14th International Conference Of Drug Regulatory Authorities (ICDRA)
3rd December 2010, Singapore

Planery 5 : Biosimilars
Diversity of Regulatory Requirements and Way Forward

National Pharmaceutical Control Bureau (NPCB) Ministry Of Health Malaysia
Just to clarify

The views and opinions expressed in the following presentation are that of the presenter and may not replicate that of NPCB or MOH Malaysia per se.

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Development Of Biosimilar Regulatory Framework Worldwide

- Canada 3/2010
- Croatia 2008
- Switzerland 2/2008
- Turkey 8/2008
- Saudi Arabia 2010
- Canada 3/2010
- Guatemala
- Mexico
- Cuba
- Brazil
- Argentina
- EU (EEA) 2005
- Japan 3/2009
- Korea 7/2009
- Taiwan 11/2008
- Singapore 8/2009
- Malaysia 8/2008
- Indonesia
- Australia 2005
- Korea 7/2009
- Japan 3/2009
- Taiwan 11/2008
- Singapore 8/2009
- Malaysia 8/2008
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- Korea 7/2009
- Japan 3/2009
- Taiwan 11/2008
- Singapore 8/2009
- Malaysia 8/2008
- Indonesia
- Australia 2005
Worldwide Situation

- EU is the first with comprehensive framework for Similar Biological Medicinal Products (Biosimilars).

- Australia, Canada, Croatia, Japan, Malaysia, Singapore, South Korea, Switzerland, Taiwan, Turkey – have followed EU principles.

- Framework in other countries in Asia, Latin America and Middle East are currently being developed.

- WHO published a guideline on evaluation of similar biotherapeutic products (SBPs) – based on EU experience, to be used globally.

- USA: Recently signed bill (March 2010).
Paradigm Shift ....
What’s In A Name?

- Biogeneric
- Generic biologic
- Multisource product / Me-too

Biosimilar .... Europe, Australia, Malaysia, Singapore, etc.
Subsequent entry biologic (SEB) .... Canada
Similar biotherapeutic products (SBPs) .... WHO
Known biological product (KBP) .... Cuba
Follow-on biologic (FOB) ..... Japan (*label Omnitrope BS), USA
Biological products ...... Brazil

Key points

- A biosimilar is a copy of a biopharmaceutical for which patent protection no longer applies
- A biosimilar is comparable with the selected reference product in terms of quality, safety and efficacy
- A biosimilar is **not a generic** biopharmaceutical
- Biosimilar is also a regulatory pathway
Guideline
‘Guideline on similar biological medicinal products’

Guideline on quality issues

Guideline on non-clinical/clinical issues

Product-class specific guidelines on nonclinical/clinical:
- Insulin
- GH
- G-CSF
- Epoetin
- IFN – alpha
- LMWH

Product specific – guidelines under development
- IFN-beta
- FSH
- mAbs

Proof of similarity with a reference product as the basis for approval

Full dossier plus head-to-head comparison to reference product

Reduced dossier, head-to-head comparison to reference product
The intention of this document is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. On the basis of proven similarities, the development of SBP will rely, in part, on non-clinical and clinical data generated from an already licensed product on the reference biotherapeutic product (RBP).
WHO Guidelines on Evaluation of Similar Biotherapeutics Products (SBPs)


- Provide **key principles for evaluation of SBPs** as a basis for setting national requirements. Scope: well-established and well-characterised biotherapeutic products such as recombinant DNA therapeutic proteins. Vaccines and plasma derived products and their recombinant analogues are out of scope.

- Effective regulatory oversight: critical for assuring quality, safety and efficacy of SBPs.

- Important issues associated with the use of SBPs that need to defined at national level include: IP, Interchangeability & substitution, labeling and prescribing information.

- **Stepwise comparability exercise** - demonstration of similarity of SBP to Reference Biotherapeutic Product (RBP) in terms of quality is a prerequisite for the reduction of the non-clinical and clinical data set requirement for licensure.

- Final guidance will be published in the WHO technical report series - ‘Living document’ that will be developed further in line with the progress in scientific knowledge and experience.

**Key message:**

Important to note that biotherapeutics which are not shown to be similar to a RBP should not be described as ‘similar’, nor called a ‘SBP’.
## Biosimilar Regulatory Framework Comparison

<table>
<thead>
<tr>
<th></th>
<th>Similarity concept</th>
<th>Interchangeability &amp; Substitution</th>
<th>Extrapolation across indications</th>
<th>Immunogenicity</th>
<th>Unique INN; pharmacovigilance required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Medicines Agency</strong></td>
<td>Concept created by EU</td>
<td>Decided at member state level in EU</td>
<td>Ok if justified both in the EU and in the WHO guidance</td>
<td>Needs to be studied in human pre and post approval in EU and according to WHO guideline</td>
<td>INN is independent from the regulatory pathway used for approval</td>
</tr>
<tr>
<td><strong>World Health Organization</strong></td>
<td>Experience of EU considered by WHO No product specific (non-clinical or clinical) guidelines</td>
<td>Not addressed in WHO guidance</td>
<td></td>
<td></td>
<td>PV is needed for all products in EU and according to WHO guideline</td>
</tr>
</tbody>
</table>

### Key Insight
Countries adopting EMA and/or WHO guidance will have a robust biosimilar approval pathway
Biosimilars
Scientific basis for abbreviated pathway
(as in: EU, Japan, Canada, WHO, others)

Demonstrate Quality, Safety, Efficacy

New Biologic → Extensive Characterization → Clinical → Pre-Clinical → Regulatory Approval → Surveillance

Biosimilar → Extensive Characterization → Clinical → Pre-Clinical → Regulatory Approval → Surveillance

Allows for abbreviated pre-clinical & clinical

Source: Centre de recherche du Centre hospitalier de l’Université de Montréal (CRCHUM)
Differences in Global Regulatory Expectations

Japan
- Reference Product must from Japan
- Comparative Pre-Clinical Studies
- Comparative Clinical Studies
- Ethnic population for clinical trials

Canada
- Reference Product Preferably from Canada
- Comparative Pre-Clinical Studies
- Comparative Clinical Studies
- Ethnic population for clinical trials

EU
- Reference Product must from EU
- Comparative Pre-Clinical studies
- Comparative Clinical Studies
- Clinical trials in EU representative population

Malaysia
- Reference Product Mal/US/EU/Can. Ref countries
- Comparative Pre-Clinical Studies
- Comparative Clinical Studies
- Global clinical data accepted

Replicate full development programs will need to be performed in each region unnecessarily effort and expenditure and unethical!
Way Forward ........

Suggested conclusions

1. One comprehensive comparability package against a reference product authorized in a highly regulated market for all regions?
   - Acceptable!
   - Legislations implications!
   - A need to develop an international mutual recognition mechanism.

2. Regulatory concern about the impact of ethnicity.
   - Will data from populations where intrinsic and extrinsic ethnic differences might exist acceptable?
   - Will biosimilar display a different spectrum of ethnicity?
   - Case-by-case considerations!

Lots of Questions ?? ....... Few answers!
# Differences in Global regulatory Expectations for Biosimilars (CMC)

<table>
<thead>
<tr>
<th>Document / Studies</th>
<th>LR</th>
<th>SR</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product characterization:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Structural analysis</td>
<td>1,2,3 Basic</td>
<td>1,2,3</td>
<td>All</td>
</tr>
<tr>
<td>2. Impurities</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3. Biological assays</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Comparability with reference product</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Bulk and Finished Product Testing:</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1. Specifications</td>
<td>1,2</td>
<td>1,2,3,4,5</td>
<td>All</td>
</tr>
<tr>
<td>2. Certificate of analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Method of analysis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Analytical validation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. Ref. std</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Justification for specifications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7. Batch analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clone details:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Information of clone and cell banks</td>
<td>No</td>
<td>1 Basic</td>
<td>All</td>
</tr>
<tr>
<td>2. Cell bank characterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Viral testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stability profile:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Report</td>
<td>1,2</td>
<td>1,2</td>
<td>All</td>
</tr>
<tr>
<td>2. Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Trend analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Forced degradation studies</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Source:**
USP-IPC 8th Annual Scientific Mtg 2/2009
Complexity increases with size

- Insulin (5.8kDa)
- Growth hormone (22.1kDa)
- Erythropoietin (34kDa)
- Monoclonal Antibody (150kDa)

Aspirin (0.18kDa)
# Potential Biosimilar Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Product</th>
<th>Approval pathway</th>
<th>Number of amino acids*</th>
<th>Approximate MW (Da)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>Rituximab</td>
<td>BLA</td>
<td>1,328</td>
<td>145,000</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>BLA</td>
<td>1,330</td>
<td>146,000</td>
</tr>
<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>BLA</td>
<td>1,330</td>
<td>148,000</td>
</tr>
<tr>
<td>Synagis</td>
<td>Palivizumab</td>
<td>BLA</td>
<td>1,320</td>
<td>148,000</td>
</tr>
<tr>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>BLA</td>
<td>1,320</td>
<td>149,000</td>
</tr>
<tr>
<td>Xolair</td>
<td>Omalizumab</td>
<td>BLA</td>
<td>1,324</td>
<td>149,000</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>BLA</td>
<td>1,308</td>
<td>149,100</td>
</tr>
<tr>
<td>Erbitux</td>
<td>Cetuximab</td>
<td>BLA</td>
<td>1,326</td>
<td>152,000</td>
</tr>
<tr>
<td>Lucentis</td>
<td>Ranibizumab</td>
<td>BLA</td>
<td>445</td>
<td>48,000</td>
</tr>
</tbody>
</table>

Lanthier et al. (2008)
Economic issues with follow-on protein products
Way Forward ………
Suggested conclusions

3. Establishing proper guidance by adopting the WHO SBPs and adding chapters on pharmacovigilance and other local issues (eg. Interchangeability & substitution, labeling and prescribing information).
This assures a quick and efficient way to an adequate and transparent biosimilars regulatory framework to ensure patient safety.

4. Consider further assistance to regulators and manufacturers such as:
   - database or lists of reference products/global reference preparation
   - possibility of pre-qualification of biosimilars.
   - capacity building / up-skilling.

5. Possibility of developing global monograph and monograph for finished product with elaborate information eg. cell banks, characterizations, impurities, post-translational modification etc.

6. Establishing regional or national network for information sharing, learning experience among NRAs, in this new regulatory area.
Biosimilars & NRA: Challenges & Expectations

- Biosimilars are a reality & shaking up the biologics market on a worldwide scale. The global regulatory landscape is evolving and to expand the global access to biologics – calls for a **consistent and efficient** approach to their regulation.

- In the light of existing scientific evidence, the regulatory standards and approval pathways for biosimilars will have to go beyond mere cost-effectiveness to protect public health. Thus, **quality and patient safety are paramount**.

- Ensuring regulatory position adequately reflects scientific advancement, expertise and resources is key. **Continuing demand for WHO assistance, leadership, guidance, support and collaboration.**

- Various guidance documents are in the making: should aim for **global consistency and harmonization**. **Accrued experience** will then allow for the regulatory authorities to optimally match guidelines to the genuine risks and benefits associated with biosimilars.

- Supporting a viable biosimilar industry is key for any government to solve the hard-pressed healthcare budgets. However, there is no short cuts. Lower cost at the expense of patient safety is no bargain.

- Transparency and open dialogue with all stakeholders is key to a robust regulatory framework. Likewise, it calls for **awareness, alertness and education for all**.
In a nutshell: The concept of biosimilarity is still in its infancy and industry, regulators and physicians alike hold the responsibility of nurturing the concept towards bringing affordable and quality medicines to the world.
Thank You for
Your kind attention

Terima kasih