Recent Trends in the Regulation of Biopharmaceuticals: Indonesian Perspectives

Dr. Roy Sparringa

National Agency for Drug and Food Control (NADFC)
Republic of Indonesia

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Introduction
The Needs of Biopharmaceutics

Over thirty years ago the first biotechnologically manufactured medicines were introduced to the market.

Human rec. Product, Mab, and other biopharmaceutics can cure life threatening disease, rare disease, and or symptomatic diseases.

Core Therapy Areas for biologics (MAT 12/2010)

- Insulins: 15.9
- Anti-TNF: 15.8
- Oncology (Mab): 12.5
- EPO: 7.6
- Multiple sclerosis: 7.3
- CFS-G: 5.0
- Blood coagulation: 3.1
- Ocular antineovasc.: 2.0
- Antiviral (no-HIV): 1.5
- Other: 16.5

*Top 5 therapy areas account for about 70% of the total market*

Global Biopharmaceutics Market Trends

- Small molecules & OTC development tend to decrease, whereas Biopharmaceuticals tends to increase.

Biopharmaceuticals forecast become the biggest selling products by 2016.
- 2010 = 130 bn $
- 2016 = 192 bn $

Source: Evaluate Pharma® (25 May 2011), World Preview 2016 (‘11.6)
Regional Market Forecast

Pharmaceutical Sales In South East Asia (USDbn)

- Laos: 14.4% CAGR
- Brunei: 8.8% CAGR
- Cambodia: 9.4% CAGR
- Myanmar: 11.9% CAGR
- Singapore: 7.1% CAGR
- Malaysia: 7.8% CAGR
- Philippines: 6.4% CAGR
- Vietnam: 14.1% CAGR
- Thailand: 6.4% CAGR
- Indonesia: 8.4% CAGR

Sources: BMI (2014)

Indonesia is the biggest pharmaceutical market in ASEAN
Indonesian Index Competitiveness in Global: Rank 46 (2011), Rank 50 (2012), Rank 38 (2013), and Rank 34 (2014)

Global Competitiveness Index

<table>
<thead>
<tr>
<th>Year</th>
<th>Rank (out of 144)</th>
<th>Score (1-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCI 2014–2015</td>
<td>34</td>
<td>4.6</td>
</tr>
<tr>
<td>GCI 2013–2014</td>
<td>38</td>
<td>4.5</td>
</tr>
<tr>
<td>GCI 2012–2013</td>
<td>50</td>
<td>4.4</td>
</tr>
<tr>
<td>GCI 2011–2012</td>
<td>46</td>
<td>4.4</td>
</tr>
</tbody>
</table>


Potency:
- 208 Pharmaceutical Industry in Indonesia
- Indonesia pharma market is growing

Challenges:
- 95% Raw material s imported
- Tight Global Market Competition
GREAT EXPANSION OF MIDDLE CLASS IN ASIA PACIFIC

Source: Pwc (2014)
Biotech market in Indonesia is still relatively small but keeps growing.

- Erythropoietin (EPO) for Renal therapy and Growth Colony Stimulating Factor (GCSF) are listed in ASKES DPHO.
- With universal healthcare coverage implementation in 2014, pharma market is estimated to grow at least 3 times fold.
  - Generic - Low price
  - Local content preference
Regulation on Biopharmaceuticals Evaluation in Indonesia
1. Ensuring **quality, safety, and efficacy** of food and drug to increase public health

2. Improving food and medicine competitiveness nationally and globally through quality assurance and innovation.
General Criteria On Evaluation (Risk-benefit Based Assessment)

Based on:
• Nonclinical data
• Clinical data

Efficacy & Safety

Based on CMC for:
• Active Substance
• Finished Product

Quality

Evaluation Criteria

Should be:
• Complete
• Objective
• Clear to ensure rational use of

Product Information
Watchdog Control

**DEPENDING ON INSPECTION**

Proactive Control

**Prevention through RMP (Risk Management Program) by Business Operator, and verified by Regulator**
Current Trends on Regulation of Biopharmaceuticals

- Biosimilar
- Manufacturing Process Changes
Regulation on Biosimilars in Indonesia
• Biosimilars are expected to relieve the burdens of patients’ medical costs and government’s health insurance budget pressure by offering same effectiveness at lower price than originals.

• Patents for biopharmaceuticals with market volume worth about 1 billion dollars will expire soon.

<table>
<thead>
<tr>
<th>Name</th>
<th>Generic name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Market size (billion US$/year)</th>
<th>Patent expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>Etanercept</td>
<td>Amgen</td>
<td>Rheumatoid arthritis</td>
<td>5.3</td>
<td>2012</td>
</tr>
<tr>
<td>Epogen</td>
<td>Epoetin-α</td>
<td>Amgen</td>
<td>Anemia</td>
<td>5.3</td>
<td>2013</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>Johnson &amp; Johnson</td>
<td>Rheumatoid arthritis</td>
<td>4.4</td>
<td>2013</td>
</tr>
<tr>
<td>Rebif</td>
<td>Interferon β-1a</td>
<td>Serono</td>
<td>Multiple sclerosis</td>
<td>1.6</td>
<td>2013</td>
</tr>
<tr>
<td>Humalog</td>
<td>Insulin lispro</td>
<td>Eli Lilly</td>
<td>Diabetes</td>
<td>1.4</td>
<td>2013</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Rutuximab</td>
<td>Genentech</td>
<td>Non-Hodgkin's lymphomas</td>
<td>4.5</td>
<td>2015</td>
</tr>
<tr>
<td>Lantus</td>
<td>Insulin glargin</td>
<td>Sanofi-Aventis</td>
<td>Diabetes</td>
<td>2.7</td>
<td>2015</td>
</tr>
<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>Abott</td>
<td>Rheumatoid arthritis</td>
<td>3.0</td>
<td>2016</td>
</tr>
</tbody>
</table>
Pipelines on Local Biosimilars Development by 2019:
- 3 biosimilars development with technological transfers
- 1 biosimilars development without technological transfers
Biotherapeutics & Biosimilars in Indonesia

- Epoeitin alfa
- Rec. Human Insulin
- r-GCSF/Filgrastim
- Rec. Interferon beta
- Rec. Interferon alfa
- Somatropin
- Low Molecular Weight Heparin (LMWH)
- Monoclonal antibody
- Biosimilar

- r-human Follicle Stimulating Hormon (r-hFSH)
Regulation on Biosimilars

**Principle:**

- Biosimilars products should demonstrate similarity on quality, safety and efficacy to Reference Biotherapeutics Product (RBP).

**Indonesia guidelines on biosimilars:**

- Mostly refers to WHO guidelines and also considered other established biosimilar guidelines.
Policy for Biosimilar Product Evaluation

Comparability Requirements in Q, S, E

Quality Characterizations

Nonclinical

Clinical

Biosimilar Product

Reference Product
Comparability Exercises for Biosimilar Products

1. Quality comparability study
   ➞ Characterisation: Physicochemical attribute, biological activity, immunochemical attributes, and impurities.

2. Nonclinical comparability study
   ➞ Minimum repeated dose toxicity study and/or pharmacodynamics study

3. Clinical comparability study
   ➞ PK/PD study, efficacy and safety, immunogenicity.
   ➞ Comparative PK/PD studies may be appropriate to demonstrate similar efficacy of the Biosimilars and the RBP in cases:
     - PK and PD properties of the RBP are well characterized;
     - at least one PD marker is a marker linked to efficacy;
     - the relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the RBP is established.
INDONESIA’s General Guideline on Evaluation of Biosimilar Products

Reference product

- Originator product approved in Indonesia
- If no approved originator products
- If the originator product no longer produced

Originator product

- Originator product that has been approved in country/ies with established evaluation system & Never rejected in Indonesia
- The most established biotherapeutic product which has been approved based on full Q, S, E evaluation & has been marketed without any Q, S, E issues

Biotherapeutic product that was firstly developed by the manufacturer and having MA based on full quality, safety, and efficacy data and having patent
Registration of a biosimilar product

Imported biosimilar products

Development process was under supervision of the NRA of country of origin

Required final development dossier

- Quality
- Non-clinical
- Clinical

Comparability Data
Registration of a biosimilar product

Locally manufactured biosimilar products

Development process will be under supervision of BPOM / NADFC

Evaluation data through IND like system: step wise approach with expert consultation on each stage of development

Comparability Clinical study can only be conducted if comparability on quality and non clinical data are considered appropriate and adequate.

Protocol of clinical study should be approved by ethical committee and BPOM / NADFC
BPOM Assistance During Biosimilars Development and Oversight

PRE IND | IND APPLICATION
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Meetings
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IND | Pre-MAA | MA | Post - MA

Trial Batch
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Small scale | Larger scale | Commercial Scale
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Drug Discovery
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GLP
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cGMP
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GCP
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Clinical Development Program
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Phase I
• Safety
• Immunogenicity

Phase II
• Immunogenicity
• Safety
• Dose Ranging

Phase III
• Efficacy
• Safety
• Immunogenicity

Phase IV
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IND Application
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MA Application
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ICDRA RECOMMENDATION ON BIOSIMILARS

1. Ensure regulatory throughout life-cycle of biotherapeutic products including biosimilars to assure quality, efficacy and safety of these products.

2. Improve efficiency of regulatory evaluation of biotherapeutic products including biosimilars in order to improve access to products of assured quality, safety and efficacy.

3. WHO guidelines on biotherapeutic products and on biosimilars.

4. Collaboration between regulators and other relevant stakeholders.

5. Regulatory convergence as a tool to increase global access to biosimilars of quality, safety and efficacy.

Various interpretation on the regulation
- Access to reference products
- Conduct of comparability study, e.g.:
  - Analytical method for higher structured characterization
  - Efficacy and safety
  - Immunogenicity
- Difference registration requirements in importing countries
- Extrapolation of indication
- Local biosimilar product development.

**WAY FORWARDS**

- Dissemination & training/workshop
- Regulatory risk assessments using regulatory best practices & guidances
- Encourage technology transfer
- Facilitate biosimilars development

**CHALLENGES ON IMPLEMENTATION OF THE BIOSIMILAR REGULATION**
Regulation on Post Approval Manufacturing Changes in Indonesia
Changes through Biotherapeutics Life Cycles

- Clinical to commercial process and facility and scale
- New manufacturing technology
- New testing methodology
- Regulatory agency requirements
- Learning more about the product and process
- Prevention of Drug Shortages
- Etc.
Regulatory Approach & Consideration

Not all changes are having the same risk/impact to Q,S,E requirements will not be the same for all changes.

Classification of Variations/Changes in Indonesia:
- Major (100 Working Days)
- Minor for approval (40 working days)
- Minor for notification

Adapted from Richard Lit  APEC 2013
Regulation on Post Approval Changes

PRINCIPLES

• Changes do not alter quality, safety & efficacy
• Comparability exercises needed ➔ using step-wise approach
  • Quality comparability is mandatory
  • Extended comparability exercise to nonclinic & clinic studies will be case-by-case.
• The amount of required data will depend on the type of changes.

REFERENCES

ICH Q5E

WHO Guideline on Post Approval Changes for Vaccine
• Different interpretation of ICH Q5E.
• Different submission package to regulators of different countries for the same variation application.
• Application of different source of product due to merger or acuisition of one industry/ manufacturer by other ➔ no/minimum comparability data.
• Difference requirements for variation submission in importing countries.
• Provision of stability data.
Case Study #1

- Change of drug substance manufacturer site (same company) with major manufacturing process difference (different fermentation medium).

Submission package by industry:
- Rationale of changes.
- Comparability drug substance manufacturing process
- Drug substance specification
- Comparability characterization of drug substance
- Drug substance validation process.
- Batch analysis of drug substance from new site.
- Commitment to submit stability data for drug product and drug substance

Required data:
- Comparability batch analysis
- Comparability real time of drug substance stability data.
- Nonclinical/clinical bridging study if indicated from characterization comparability
Case Study #2

• Changes drug product process (scale-up from 45 L to 225 L).

Submission package by industry:
- Rationale of changes.
- Comparability drug product manufacturing process.
- Drug product specification.
- Drug product validation process.
- Batch analysis of drug product.
- Commitment to submit stability data for drug product.

Required data:
- Comparability batch analysis.
- Comparability of validation process.
- Real time stability data of finished product.
• The need and development of biopharmaceutics are increasing, therefore regulation for assurance of good Q,S,E of biopharmaceutics is required.

• Biosimilars and post approval changes are current of regulatory challenges.

• Global harmonization & convergence can become a solution for different interpretation of regulation.
Thank you