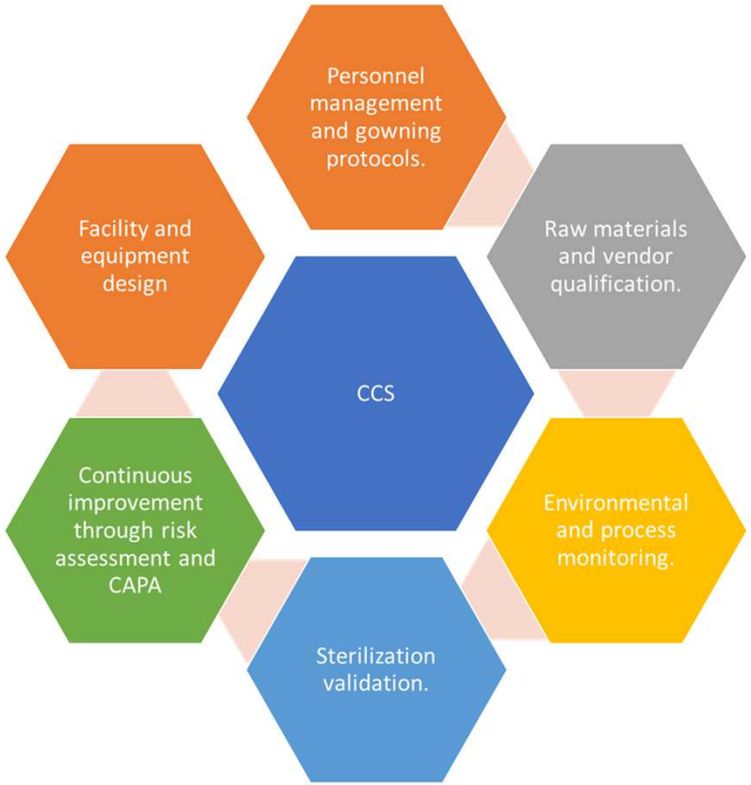
Core framework for decision-making, emphasizing proactive control of contamination risks.

Integrated system focusing on all aspects of product lifecycle and contamination prevention.

Detailed strategy to prevent microbial, particulate, and pyrogen contamination throughout the production process

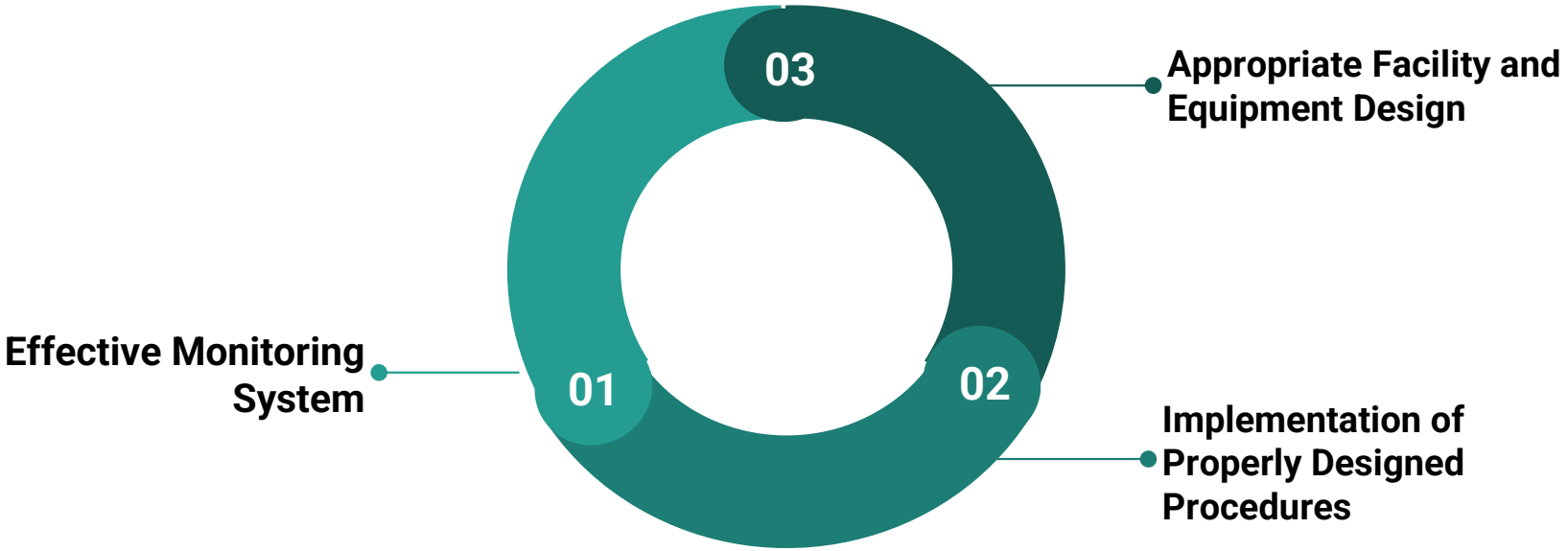
Contamination Control Strategy (CCS)

- Defining the design and critical control points (CCPs).
- Evaluating the effectiveness of all controls implemented (design, procedures, technical actions, and organization).
- Monitoring all steps taken to control risks to the quality and safety of the drugs.
- This should be implemented throughout the sterile product manufacturing facilities.
- Its effectiveness should be reviewed periodically and updated for continuous improvement.
- The development and creation of the Contamination Control Strategy (CCS) require a detailed understanding of the processes and techniques involved.
- It is part of the Sterile Manufacturing and Inspection Framework (SMIF).
- It should not solely rely on the results of sterility tests or other quality aspects conducted at the final process or finished product.



Quality Risk Management

Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.

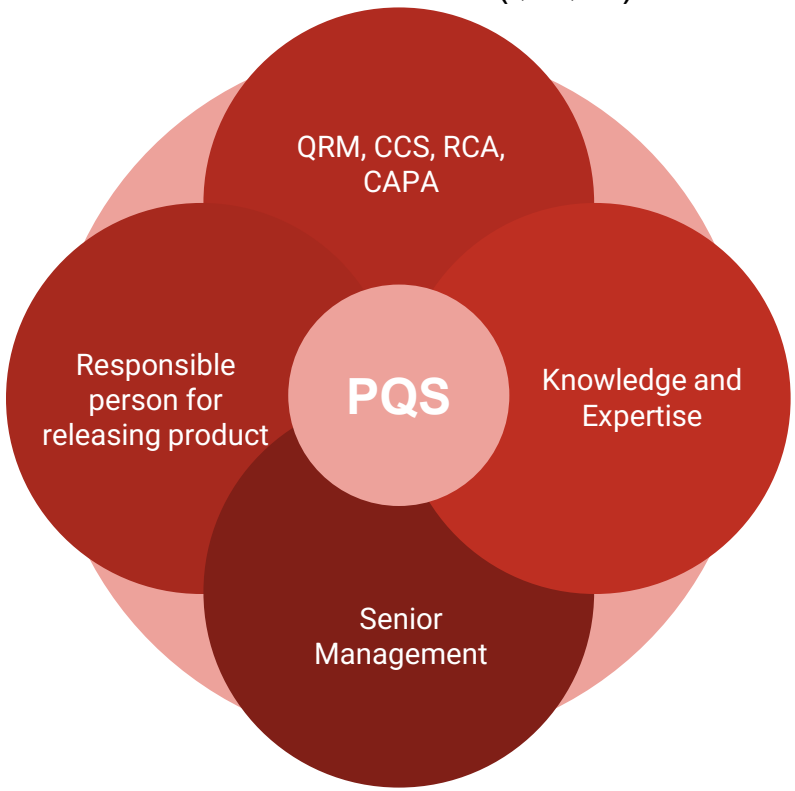


Pharmaceutical Quality System

- Sterile product manufacturing is a complex activity.
- It is produced under special requirements to minimize the risk of microbial, particulate, and pyrogen/endotoxin contamination.

PIC/S Annex 1 – 3.1 (vii)

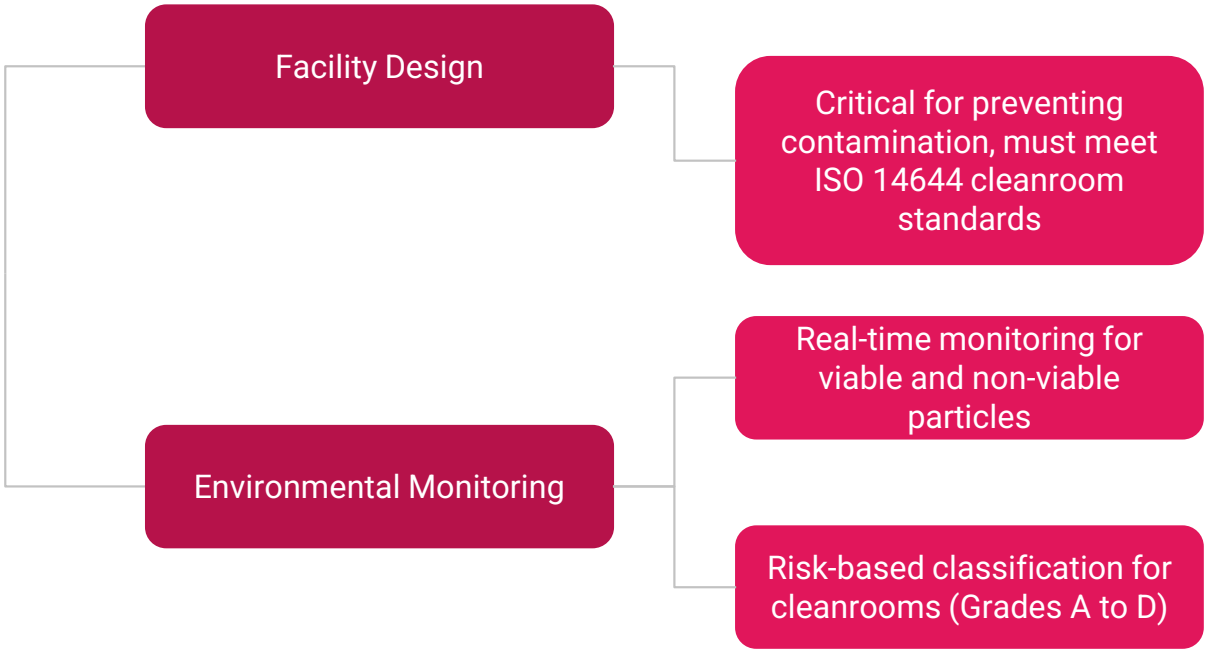
PIC/S Annex 1 – 3.1 (i, iii, iv)



PIC/S Annex 1 – 3.1 (ii)

PIC/S Annex 1 – 3.1 (v)

Facility Design and Environmental Monitoring



What are the main changes that new Annex 1 brings to **premises**?

- Better and detailed description of requirements related to material and personnel transfer via airlocks – with requirements of unidirectional movement (separate airlocks for entry and exit) or separation in time
- Detailed procedure for transfer to grade B (list of approved materials/equipment)
- Detailed description of cleanrooms QUALIFICATION - overall approach, scope of qualification, meaning of classification
- Updated limits for cleanroom classification for 5 microns particles
- New notes concerning microbial testing by alternative methods – correlation to CFU
- Requalification of cleanrooms – definition of scope and frequency

What are the main changes that new Annex 1 brings to barrier technologies?

- New Annex 1 provides much more details about barrier technologies (e.g. isolators and Restricted Access Barrier System (RABS)) compared with previous version (it only briefly mentioned isolators)
- requirements to design, background, use of gloves, decontamination

What are the main changes that new Annex 1 brings to personnel?

- Requirements related to access to Grade A/B are described in details including requirements for personnel training, qualification /requalification or disqualification
- Focus on the necessary competencies in microbiology and sterility assurance
- Detailed description of requirements for gowning for Grade A/B

What are the main changes that new Annex 1 brings to preparation methods?

- Aseptic preparation and processing – much more detailed description of requirements (including CCS, aseptic connections, manipulations, interventions, steps in aseptic processing)
- Finishing of sterile products – requirements described in more details
- Sterilization - much more details are provided, including description of handling of bioindicators

What are the main changes that new Annex 1 brings to in-process controls?

- PUPSIT (pre-use post sterilization integrity testing) is mandatory, detailed requirements defined also for cases when PUPSIT may not be applicable
- Gas filter handling - requirements for critical and non-critical gases specified in more details
- Container closure integrity testing – much more details, including types of containers which are or are not subject of 100% integrity testing
- Visual inspection – much more detailed requirements defined, including maintain of defects library (examples), proper investigation

What are the main changes that new Annex 1 brings to environmental and process monitoring?

- Newly created chapter (separated from qualification requirements) that is dedicated to monitoring and Aseptic Process Simulation
- Environmental monitoring ;program – much more details provided, including overall program considerations, trending requirements, identification of microflora, action limits for different grades for total particles and viable particles, monitoring of Grade A (including sample volume)
- Viable particles – detailed requirements, including needs to identify microorganisms species from grade A/B

Challenges

Challenges Faced in Indonesia's Implementation

Upgrading to meet Annex 1's stringent facility design and equipment requirements.

Infrastructure and Technology

Lack of expertise and resources in aseptic processing and sterile production environments

Cost and Investment

Higher costs for adopting isolator and RABS technologies.

Training and Personnel

BPOM's Role in Supporting Annex 1 Adoption

Regulatory Guidance and Support	Capacity Building	Ongoing Inspections and Audits
Issuance of revised guidelines aligned with Annex 1. Collaboration with industry to promote adoption of new technologies (e.g., RABS, isolators).	Organizing training programs for manufacturers and regulators. Strengthening quality risk management practice	Ensuring compliance with CPOB 2024 and Annex 1

SUMMARY

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- Annex 1 presents both challenges and opportunities for Indonesia.
- BPOM's proactive approach in supporting industry adoption through clear guidelines, training, and inspections.
- Commitment to improving sterile product manufacturing quality and ensuring patient safety.

Thank You!