OUTLINE

- Malaysian regulatory system
- Biosimilars oversight
- mAbs biosimilars & challenges
- ASEAN biosimilar regulatory landscape
- Cell and gene therapy products (CGTPs)
- Conclusion
The Guidelines Should Be Read Together In Accordance To The Legal Requirements of ....


2. The Poison Regulations (Psychototropic Substances) 1989

3. Sale of Drugs Act 1952 (Act 386)

- where controlled medicines are involved
Mission: To safeguard the nation’s health through scientific excellence in the regulatory control of medicinal products and cosmetics

...in the Malaysian market are, of QUALITY, SAFE (Natural & Cosmetic Products) & EFFECTIVE (Therapeutic Products)
Overview of Product Registration
Biologics – Complexity increases with size (molecular heavyweights)

- EPO 34kDa
- GH 22kDa
- IFN 19kDa
Manufacturing complexities – A challenge from Production to Testing

“One process - One product” paradigm
Biosimilars: biological medicines developed to mimic, as closely as possible, the quality, efficacy and safety of existing approved biologics (innovator), following patent expiry.

The word biosimilar is telling: similar but not same / identical, therefore non-equivalent. Thus, it is not like true generic drug and cannot be called biogeneric.

The generic paradigm does not work, hence biosimilar needs a new regulatory pathway, with comparability study is key to demonstrate biosimilarity with the reference product.

Malaysia’s guidance document and guidelines for registration of biosimilar (implemented August 2008), adopted from EMA guidelines including product-specific guidelines, with little adaptations.

Reference product: a product already approved on the basis of a complete dossier (quality, safety, efficacy), with sufficient duration of use, chosen as a reference product by the biosimilar manufacturer.
Target-directed development of biosimilars results in a front-loaded CMC effort as compared to originator.
### Biosimilar products registered in Malaysia (as of March 2014)

<table>
<thead>
<tr>
<th>Substance name</th>
<th>Product &amp; Company</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF (Filgrastim)</td>
<td>Zarzio® - Sandoz</td>
<td>Mar 2012</td>
</tr>
<tr>
<td></td>
<td>Nivestim® - Hospira</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Somatropin (HGH)</td>
<td>Scitropin® - Sandoz</td>
<td>Aug 2010</td>
</tr>
<tr>
<td>Erythropoietin-alfa</td>
<td>Binocrit® - Sandoz</td>
<td>Mar 2011</td>
</tr>
<tr>
<td>r Human Insulin</td>
<td>Insugens® - Biocon, India</td>
<td>Jan 2014</td>
</tr>
</tbody>
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* Remsima Injection, Celltrion received Feb 2014 – under evaluation
The Malaysian biologic manufacturing sector has grown steadily, fueled by government support and incentives to nurture biologic manufacturing talents and business opportunities.

Approved with conditionns - Implementation of RMP - Post market surveillance, a registry of Insugen in Malaysia, to submit PBRER.

Biocon Ltd – biopharmaceutical manufacturing and R&D facility in Bio-XCell, a biotech park and ecosystem in Iskandar Malaysia – Johor

In the first phase Biocon invests $ 200 million in facility which is to be operation by 2015. The project also focus on R&D and production of other products at a later phase.
The demand for EPO to treat chronic kidney patients is expected to grow. This increasing demand will create a serious strain on Malaysia’s Healthcare Resources.
Monoclonal Antibodies (mAbs) “protein tango”

The next wave of Biosimilars ………

Monospecific antibodies that are produced by a single clone of immune cells. They have become an important tool in molecular biology and medicines, and the basis of many biologics.

<table>
<thead>
<tr>
<th>Safety and Efficacy is dependent on correct structure or a defined mixture of correct structures</th>
</tr>
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<tbody>
<tr>
<td>Post-translational modifications and Complex foldings of protein are determined by amino acid sequence, by cell lines and by manufacturing conditions</td>
</tr>
</tbody>
</table>

Cell surface receptor ‘exquisite specificity’

150,000 Da
The mechanism of action of mAb is complex and may involve contributions from multiple mechanisms.
Maturing antibody-drug conjugate pipeline hits 30

Driven by recent clinical breakthrough and technological progress, 30 ADCs against 24 targets are now in trials for blood cancers and solid tumors.

Antibody-drug conjugate and desired characteristics

**Antibody**
- Maintains characteristics when linked to the requisite number of cytotoxic molecules via linker
- Targeted at a well-characterized antigen
- Targeted at an antigen found only on target cells
- Targeted at an antigen that is not downregulated on Ab binding
- Minimal non-specific binding

**Cytotoxic agent**
- Non-immunogenic
- Non-toxic (dormant or inactive) during circulation in the blood
- Highly potent in small quantities such that two to four molecules are sufficient

**Linker**
- Stable to ensure ADC remains intact until it reaches target
- Does not alter the Ab characteristics (pharmacokinetics)
- Ensures that the cytotoxic agent is functional once at target site
### Association of South East Asian Nations

<table>
<thead>
<tr>
<th>Country</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>8 August 1967</td>
</tr>
<tr>
<td>Brunei Darussalam</td>
<td>7 January 1984</td>
</tr>
<tr>
<td>Indonesia</td>
<td>8 August 1967</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>28 July 1995</td>
</tr>
<tr>
<td>Singapore</td>
<td>8 August 1967</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>23 July 1997</td>
</tr>
<tr>
<td>The Philippines</td>
<td>8 August 1967</td>
</tr>
<tr>
<td>Myanmar</td>
<td>23 July 1997</td>
</tr>
<tr>
<td>Thailand</td>
<td>8 August 1967</td>
</tr>
<tr>
<td>Cambodia</td>
<td>16 December 1998</td>
</tr>
</tbody>
</table>
The formation Pharmaceutical Product Working Group (PPWG) in 1999 was to develop a harmonization scheme and to complement and facilitate the objective of ASEAN Free Trade Area (AFTA), particularly elimination of technical barriers to trade posed by these regulations without compromising on drug quality, safety and efficacy.

Creation **ASEAN Economic Community (AEC)**: regional economic integration by end of 2015. AEC envisages a) single market and production base b) high competitive economic region – integrated into global economy. ASEAN ranks as the 8th largest economy in the world, with combined GDP of USD 3 trillion.

This is a reflection of member states interdependence and will create a market of 617 million people. There will be free flow of goods, services, investments, capital and labour.

So far, there was not much activity in biologics except begin to work on harmonization of vaccines regulation. Malaysia is chairman of EAC in 2015, to encourage countries to develop or adopt the WHO Guidelines on SBPs will be an important agenda.
The WHO biosimilar guideline, aimed at providing a consistent scientific standard, is the model for many newly developed biosimilar pathways.

Note: ASEAN Countries
1. Philippines 2014
2. Indonesia (draft)
3. Thailand (draft)
4. Cambodia
5. Laos PDR
6. Vietnam
7. Brunei DS
Challenges with “bio-copies”: Gaps in Product Quality and Potential Safety


How Bio-questionable are the Different Recombinant Human Erythropoietin Copy Products in Thailand?

Liem Andhyk Halim • Vera Brinks • Wim Jiskoot • Stefan Romeijn • Kearniz Praditpomsilpa • Anunchai Assawamakin • Huub Schellekens

Published online 21 Nov 2013 Pharma Research

High prevalence of PRCA in Thailand associated with increase in number of rhEPO copy products approved based on generic regulatory pathway:
The conclusion of the study in 2008: i) There were impurities (or diversities in biochemical composition) among “biosimilars” in Thailand ii) The clinical impact of these findings to efficacies and drug safety remained unclear.

In 2013, the study tested host cell impurities, endotoxin etc. Some of the tested copy products differ significantly from originator Epogen, there were gaps in product quality and potential safety, until then the copy products remain bio-questionable.

Since January 2014, all registered EPO had been ask to be reevaluated with RMP, firstly Quality-wise (18 registered products)
These resolutions constitute important milestones for patient worldwide, as they aim to support NRAs particularly in developing countries, to **strengthen their capacity** in the area of the regulation of Biotherapeutic products (BPs), including (SBPs).

Countries to **implement regulatory frameworks** for SBPs (WHO guidelines) that promote equitable access to **quality, safe, effective and affordable** medical products.

Encourage and promote cooperation and exchange of information among MS in relation to BPs and SBPs whilst **working towards regulatory convergence** supporting global development of biosimilars to ensure the implementation of high regulatory standards.

Strengthen regulatory functions, especially **clinical evaluation** and **pharmacovigilance**, including proactive collection of PV data.
Healthcare Need (4th Pillar)

- Next thing in the evolution of medicine due to progress in immunology, cell & molecular biology – bridged the gulf between “bench & bedside”
- Rebirth – concept of “advanced cellular therapy” – new treatment opportunities for diseases, regenerative – unmet medical needs and has potential impact. esp. in diseases with limited therapeutic options currently.
- Cellular therapy fits within the large and even more diverse regenerative medicines (RM). RM uses a combination of several technological approaches – which may include, but not limited to, the use of soluble molecules, gene therapy, stem cells transplantation, tissue engineering and the reprogramming of cells and tissue types

Source: Mason C et al 2011 Future Medicine
Paradigm Shift: ……

genes and manipulated cells as products.

Aspirin

Filgrastim

mAb

Eucaryotic cell

Delicate living matter with a metabolism and energy needs ….
Sales of Drugs Act 1952
Control Of Drugs and Cosmetic Regulations CDCR 1984
- CGTPs regulated: as biological products (Quality, Efficacy, Safety)
Scope CGTPs: What are they?

- Somatic cell therapy products
  - Stem cells (Haemopoetic, mesenchymal, chondrocytes, myoblasts, keratinocytes, pancreatic islets, iPS)

- Cancer vaccines and immunotherapies
  - Dendritic cells, gene-engineered T cells, lymphocyte based therapies, cancer cell based therapies, peptides

- Tissue engineered products

- Gene therapy products

Genetically modified cells
Regulatory Framework & Guiding Principles

- Public health protection and patient safety
- The framework based on science & international best practices modeled from benchmarked regulatory authorities (established internationally).
- Integrated Approach/Jurisdictions
- Consistent and integrated with existing legislative framework
- Tiered risk based approach – level of regulation commensurate to the degree risk posed by product characteristic
- Intended to provide greater flexibility to encourage innovation.
- Do not impose unnecessary regulatory burdens or inhibits progress

Therefore:

- Ministry of Health (MOH – Medical Development & Medical Practice Divisions) to regulate the clinical use/procedures of all CGTPs
- Medical Device Authority, MOH responsible for devices
- NPCB to regulate quality, safety and efficacy of high risk CGTPs like other biologics under CDCR 1984.
CLASS I & II CTP: tiered-risk

CLASS I: FOUR criteria for lower risk products: The cells and tissue are

1. Not more than minimal manipulation (not activated, expanded *ex vivo*, or *genetically modified*)
2. Intended for homologous clinical use
3. Not combined with another article (eg. a drug or device)
4. Primary function in the recipient is not systemic effect or dependent upon the metabolic activity of the cells. (except for autologous or family related allogeneic* use)

THEN ....

- No pre-market approval (IND/BLA not required)
- Comply with tissue rule. (**Good Tissue Practices** are required)
- Site/facility licensure and listing products.

CLASS II: IF a cell therapy product does not meet one or more of the four major criteria defining minimally manipulated products

THEN .....  

- Regulated through registration (IND), clinical trial pathway
- GMPs AND GTPs required
- Demonstration of **safety and efficacy**.
Schematic diagram of proposed regulatory pathway

<table>
<thead>
<tr>
<th>General</th>
<th>Requirements of GTP, GMP, GCP for Cell and Gene Therapy</th>
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<tbody>
<tr>
<td>Class</td>
<td>I</td>
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<tr>
<td></td>
<td>Novel Cell and Gene Therapies</td>
</tr>
<tr>
<td>Pre-Market Review/Approval</td>
<td>Cell Products Exempted from Marketing Authorization</td>
</tr>
<tr>
<td>Marketing Authorization</td>
<td>Monograph/product profiling</td>
</tr>
<tr>
<td>Post Marketing</td>
<td>Routine Pharmacovigilance</td>
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</table>
Gene therapies are novel and complex products that can offer unique challenges in product development. However, recent history of gene therapy has been a mixture of promise and disappointment, hence it has not yet found a place in the mainstream of therapeutics, particular after some well publicized setbacks that deal with the safety and efficacy aspects of the products.

Besides there are still many technical issues to be addressed. There are still numerous guidelines in development as knowledge and experience evolve in this field. Because gene therapy products are being developed around the world ICH via the ICH Gene Therapy Discussion Group are actively engaged in development of new guidelines, three of which are available on the ICH website (http://www.ich.org/consideration-documents.html - on inadvertent germline integration, oncolytic viruses, and virus and vector shedding.)

Malaysian regulatory authority decided to follow the path laid down by the European Medicines Agency (EMA) and United States Food and Drug Administration (USFDA) and adopted their guidelines fully.

Hence, as for now it is decided that application for registration for gene therapy products will only be accepted if the product had already been approved by the one of the reference regulatory agencies eg. USFDA, EMA or Health Canada.
In a nutshell ….. many

- Biosimilars are a reality and provide a high quality and cost effective access to critical therapies – however “you have to do them right“

- Eventually, **biosimilars will bring down the cost** and create economic space for new biologics. Taking advantage of advances in technology, some of the products may even be better than the original, brand-name drug. **With biosimilars the world of generics and innovation merge to generate a new breed of products entirely**

- There is **genuine potential** in stem cells, but converting that potential to a product is not trivial. Science, even with broad-band, takes time

- The regulations fundamentally **support good clinical care by increasing safety and control**, and enable good science by improving the quality and reliability of data. These outcomes are in everyone’s interest.

- Regulations for CGTPs are still evolving, as befits a relatively young, developing field, and they merit careful attention. Ensuring **regulatory position adequately reflects scientific advances/expertise** is key

- Share and leverage experience learned in International workshops/conferences eg. WHO implementation workshops, CASSS forums, APEC etc. **Implement existing WHO guidelines on SBPs** and subsequent updates in full. (ICDRA, Rio 2014) recommendation for ASEAN countries.
Thank you for your kind attention