WHO Collaborating Centre for Regulatory Pharmaceuticals

# EVOLVING REGULATORY LANDSCAPE AND CHALLENGES IN EVALUATING BIOSIMILARS

**1ST National Bio-Therapeutic Congress**
**Petaling Jaya Hilton**
**22nd November 2014**


**Arpah Abas**

**Head Of Biotech Section**

**Product Registration Centre**

**National Pharmaceutical Control Bureau**

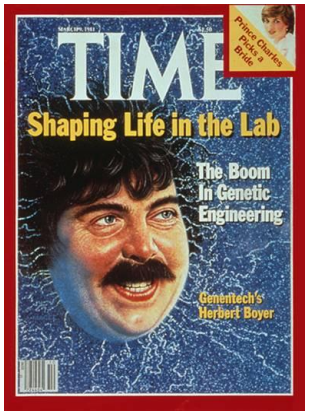
**arpah@bpfk.gov.my**

# OUTLINE:

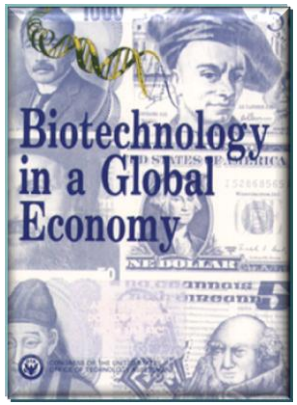
- **The beginning …….**
- **Protein Science & Therapeutics**
- **Biosimilar paradigm**
- **Worldwide biosimilar landscape**
- **mAbs & regulatory challenges**
- **Contentious issues**
- **Way Forward**

# BIOTECH - where are we now ?






H.Boyer " godfather of modern biotech"




*Source: IMS Health*

- Biologics were introduced in the market in the early 80's, setting new milestones, life-saving medical treatments for plethora of serious incurable diseases and offering improvements in **quality of life** of patients.
- The biologic medicines market is expected to grow to $190-200 billion by 2015, with biosimilars a small but growing proportion of $ 2-2.5 billion. The statistics are eye-opening – by 2015, 8 of top 10 drugs will be biologics.
- Next 5 years – changing industry dynamics …..
- "Charmed life" – facing a new reality (patent expiry, loss of exclusivity, competition from biosimilars, crowded therapy, price scrutiny, safety concerns ….)

Steve Job **" the biggest innovations of the 21st century will be at the intersection of biology and technology "**

**Biotechnology** therefore, is a **SUCCESS STORY**

# The First Article Describing The Issues When Patents Of Biologics Will Expire

Opinion TRENDS in Pharmacological Sciences Vol.23 No.3 March 2002 119

## 'Biogenerics': the off-patent biotech products

Huub Schellekens and Jean-Charles Ryff

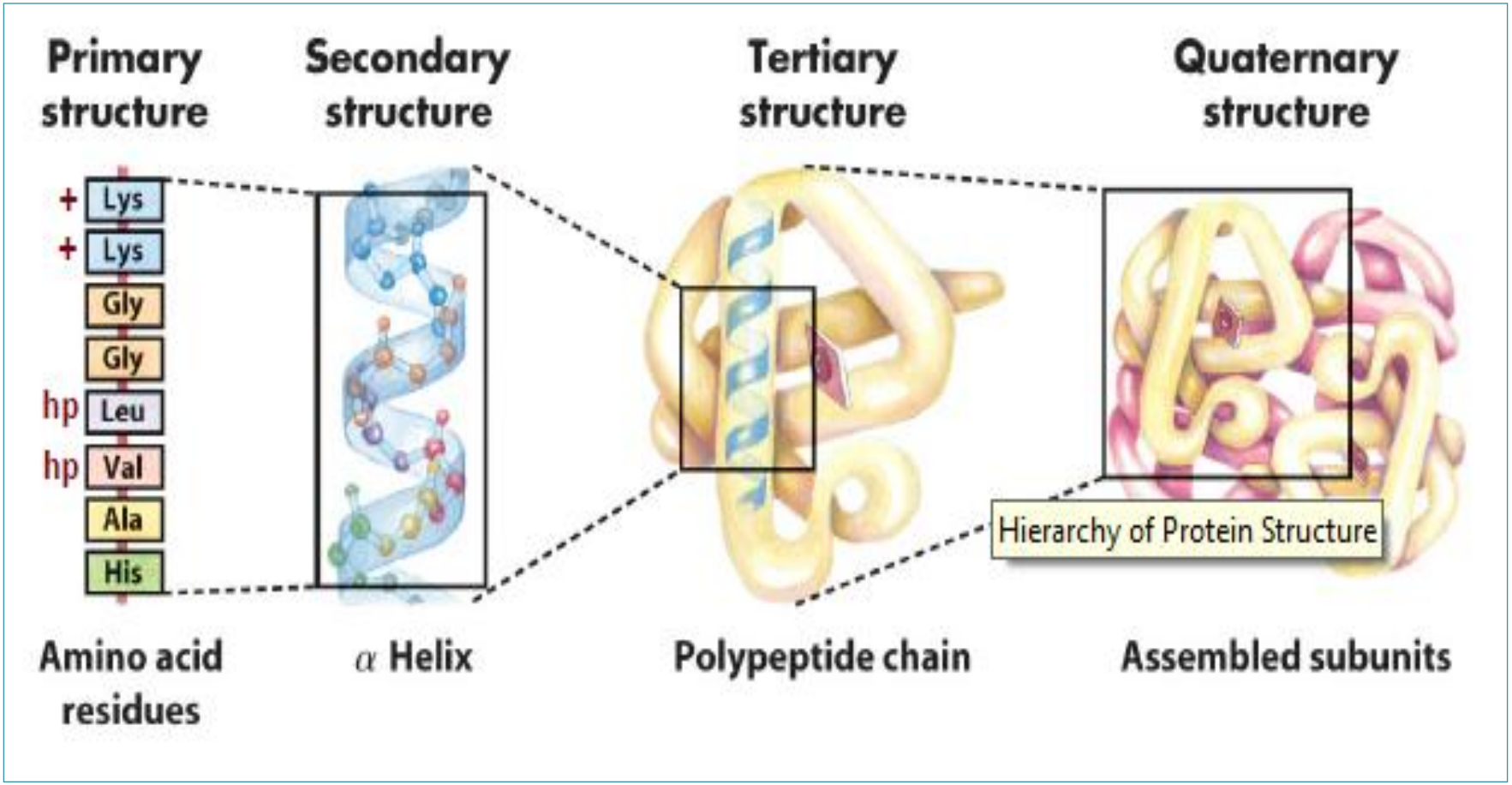
**The first patents of biopharmaceuticals derived from recombinant DNA will expire shortly, which raises the possibility of marketing generic products ('biogenerics') with limited documentation, similar to that which occurs with conventional pharmaceuticals. We propose the term off-patent biotechnological products (OPBPs) as an alternative to biogenerics when describing such products. It is questionable whether the majority of OPBPs can be classified as similar to the innovator products, considering the size and complexity of the molecules and the many factors that influence biological activity. There are three classes of OPBPs, each of which needs to meet different regulatory demands when seeking marketing authorization.**

study in volunteers that compares pharmacokinetics and/or pharmacodynamics. The question is whether such limited information is sufficient to ensure the efficacy and safety of the majority of biopharmaceuticals that are derived from recombinant DNA.

### Biopharmaceuticals

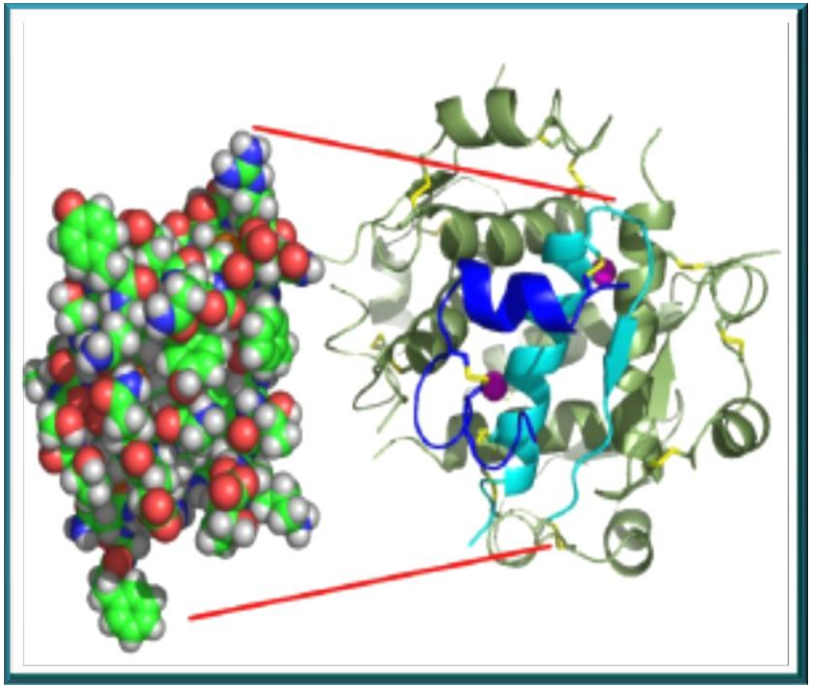
Most biopharmaceuticals are large, complex molecules that, for several reasons, are heterogeneous. Some heterogeneity is caused by the combination of vector and host cell used to produce the biopharmaceutical, and includes clipping (premature termination of translation) and differences in the sites and amount of glycosylation [1,2]. Protein modification might occur during production, depending on the fermentation and cell culture conditions [3]. The extraction and purification procedures can also add to the heterogeneity, as can process-related impurities and the introduction of contaminants that might appear in the final product [4–6]. Lastly, formulation and storage conditions might alter the biological properties and, thus, the response, as a result of physicochemical or physical

# Protein Structure ⇒ Protein Therapeutics

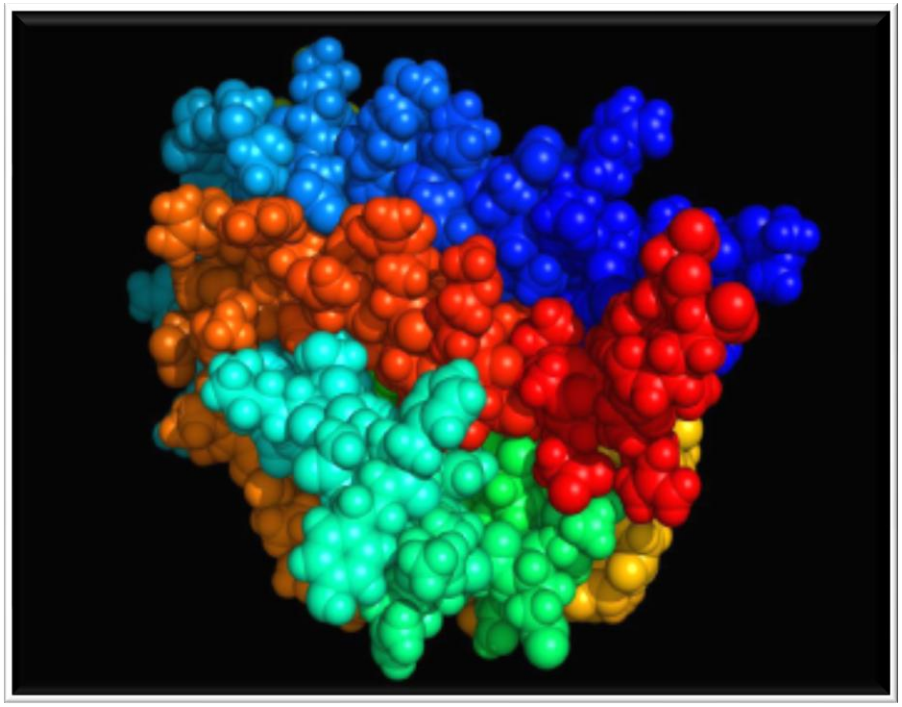


# Biologics - Complexity increases with size


(180Da)

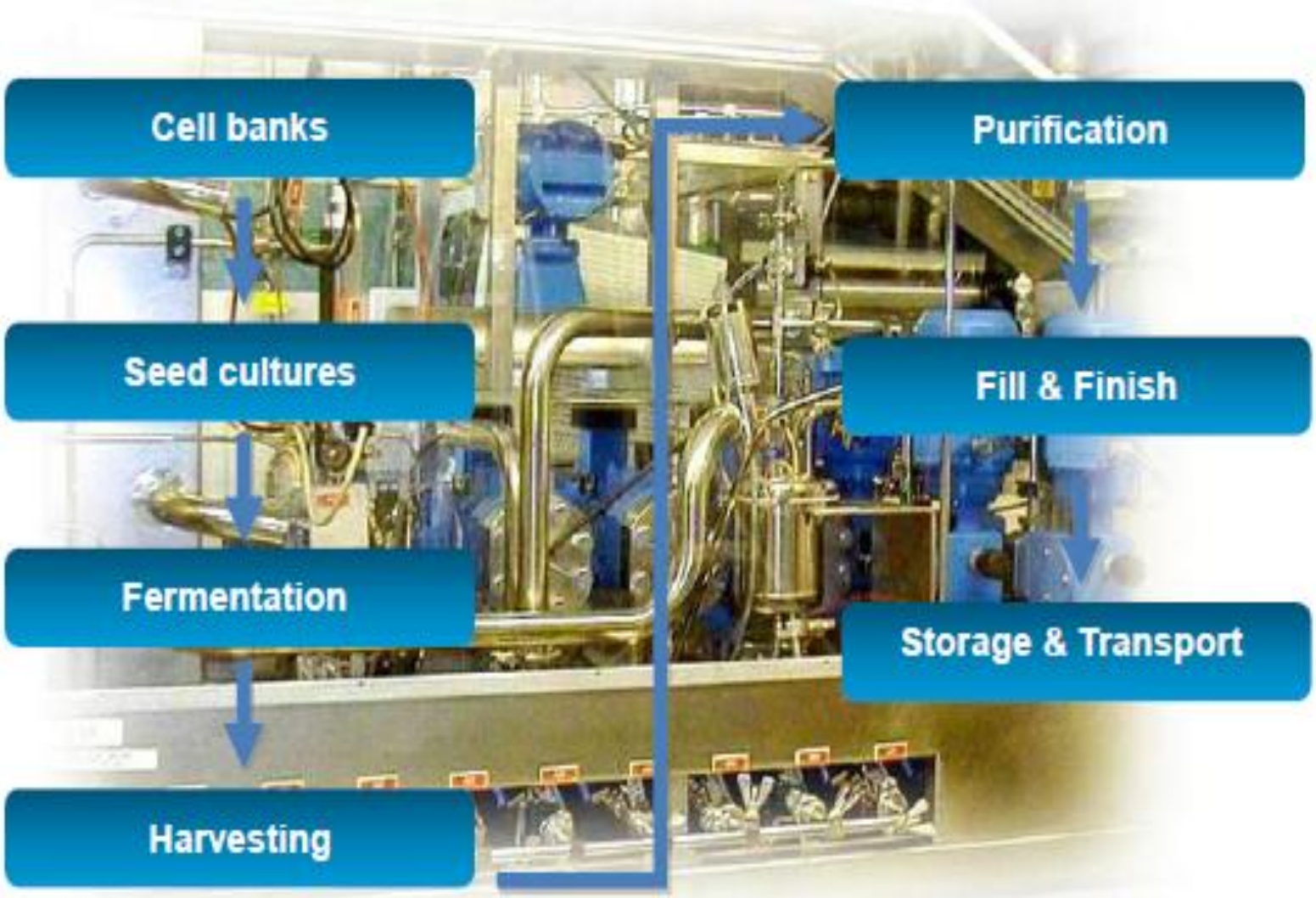


Insulin (5,000 Da)



EPO(34,000Da)

# Manufacturing Complexities
# A challenge from production to testing



# What is a Biosimilar?

- 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 t**elling: 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.

- Biosimilars are not new medicines from an efficacy perspective, they do not bring any new clinical benefits.

# Why Biosimilars Needed & Why Now? …..

- Growing ageing population and an increase in chronic diseases, rendering the rise in global demand for effective and safe biologics inevitable.

- **Cost containment**

  Inordinate impact of the soaring costs of biologics on the drug budgets of the healthcare system – limiting access to patients.

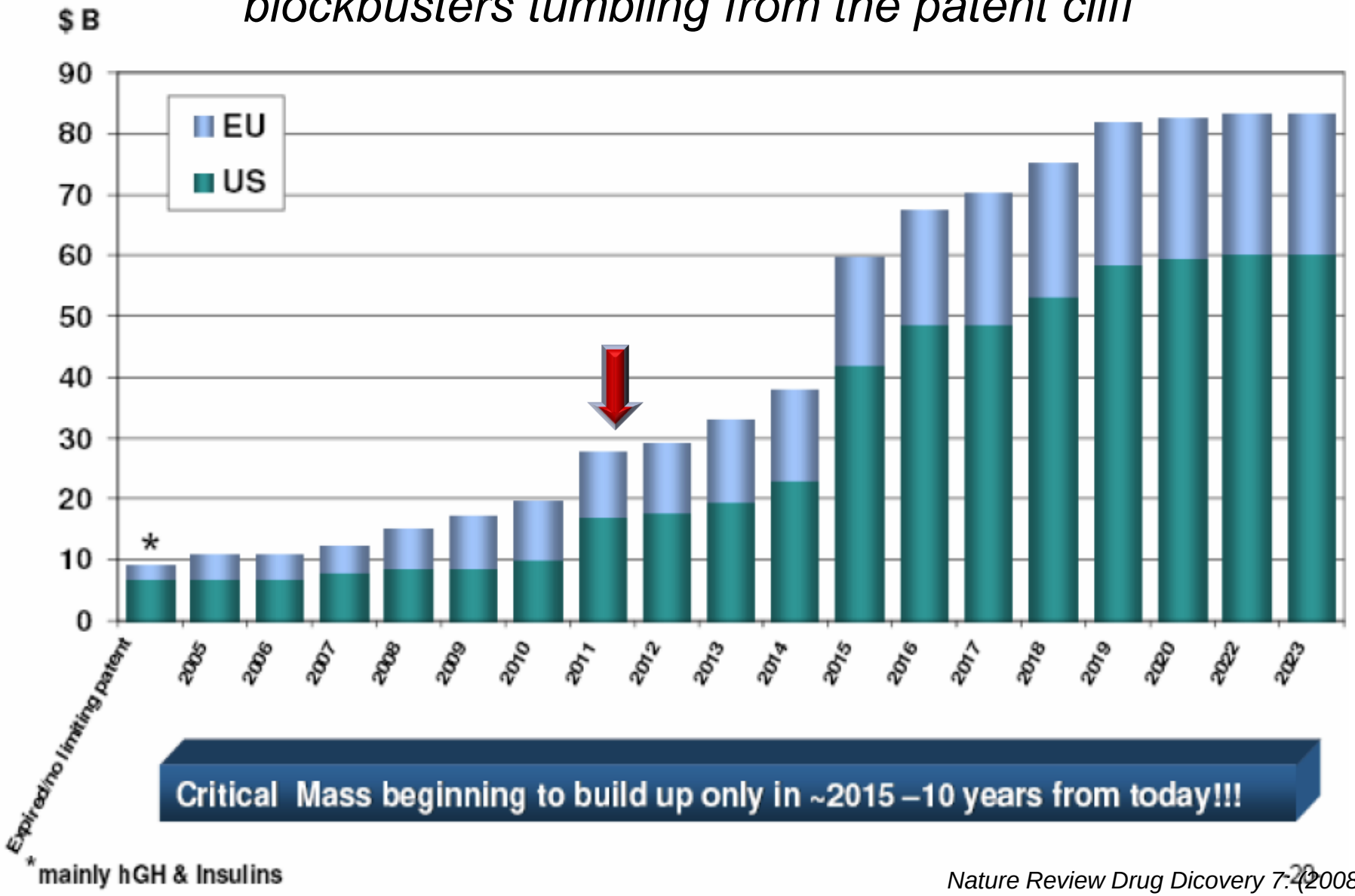
- **The ‘ patent cliff ’**

  The imminent patent expiration of many biotechnological products opening a new market sector. The sheer volume of expiries beyond 2012 is unprecedented.

Malaysia’s Bio-economy Transformation Program (BTP) includes 2 Entry Point Projects (EPP) i.e Biosimilars and Regenerative Medicines.

# Patent Expiries – the Opportunity Driver

*'blockbusters tumbling from the patent cliff'*




*Nature Review Drug Dicovery 7:(2008)*

# Generics Pathway …..

" Same (Identity) " = " Identical (Identity) "

**Pharmaceutical Equivalence** + **Bioequivalence** = **Therapeutic Equivalence**

Same active ingredients, dosage form, administration route & strength

Same rate & extent of absorbance & availbility at site (80-125%)

Interchangeability Rating

" Same" structure = "Same" function

Source: Kozlowski M.D

# Biosimilars: Paradigm shift

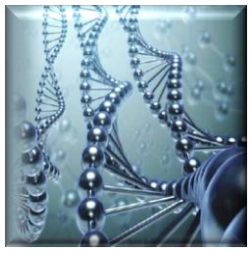
## *(equivalent, same, different, similar !! ! )*

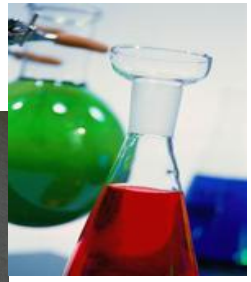
- **Complete product & process development of the biosimilar product (Know your protein)**

**Scientific basis of approval:**

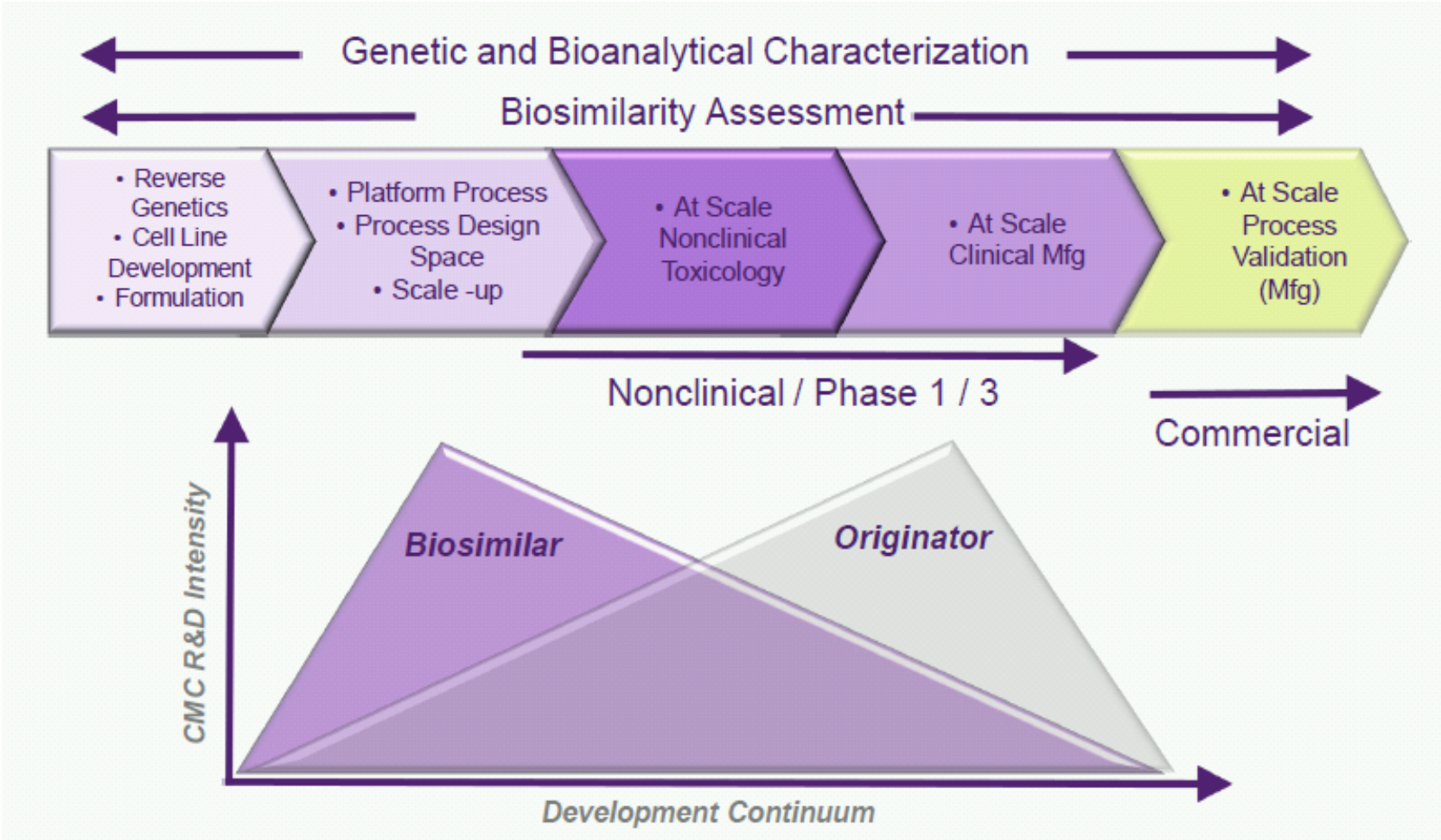
- **Similar ≠ Same**
  - Everything else follows from this:
  - Define and characterize the reference product
  - Confirm **comparability** of the biosimilar product with the reference product

  - Quality/CMC (characterization), non-clinical (PK/PD, repeat dose toxicity, local tolerance), clinical trials (PK/PD, efficacy & safety studies)
  - Risk Management Plan & robust pharmacovigilance



# Target-directed development of biosimilars results in a front-loaded CMC effort as compared to originator.



# The target directed approach for innovative biopharmaceutical & for biosimilar

| | New biopharmaceutical | Biosimilar |
|---|---|---|
| **Define target** | Quality, safety, efficacy<br>Performance: robust process, low COGS<br>Facility-fit | |
| | Comparability to previous clinical product | Comparability to originator product |
| **Process development** | If applicable, start from platform process; rational DoE<br>Extensive product quality analytics | |
| | **2-step development**<br>(early phase, late-phase) → more time to gain experience with cell line/ product | **1-step development**<br>→ most efficient capacity use<br>increased challenge: rarely platform process useable, tight targets (e.g. glycosylation) to combine with high yield |
| **Characteriza-tion** | Extensive set of state-of-the-art analytical methods (phys.-chem., biological) | |
| | Growing knowledge of observed structure-function relationships | Deep understanding of all potential structure-function relations |
| | Pre-clinics – Ph I – Ph II – Ph III | Pre-clinics – Ph I – Ph III<br>High chance of success |

# Challenges with “biocopies” : Gaps in Product Quality and Potential Safety

**Biosimilar rhuman erythropoeitin induces production of neutralising antibodies**. International Society of Nephology, 23 March 2011 *(Thai 1/500, International 1/3000)*

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

Published online 21 Nov 2013 Pharma Research

Liem Andhyk Halim • Vera Brinks • Wim Jiskoot • Stefan Romeijn • Kearkiat Praditpornsilpa • Anunchai Assawamakin • Huub Schellekens

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)

# WHA 67.21: Access to biotherapeutic products (BPs) including similar biotherapeutic products (SBPs) and ensuring quality, safety and efficacy – 24 May 2014

- 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 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.

# Biosimilar Regulation/Guideline: Global Development

2005 2006 2007 2008 2009 2010 2011 2012

EU

TUR

MYS

TWN

AUS

KOR

JPN

SIN

WHO

CAN

ZAF

BRA

SAU

The WHO biosimilar guideline, aimed at providing a consistent scientific standard, is the model for many newly developed biosimilar pathways

ARG

MEX

CUB

IRI

IND

PER

USA *(BPCI Act)* (draft)

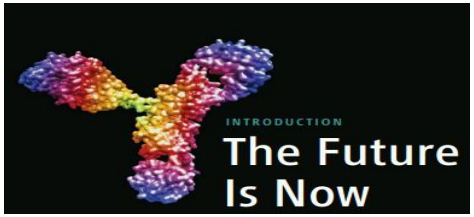
COL (draft)

JOR (draft)

THA (draft)

IDN (draft)

# Monoclonal Antibodies (mAbs)



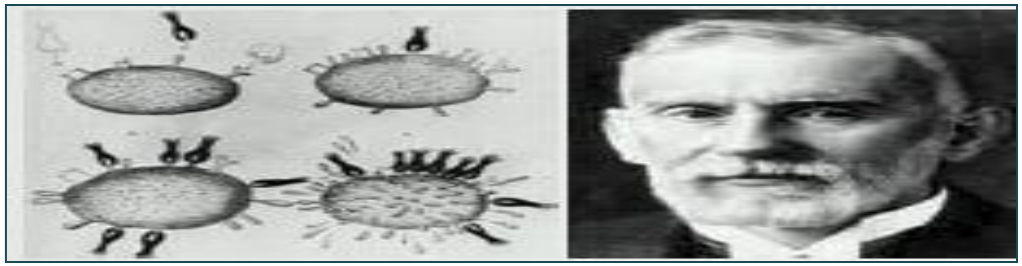

- **1986 Paul Ehrlich (1908 nobel prize): “side chain theory”**

  More than 100 years since Paul Ehrlich coined “magische Kugel” or “magic bullet” scientists have been striving to develop targeted therapies for diseases ranging from cancer to Crohn’s disease.

- Today, mAbs have emerged as long-sought vehicles for the targeted delivery of potent chemotherapeutic agents and as powerful tools to manipulate anticancer immune responses. More than 30 mAbs have been approved by USFDA, and many more candidates are in clinical trial. Antibody therapeutics are now multibillion-dollar industry.

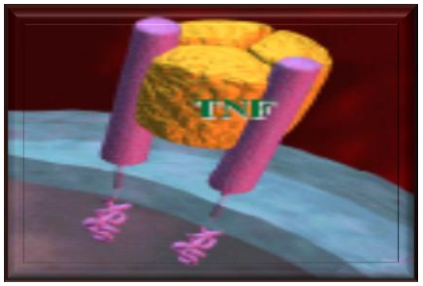
- mAbs represents the largest and most rapidly growing class of biological medicines on the global market. Antibody therapeutics are now multibillion-dollar industry.

- Antibody therapeutics are not limited to mAbs alone anymore; antibodies specific for more than one target (bispecific antibodies) and antibody-drug conjugates (ADC) – to generate therapeutics that are more specific, more stable and more effective.



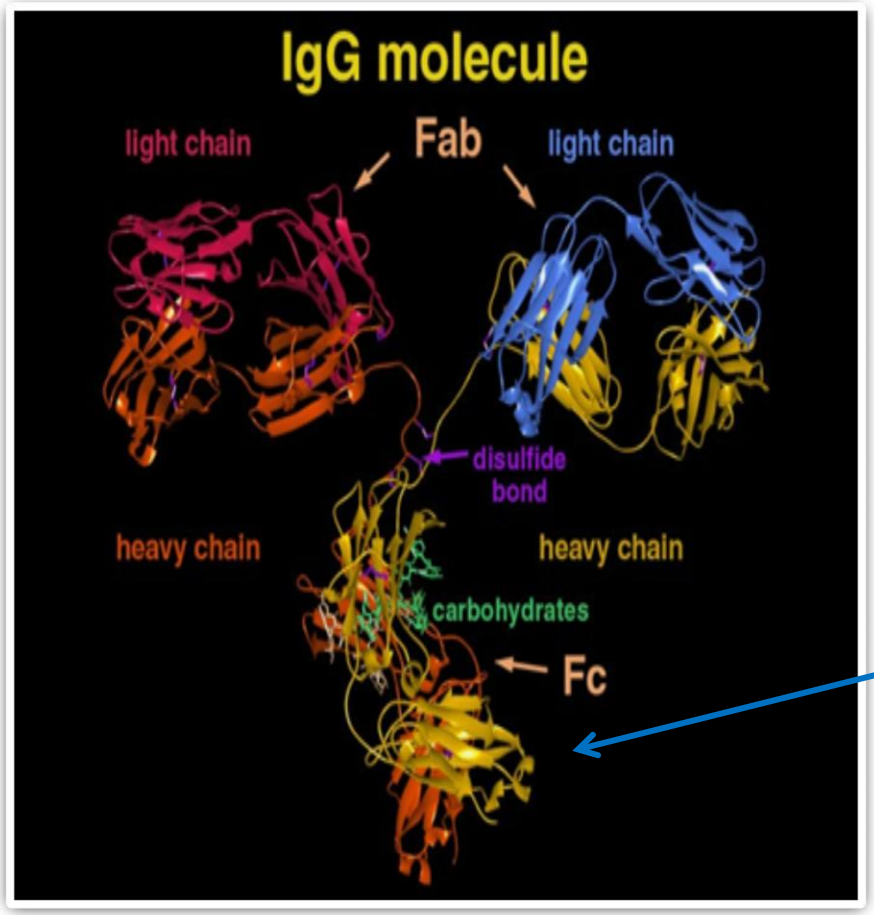
# Monoclonal Antibodies (mAbs)

The next wave of Biosimilars …….




**Cell surface receptor**
**'exquisite specificity'**

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



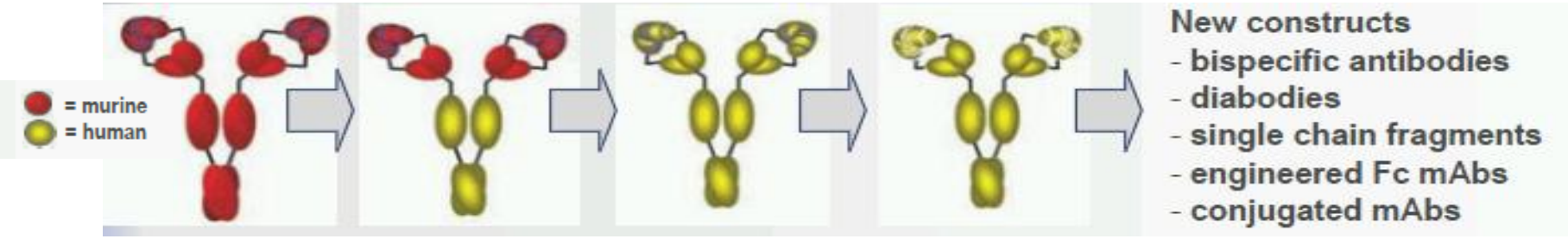

**150,000 Da**

**Safety and Efficacy is dependent on correct structure or a defined mixture of correct structures**

**Post-translational modifications and Complex foldings of protein**

**are determined by amino acid sequence, by cell lines and by manufacturing conditions**

# Evolution of Monoclonal Antibodies ("mAbs")




| **Murine mAb** | **Chimeric mAb** | **Humanised mAb** | **Fully human mAb** |
|---|---|---|---|
| - omab - | -iximab - | - zumab - | - umab - |
| Arcitumomab | Infliximab | Trastuzumab | Adalimumab |
| (1996) | (1999) | (2000) | (2003) |

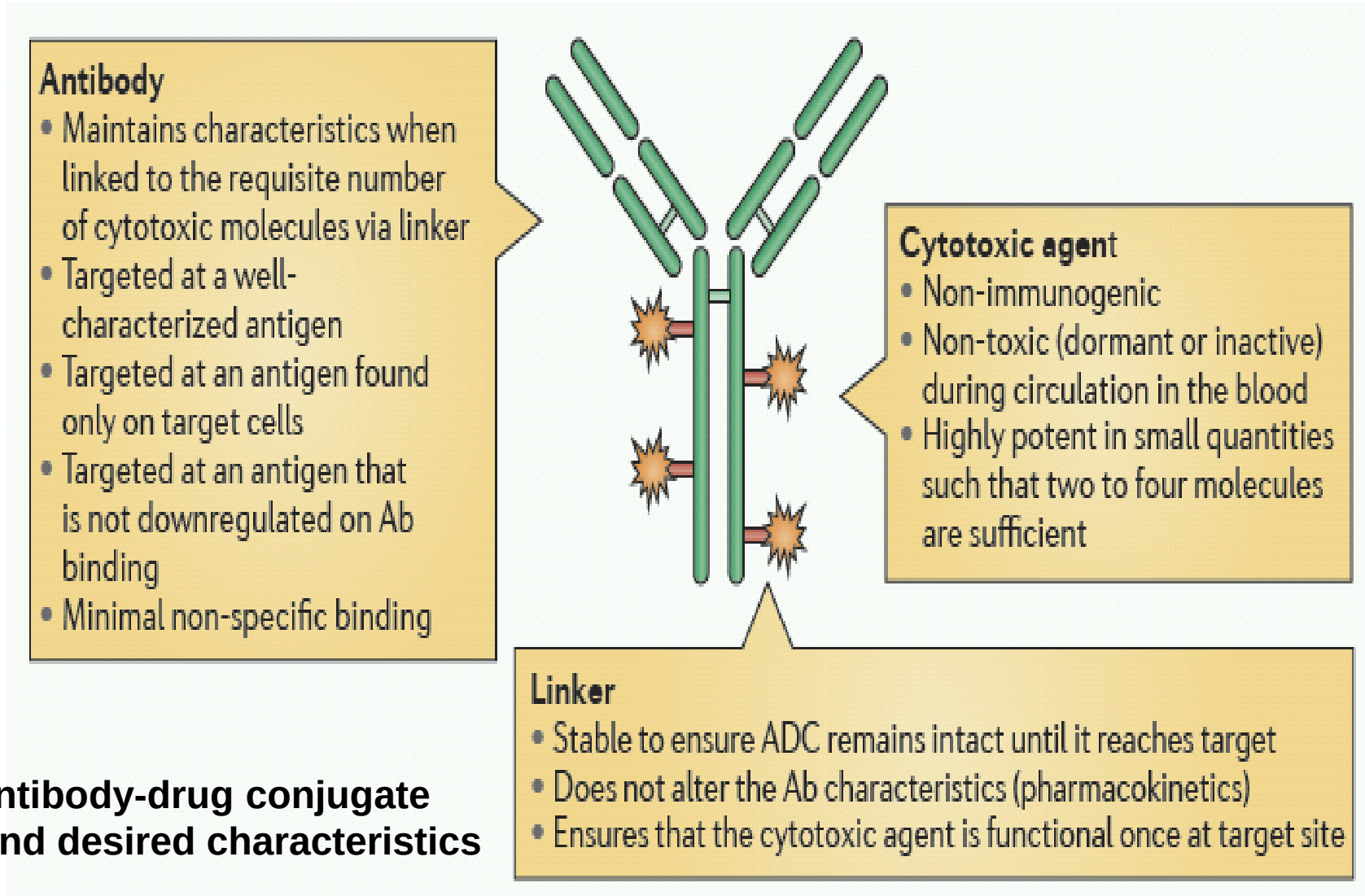
**Immunogenicity**

mAbs special considerations:

- highly immunogenic and complex engineered biotherapeutics
- MOAs are in many cases extremely hard to identify or understand
- potential for more micro-herteogenic-related variants eg. amino acid modifications, aggregation or N- or C- terminal variants : extensive analyses using state-of-the-art and orthogonal technologies

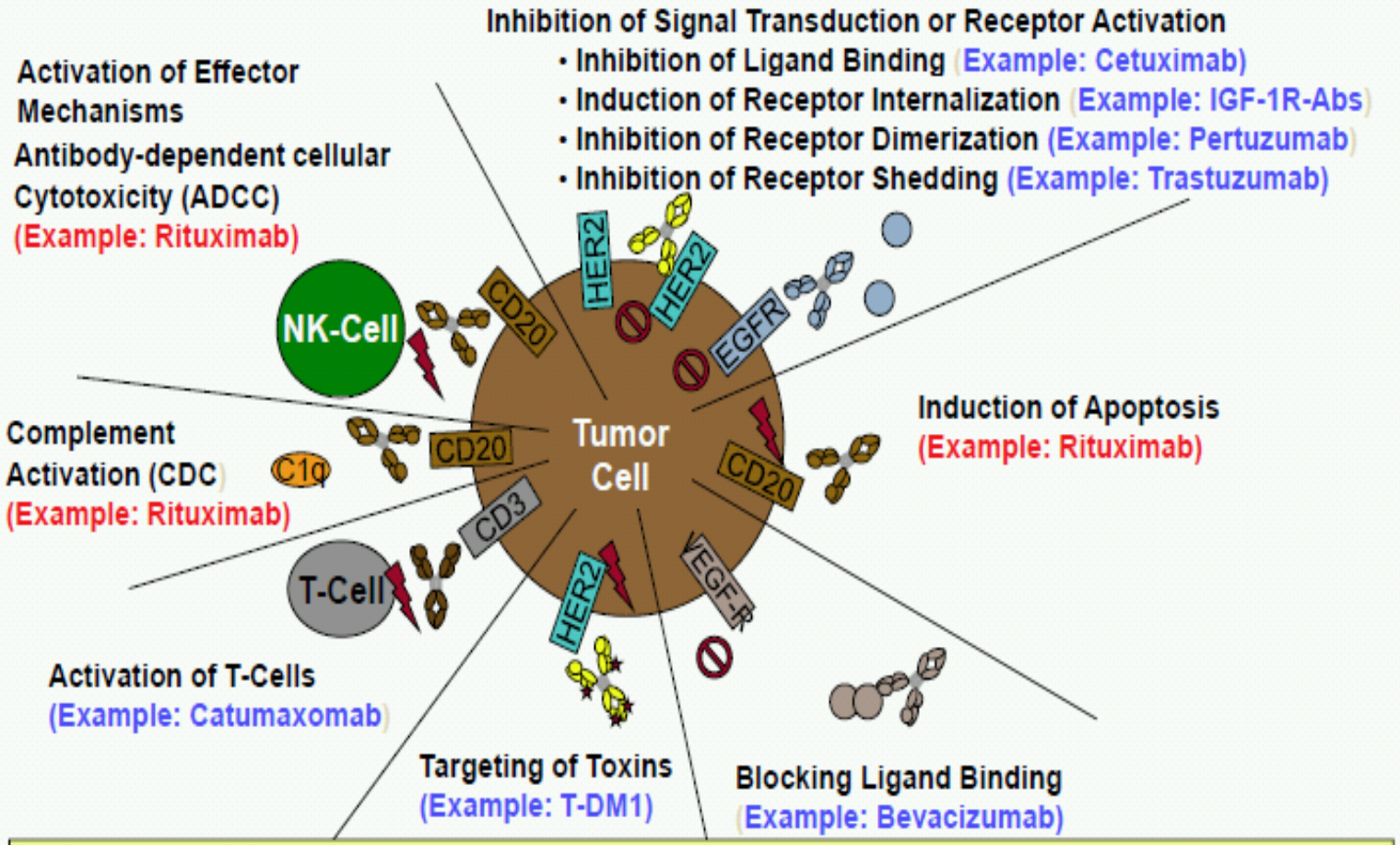
# Maturing antibody-drug conjugate pipeline hits 30

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




**Antibody-drug conjugate and desired characteristics**

# The mechanism of action of mAb is complex and may involve contributions from multiple mechanisms




The *in-vivo* net contribution of different modes of action described for one mAb is often incompletely understood and may also be different in different indications.

*Modified from: Hasmann et al, 2009* Amgen

# FIRST-IN-MAN TRIAL (MARCH 2006)
## Te Genero and TGN 1412

# TGN 1412

(also known as CD28-SuperMAB)

- Humanized mAb binding to, and strong agonist for the CD 28 receptor on human T cells
- Intended for treatment of B cell chronic lymphocytic leukemia (B-CLL)
- Preclinical safety studies apparently showed no serious side effects (in primates) at a dose of 50 mg/kg/day over 4 weeks
- First-in-man dose 0.1 mg/kg
- Catastrophic organ failure soon after administration of the product


BBC NEWS

UK version | International version | About the versions | Low graphics

Last Updated: Wednesday, 15 March 2006, 13:37 GMT

E-mail this to a friend | Printable version

**Drugs trial men 'seriously ill'**

**Six men are still in intensive care after being taken ill during a clinical drugs test in north-west London.**

The healthy volunteers were trying an anti-inflammatory drug at a private research unit based at Northwick Park Hospital when they suffered a reaction.



The six are being treated at Northwick Park hospital


# Lessons from …….
# TGN 1412 case

- Cynomolgus monkey as ‘relevant’ model
- No surrogate model (substructure of CD28)

➢ Acute life-threatening **(“cytokine storm”)** side effects in all healthy volunteers.

- Predictivity in animal data not 100% (estimates 70-80%)
- Animal studies offer little or no value in predicting immunogenicity in human.

➢ Nevertheless non-clinical data of highest importance

➢ It should clearly said that even with TGN 1412 incident, mAbs have not proven to be “high risk” molecule *per se*


# Immunogenicity – A unique Safety Issue For Biotech Medicines



- Immunogenicity cannot be predicted with pre-clinical or non-human studies
- A risk-based approach/strategy is advocated
- A risk profile should be formulated, and a battery of clinical and non-clinical tests/assays should be adopted that appropriately reflects level of risk.
- A risk-based bioanalytical strategy for the assessment of antibody immune responses against biological drugs

*Ref: Shankar G, Pendley.C, Stein K.E (2007) Nat Biotechnol, 25(5):555-56*

- Overall, based on experience 10-year after EU regulation, the regulatory standard has been validated as **suitably cautious** by the absence of observed differences in clinically relevant immunogenicity, between biosimilar and innovator pdts post-authorisation

*Ref: Paul D Chamberlin: Multidisciplinary approach to evaluating immunogenicity of biosimilars 10 years European experience Biosimilars 2014:4 23-43*

# Typical Pitfalls in Application for MA of Biosimilar in Malaysia



- Generally paucity of data on development, manufacture and control for both DS and DP and validation of infectious agents elimination. No comparability studies.
- Batch-to-batch consistency not demonstrated
- Biosimilarity not addressed in terms of formulation, specifications, stability.
- Quality control: Inadequate assay formats and incomplete assay validation.
- Non comprehensive and inadequate characterisation
- Inadequate clinical studies, poor designs (non-comparative, observational, small number)
- Safety: lack of risk management strategies, incomplete PSUR
- Lack of information on handling and storage

# BIOSIMILARS REGISTERED IN MALAYSIA


| INN | Product brandname | Company | Indication | RBP (company) | Date Approved |
|---|---|---|---|---|---|
| Somatropin | SciTropin | Sandoz | Growth disturbance in children & Growth hormone deficiency in adults | Genotropin (Pfizer) | August 2010 |
| Epoetin alfa | Binocrit | Sandoz | Renal anemia, cancer & predonation preparation for autologous and allogeneic blood transfusion | Eprex (J&J) | March 2011 |
| Filgrastim | Zarzio | Sandoz | Cancer, HSCT & chronic neutropenia | Neupogen (Roche) | March 2012 |
| Filgrastim | Nivestim | Hospira | Cancer, HSCT & chronic neutropenia | Neupogen (Roche) | August 2013 |
| recombinant Human Insulin | Insugen | Biocon | Diabetes mellitus | Actrapid / Insulatard / Mixtard (Novo Nordisk) | January 2014 |

The Malaysian biologic manufacturing sector has grown steadily, fueled by government support and incentives to nurture biologic manufacturing talents and business opportunitie

# Biosimilar Insulin - Biocon (Insugens®)

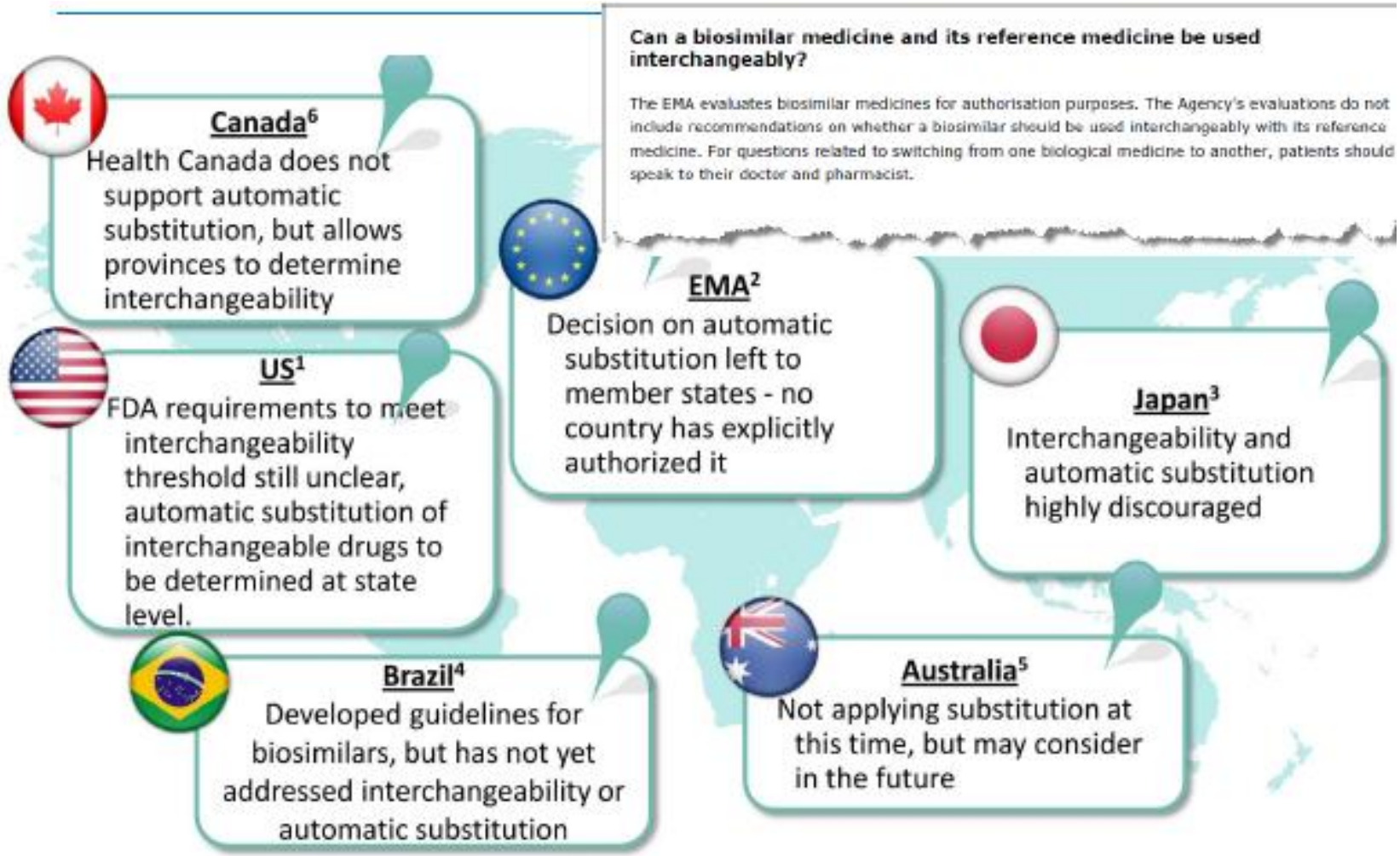
- Approved with conditions - Implementation of RMP
  - Post market surveillance, a registry of Insugen in Malaysia, to submit PBRER.
- Biocon Ltd – biopharmaceutical manufacturing and R&D facility in Bio-Xcell, a biotech park and ecosystem in Iskandar Malaysia – Johor
- In the first phase Biocon invests $161 million in facility which is to be in operation by 2015. The project also focus on R&D and production of other products at a later phase.
- Delivery devices are important facets of patients' experiences with insulin, affecting comfort, convenience, adherence and outcome. Thus, Insupen® may serve as a key market differentiator.

# Challenging issues: Interchangeability/Substitution



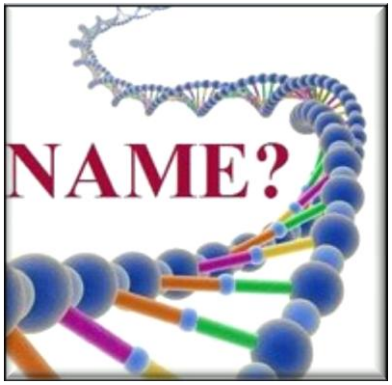
- For a designation of interchangeable, applicant must provide evidence that, in any given patient, the biosimilar product yields the same clinical result as the comparator and that it presents no risk to safety or efficacy if the patient alternates or is switched between products.
- No automatic substitution. Repeated substitution will prevent accurate pharmacovigilance (PV).
- INN should not be relied upon as the only means of product identification, nor as the sole indicator of product interchangeability.
- Need a rigorous PV system, embrace robust tools and methods for risk-based PV to build database and enable traceability.

# Interchangeability and Automatic Substitution of Biosimilars Worldwide



# The WHO's proposed "Biological Qualifier" (BQ)

- INN is a unique generic name and is recognised globally and its public property. Intended for use in drug regulation, prescription, pharmacopoiea, labeling, scientific and literature.
- BQ = is a randomly generated four - letter code that would be printed after the international non-proprietary name (INN) of all biological products, whether branded or biosimilar.
- The draft is out for consultation until 19 September, 2014, is intended as a compromise between R&D industry's call for a separate INN for biosimilars and the generics industry's preference for biosimilars to have the same INN as the reference drug.




# Frequent concerns about biosimilars and what clinicians should know

1. **Fear of low quality/substandard of biosimilars and the uncertainties associated with the "similar but not identical" paradigm.**
2. **Safety database of biosimilars could be insufficient at the time of approval, with immunogenicity being a particular concern.**
3. **The validity of criteria in determining comparability of the efficacy between a biosimilar and the respective reference product.**
4. **Whether biosimilar should be considered interchangeable, which may result in substitution at the pharmacy level without the knowledge of the physician.**

- **Regulatory oversight and scrutiny are important to ensure the safety use of any biological. The biosimilar philosophy – based on sound science and inclusion of extensive comparability exercise provide reassurances that the biosimilar in highly similar with the respective reference product in terms of quality, safety and efficacy. Active post authorization surveillance is a key factor.**

*Ref: Weise M et al Blood, 20 December 2012 Vol.120, No. 6*

**" Science and evidence should form the foundation of decision making " – Datuk Seri Dr S Subramanian, Health Minister (FAPA)**

# Conclusion & way forward ……




- **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, ADCs are giving new life to targets. With biosimilars the world of generics and innovation merge to generate a new breed of products entirely**
- **Supporting a viable biosimilar industry is key for any government to ease the hard-pressed healthcare budgets. The development of and reliable access to safe and reasonably priced biosimilars will undoubtedly improve worldwide healthcare outcomes.**
- **Regulatory agencies around the world are at different stages of implementing biosimilar guidelines. Likewise it calls for:-**

**Awareness**

**Education**

**Alertness**

# Thank you for your attention

Similar …… yet different !!!

*Further readings:*


*1. Regulatory gudelines for biosimilars in Malaysia. Biologicals 39(2011) 339-142*

*2. The role of quality assessment in the determination of overall biosimilarity: A stimulated case study exercise. Biologicals 42(2014)128-132*

*3 . Regulations of Biologics in Malaysia. GaBI Journal Vol.3 (2014) Issue 4*


TERIMA KASIH