CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS

The 2nd Indonesia-Japan Symposium
Jakarta, 21 May 2014

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
Change of public lifestyle
Increase of Public expectation on Health Protection
Infrastructure and Human Resources readiness in Drug Control

EFFECTIVE AND ROBUST REGULATORY SYSTEM FOR DRUG CONTROL

National Agency of Drug and Food Control – Republic of Indonesia
Regulation for Managing API in Indonesia

- 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
"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

**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
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

Most Imported APIs 2012
(Based on Importation Certificate)

- China, India, US, Italy
- China, Spain, India, Italy, Singapore, Slovenia, Austria
- Korea, China, Germany
- Switzerland, India, China, Taiwan, India, US
- Japan, Germany, Korea, India, US, Japan
- India, Spain
- Mexico, China, Switzerland, Germany, Spain
- India, Switzerland, Malaysia
- Hongkong, Japan, China, Korea, Switzerland, India, Austria
- China, Germany, US, France, India, Denmark, Switzerland
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

National Agency of Drug and Food Control - Republic of Indonesia
Lesson learned from APIs Cases

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

- Changed of API source
- Contaminated API
- Quality and specification similar with pre-market documents?
- Evaluation of quality documents? Re-testing?
- Death and increasing of Adverse Drug Reaction

IMPORTANCE OF RISK ASSESSMENT!
Strategy of API Control (1)

Pre-Market
- GRP

API proposed on pre market same with post market?

Post-Market
- SKI
- Under development
- Monifar

Importation → Distribution → Use in manufacturing
- NSW
- GDP
- GMP

National Agency of Drug and Food Control - Republic of Indonesia
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)
Development of E-report and APIs Database
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 Binfo) 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. Importer’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)

- You can search the certification database by:
  - Name of the certified substance or
  - Monograph number or
  - Holder of the certificate or
  - Certificate number or
  - Issue date of certificate or
  - Expiry date of certificate
  - Status of the certificate

- The substance name is equal to the monograph name and the subtitle for chemical, herbal and double certificates and is the substance name for TSE certificates

If you are interested in all types of certificates, please select the button beside “all”. If you are only interested in TSE or herbal certificates, please select the button beside your required choice and only TSE or herbal certificates will be displayed as a result of your choice.

Search a [Substance Name] that [Contains]
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

- Pharmaceutical Industries in Indonesia are highly dependent on imported APIs, therefore control of the APIs is one of the critical aspects in GMP Implementation.
- Pharmaceutical Industry should pay more attention to the Business Continuity Plan (BCP) and implement Quality Risk Management in the selection of supplier.
- 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