CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS

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OUTLINE

- Background
- Regulation for Managing API in Indonesia
- Definition
- Managing API Source in Accordance with GDP
- Risk Assessment in API Importation
- Development of E-report and Database of APIs

Indonesia's Challenges in Control of Drugs

Increase of marketed drug

Increase of Public expectation on Health Protection

Change of public lifestyle

Infrastructure and Human Resources readiness in Drug Control

EFFECTIVE AND ROBUST
REGULATORY SYSTEM FOR DRUG CONTROL

Regulation for Managing API in Indonesia

BADAN POM
Badan Pengawas Obat dan Makanan

- MoH Regulation 1799/2010 →Pharmaceutical manufacturer
- MoH Regulation 1148/2011 → Wholesalers
- Indonesian GMP 2012 → Starting Materials
- Indonesian GDP 2012 →Repackaging, relabelling, Qualification of suppliers
- Regulation of The Head of NADFC Number 28 of 2031 on Importation Control of Starting Materials (drug, traditional medicine, health supplement, food)
- Regulation of The Head of NADFC Number HK 03.1.23.10.11.08481 of 2011 on Criteria and Procedure of Drug Registration

Definition

"active pharmaceutical ingredient (API)
Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings."

(WHO TRS 961)

Regulatory Framework for APIs Control in Indonesia

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Badan Pengawas Obat dan Makanan

SYSTEM

- Strengthen pre market evaluation for API
- NSW importation to establish API database
- Implement GMP for API Manufacture
- Pharmacopoeia, GMP code and technical guideline

IMPLEMENTATION

- GMP Inspection
- Standardization of quality (BE for selected API)
- Monitor and review of imported API (Importation and Distribution of API)
- Regulatory advice for API's Manufacturer: API R&D

CONTINUOUS IMPROVEMENT

- Gap Analysis: Benchmarking to Int'l Org & Recognized NRA, Update
- Monitor and review of imported API
- Regulatory advice for API's Manufacturer: API R&D

Managing API Source in Accordance with GDP

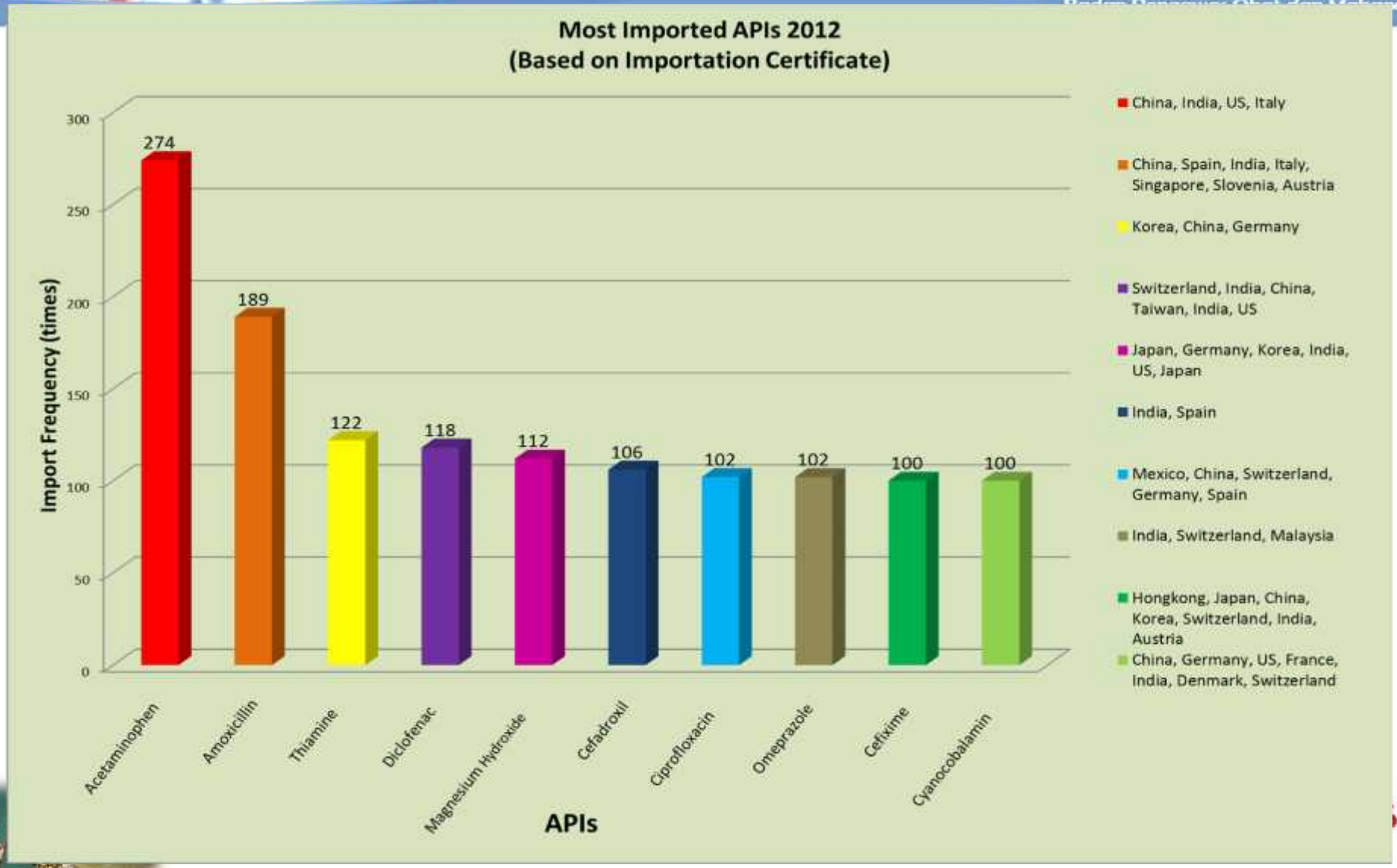
BADAN POM
Badan Pengawas Obat dan Makanan

Chapter IV
Operations
-- Qualification of Suppliers

Annex I
Starting Materials
-- Repackaging and Relabelling
-- Handling of Non-Conforming Materials
-- Documentation

Risk Assessment in API Importation

Demand of API Importation



Key Aspect of API

Manufacturer: location, sites, legal/license

Standard & Properties

- Structure and characterization
- Physicochemical properties
- Manufacture
- Impurities
- Controls
- Reference Standards
- Containers and Closures
- Stability

Detailed Information Provided in Dossier

Manufacturing Process

Starting Materials (for synthesis)

Reaction Intermediate(s)

API starting material

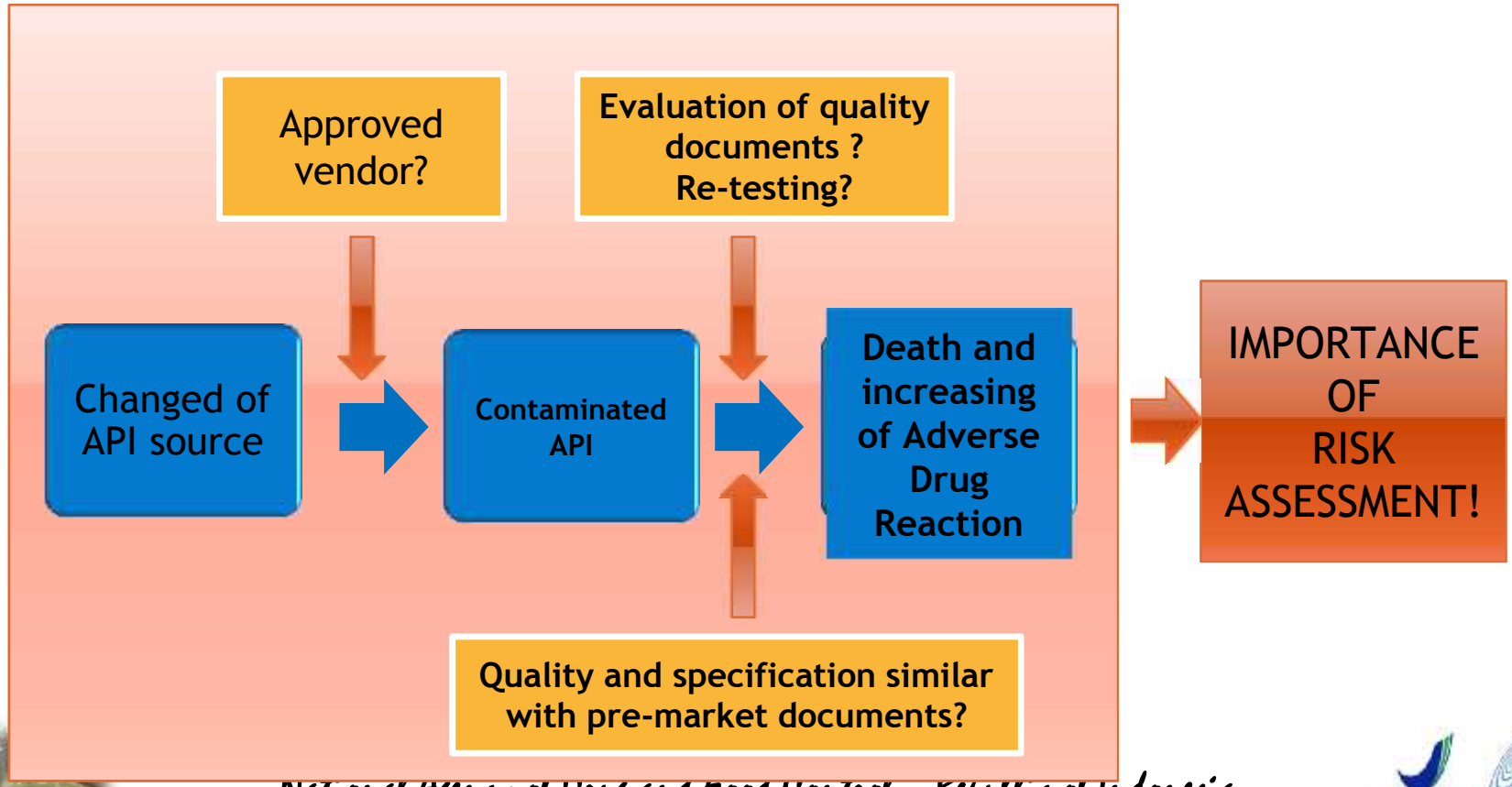
API intermediate(s)

Final API

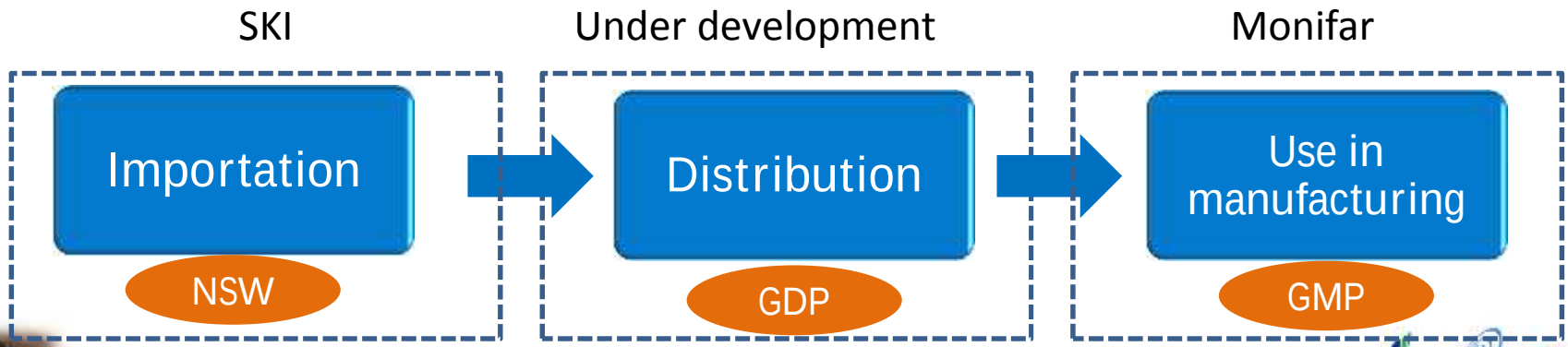
Comply to GMP

Lesson learned from APIs Cases

Example: WHO Alert No. 126, 24th January 2013 about contaminated API (Dextromethorphan) → serious incident that caused death in Pakistan



Strategy of API Control (1)



Cont...

Importation Control of Starting material including API

- National Single Window : integrated system for importation control of the medicinal products and starting materials into Indonesian territory
- Every importation of starting materials by pharmaceutical industries or distributors must be conducted in accordance with legislations and must get approval from The Head of NADFC.
- The form of approval from The Head of NADFC is Letter/Certificate of Importation (SKI), that valid only for one-time importation.

Strategy of API Control (2)

WAS BBO

2012

Pengumpulan DMF untuk Pembuatan Database

2013

- Penyusunan database BBO impor
- Penyusunan dan sosialisasi regulasi
- Sertifikasi industri BBO dalam negeri

2014

Impor bahan baku obat berasal dari industri BBO yang menerapkan GMP

BBO

QUALITY; STANDARD

PEMBUATAN

GMP

- KEPATUHAN
- INKONSISTENSI

DISTRIBUSI

GDP

- PENYIMPANGAN
- FASILITAS SIMPAN

Development of E-report and APIs Database

Cont.

E-report of API distribution

- Manufacturer / importer should report every 3 months to NADFC
- Shared responsibility across supply chain
- Can be used to permit traceability of the API from the manufacturer / importer to the drug manufacturer → to ensure supply chain integrity
- Communication with Ministry of Health (Ditjen Binfar) for sinergism of e-report

Developing Database for Imported APIs

Purpose: As reference/ recommendation for Pharmaceutical Industries or Wholesalers in Importing qualified APIs. Data gathered from DMF; Certificate of Importation

Information included:

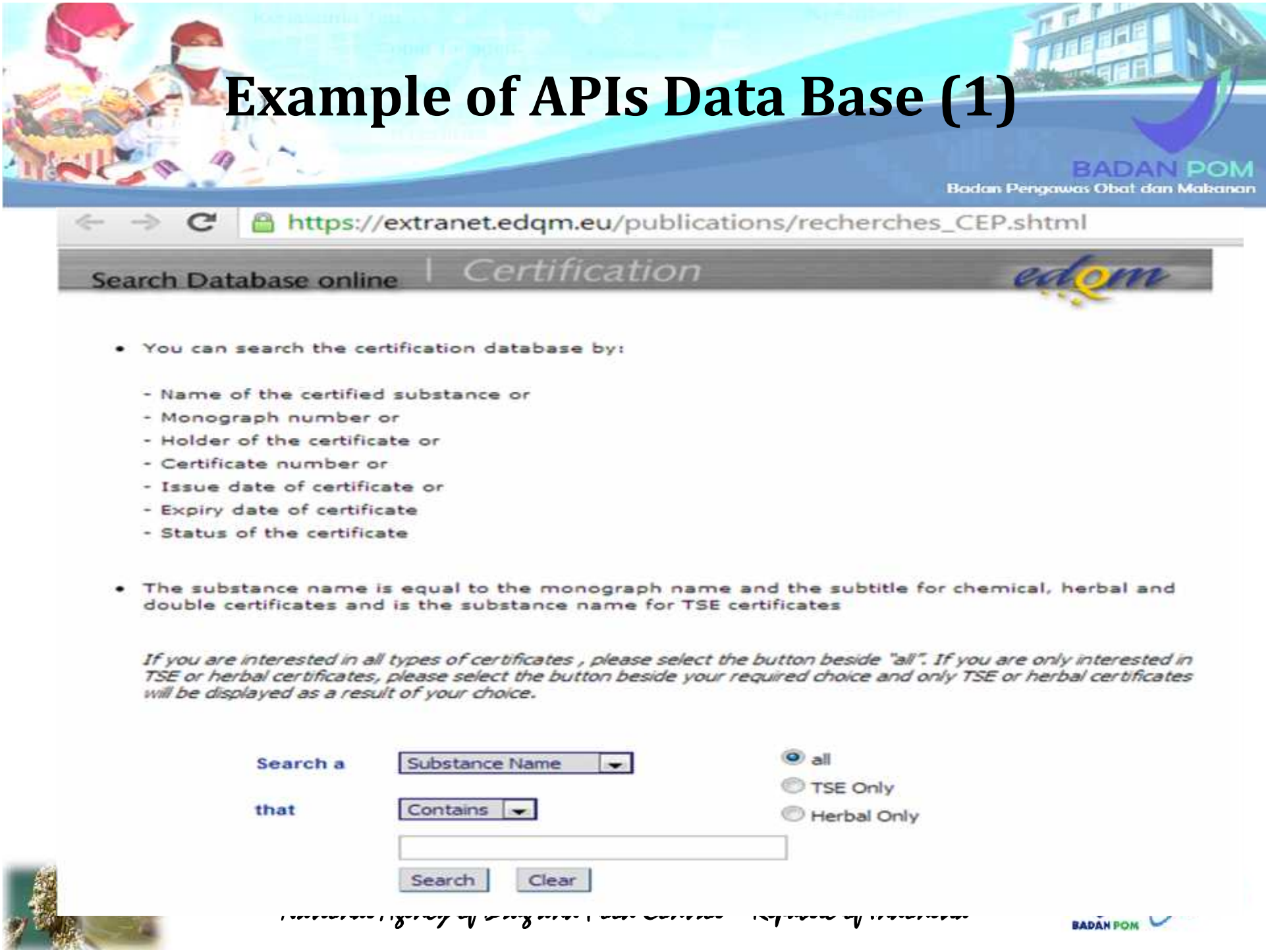
1. Name of the APIs
2. Dosage Form
3. CAS No and HS Code
4. Manufacturer's Name
5. Manufacturer's Address
6. Type of Commodity
7. Importir's Name
8. Valid Certificate of Good Manufacturing Practices (GMP) or Drug Master File (DMF) or Certificate of Suitability (CEP)

- CAS No. is an unique number designated for each chemical substance
- HS Code is a nomenclature system to identify goods in international trade. HS is prepared and assigned by the World Custom Organization (WCO).
- In database, CAS No. and HS Code will be used to identify APIs

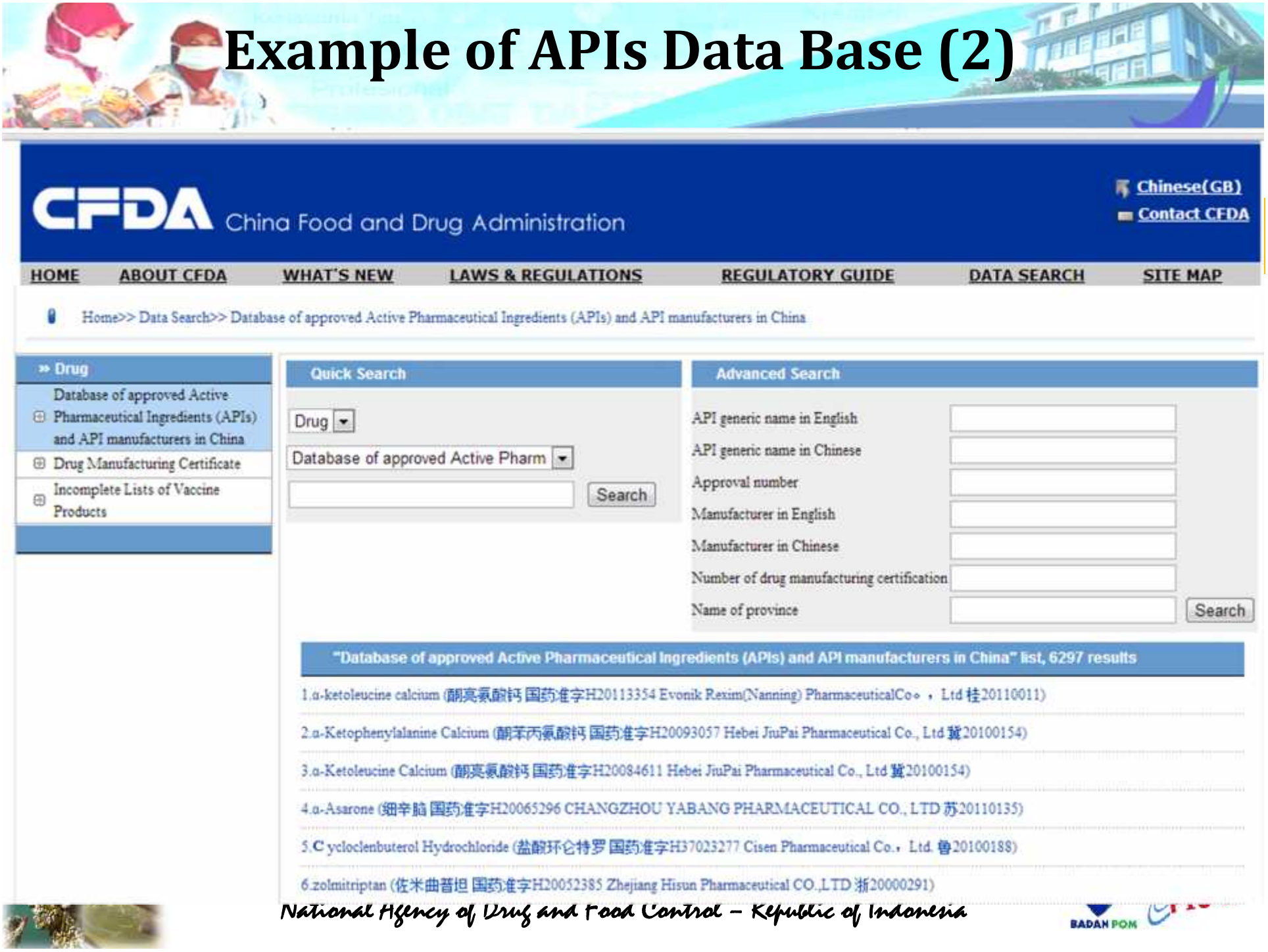
Strategy toward Development List of Recognized API

- Monitor and review database of imported API
- Screen regularly based on risk and benefit:
  - Frequency of importation,
  - API with documented BE study
  - API with DMF (API Master File)
  - Inclusion in the WHO PQ API, FDA, TGA and other recognized NRA
  - Product recall investigation
- New source of API should based on MA or Variation approval

Example of APIs Data Base (1)



Example of APIs Data Base (2)



Challenges (1)

Regulator

- Document review: need a special experience to catch critical information on API that may lead to specific parameter of the dosage form.
- Some necessary quality indicating may not have enough information
- Knowledge should be updated continuously How to get access to global and trend of development and manufacturing of API
- Strengthen Capacity building to evaluate APIMF and any API variation in post license period
- Catching up to the current analytical method in the laboratory and availability of Reference Standard

Challenges (2)

Applicant/Manufacturer

- How to get access to APIMF(open and/or restricted part)
- Limited access of information related to important quality parameter or any changes of API some time lead to delaying response to the regulator
- API market is a forest from underground to very high quality, one substance may have 10 levels of quality
- How to find reliable supplier, consistent quality and supply
- Price may not related to Quality if Vendor Qualification not done carefully

Opportunity to Approach Challenges

- Regulatory communication with the industry and its association can help to solve the burden of information access of API
- Use reference Information from WHO and other recognized DRA on list of approved API. (Possibility of regulatory network on API Qualification especially by recognized DRA)
- Regular review of API database (importation) in the country may help to screen unqualified API Sources
- API (generic) used in a proven BE study can be used as reference source

Conclusion

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- Pharmaceutical Industries in Indonesia are highly dependent to imported APIs, therefore control of the APIs is one of the critical aspect in GMP Implementation.
- Pharmaceutical Industry should pay more attention to the Business Continuity Plan (BCP) and implement Quality Risk Management in the selection of suplier
- One gate policy for importation could help minimize the risk of inconsistent quality and/ or unrecognized API
- E-report of API distribution will prevent diversion to illegal channel → importer should report every 3 months
- All parties in API supply chain have a responsibility to ensure the quality of the products and that the integrity of the distribution chain is maintained from the importers (wholesalers) to the manufacturers

TERIMA KASIH