Assistant Professor Wisit Tangkeangsirisin, PhD, Thailand

- Assistant Professor, Faculty of Pharmacy, Silpakorn University, Thailand

GaBI Educational Workshops

23 June 2019, G Hotel, Penang, Malaysia

2nd ASEAN Educational Workshop on
REGULATORY CONSIDERATIONS FOR BIOSIMILARS

Biological/biosimilar regulatory development in the global and ASEAN community: experience from Thailand

Assistant Professor Wisit Tangkeangsirisin, PhD

23 June 2019

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GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

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Pro Pharma Communications International

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Biological/biosimilar regulatory development in the global and ASEAN community: Experience from Thailand

Wisit Tangkeangsirisin, PhD

Faculty of Pharmacy

Silpakorn University, THAILAND

The 2nd ASEAN Educational Workshop on Regulatory Considerations for Biosimilars

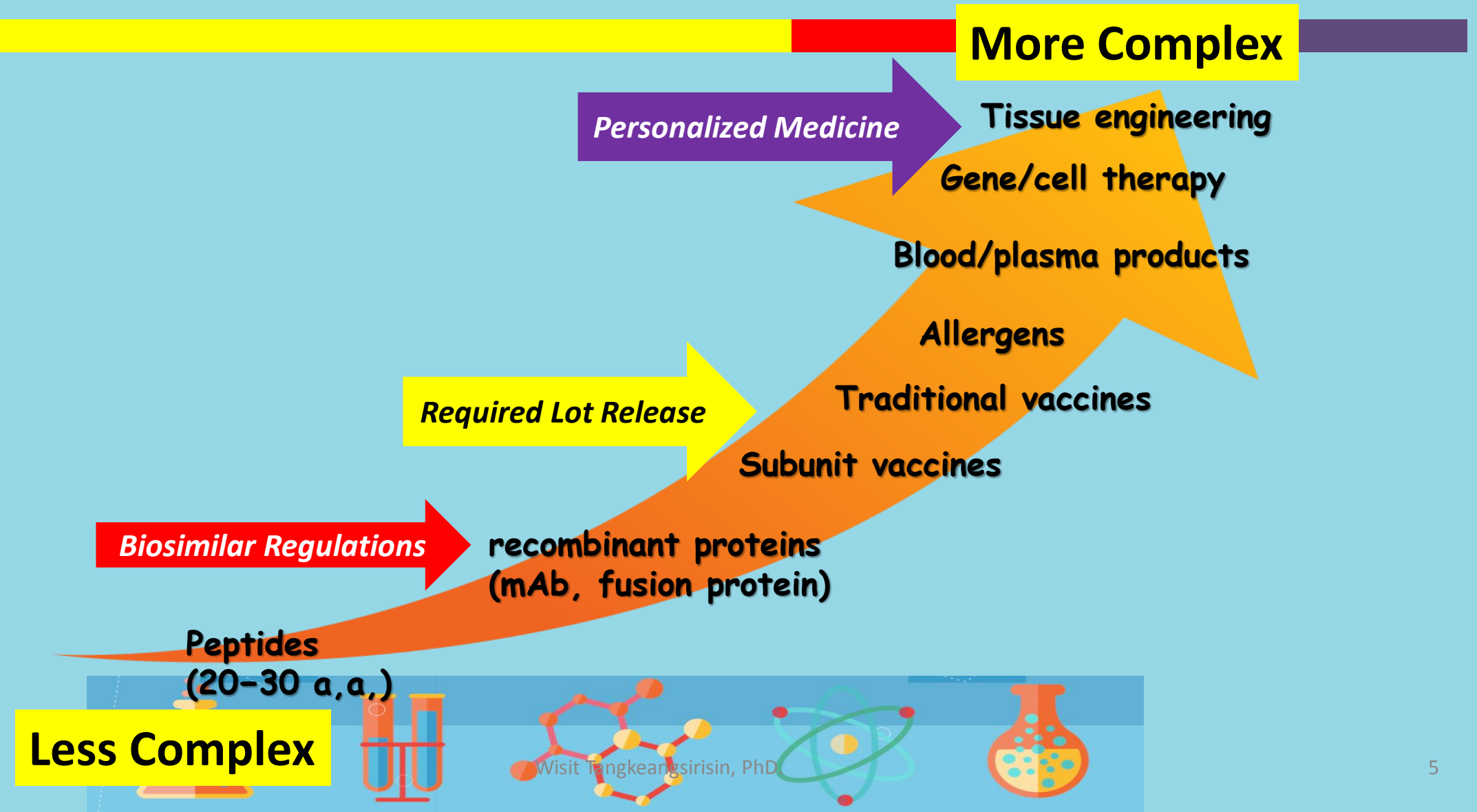
AGENDA

What is Biological/Biosimilar?

Biosimilar Approval Foundation

Biosimilar Global, ASEAN and Thailand Regulation

Heterogeneity of Biologicals



Biosimilar Definition

A biosimilar is a biological medicine **highly similar to the reference medicine**. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. (EMA)

A biosimilar is a biological product that **is highly similar to and has no clinically meaningful differences** from an existing FDA-approved reference product. (USFDA)

Which biologicals are in the scope of Biosimilar?

~~Vaccines~~

~~Blood Products~~

Recombinant Proteins

Monoclonal Antibodies

~~Transgenic cells/ Cell therapy~~

Biopharmaceuticals
(Recombinant Therapeutic Proteins)

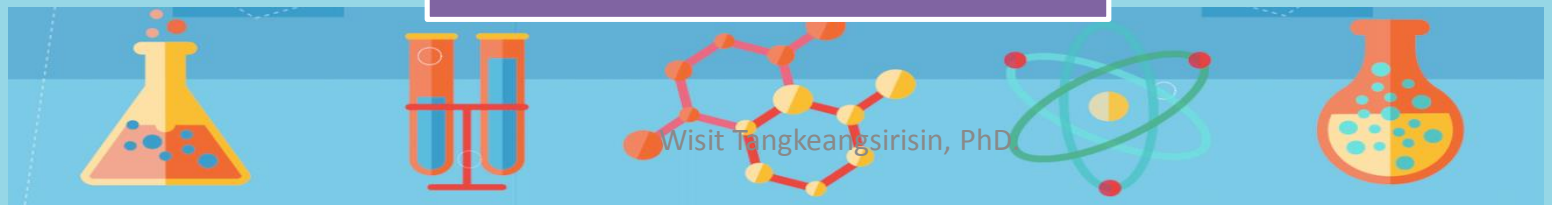
EMA guidelines – can be adapted to all biologics including blood products, vaccines
WHO guidelines and others – adapted only well established and well characterized biotherapeutic products

Biosimilars are not Generics

200 to 1,000 times larger

Far more structurally complex

Manufactured in living cells instead of via chemical synthesis

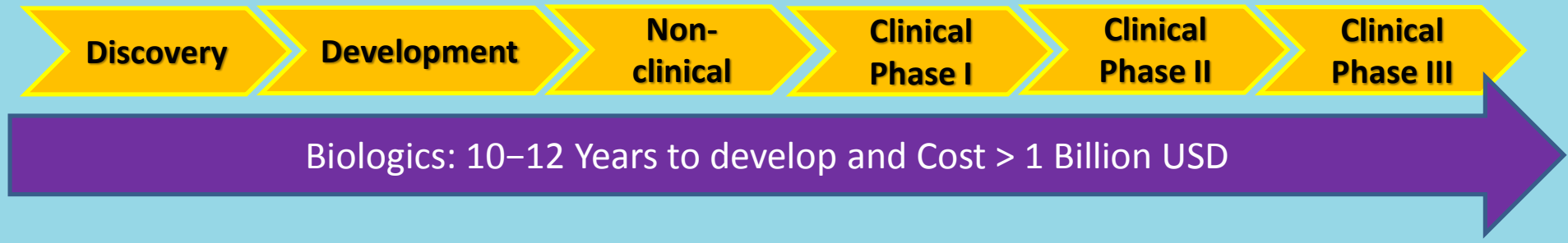


Significance and Needs

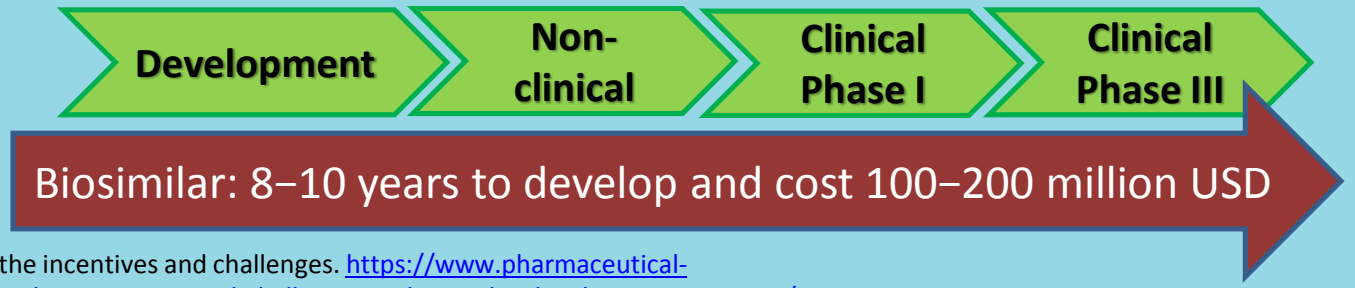
WHY BIOSIMILAR??

Reduced cost for production of biosimilars

Original Reference Biological Development Scheme

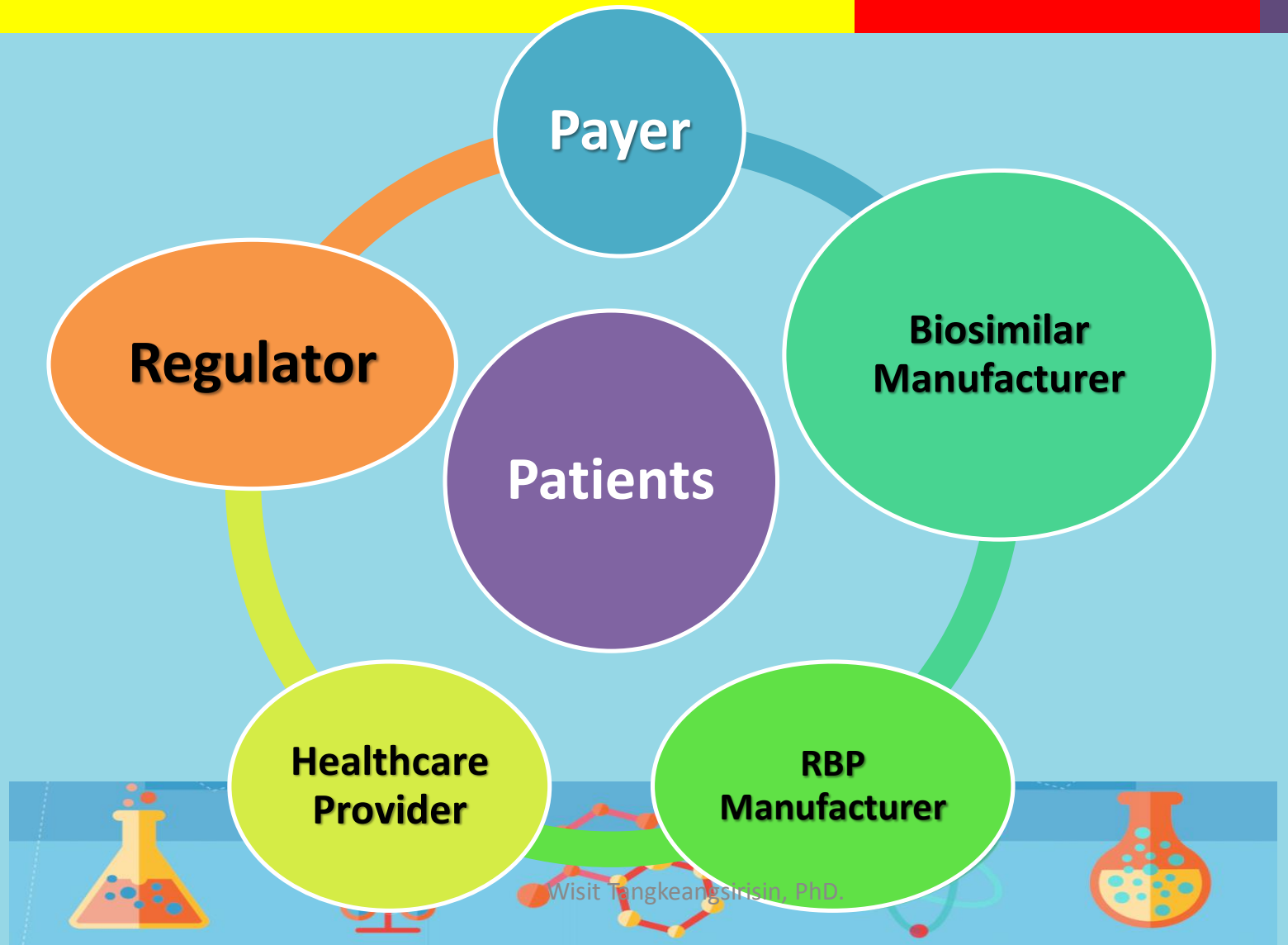


Biosimilar Development Scheme



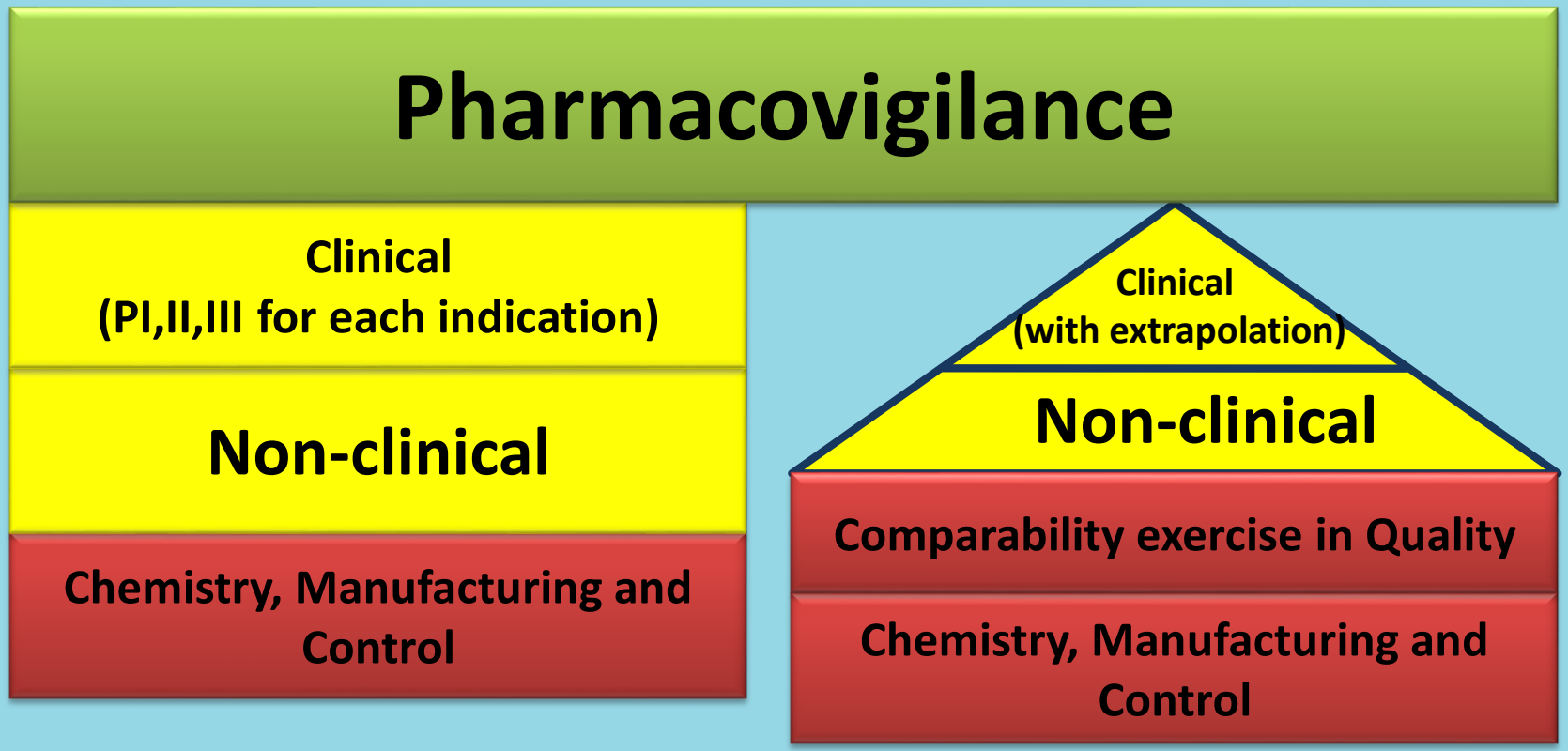
GBI Research. 2017. Biosimilar development the incentives and challenges. https://www.pharmaceutical-technology.com/comment/commentwhat-are-the-incentives-and-challenges-to-biosimilar-development-5751024/

Stakeholder of Biosimilars



BIOSIMILAR DEVELOPMENT

Approval of Biosimilar vs. Originator Biological



Extrapolation of Indication

- **Incentive of Biosimilar**
- **Most NRAs agree that biosimilars do not need to show safety and efficacy for every indication as the reference product with adequate justification.**

Comparable populations

Similar Pathogenesis

Same mode of action

Key Steps in Biosimilar Development & Marketing

Quality Target Product Profiling

Extensive Comparability Studies in Analytical

(a) pivotal clinical comparability study

Extrapolation of Indications

During Development

Approval

Interchangeability

Market Perception and Concern

Post Approval Challenge

Market Challenge Issues

Biosimilar is not built through traditional clinical training (Educational issues)

Interchangeability

Perceptions and Concerns brings to unsuccessful communication to patients (nocebo effect)

INTERCHANGEABILITY / SUBSTITUTABILITY /SWITCHING

Interchangeability, Substitution and Switching

- **Interchangeability –** *Health Regulatory Authority* Designation
- **Substitution** – *Pharmacist Action*
  - If without the prescribing physician's permission or knowledge, it is considered 'automatic' or 'involuntary' substitution
- **Switching** - *Physician Decision*

Interchangeability

- **In EU**, the biosimilar approval **do not automatically allow interchangeability**
- ***Interchangeability/switching remains a national decision.***
- After 10 years experience of biosimilar in the market, several EU countries change regulations to ***less stringency on interchangeability/switching/ substitution*.**

BIOSIMILAR GLOBAL REGULATION

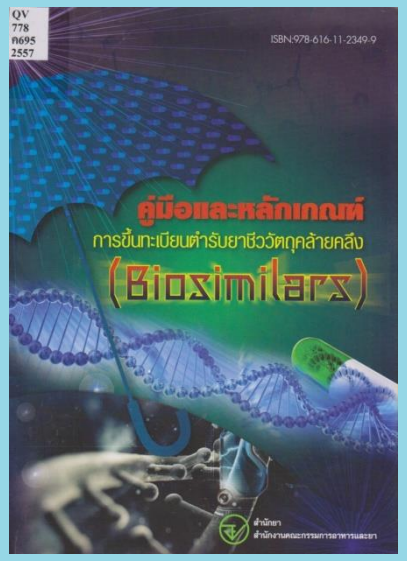
Regulatory Convergence Biosimilars/Biologicals

EMA becomes reference for other Competent Authorities

WHO recommends authorities to approved biosimilar

Thailand Biosimilar Guidelines

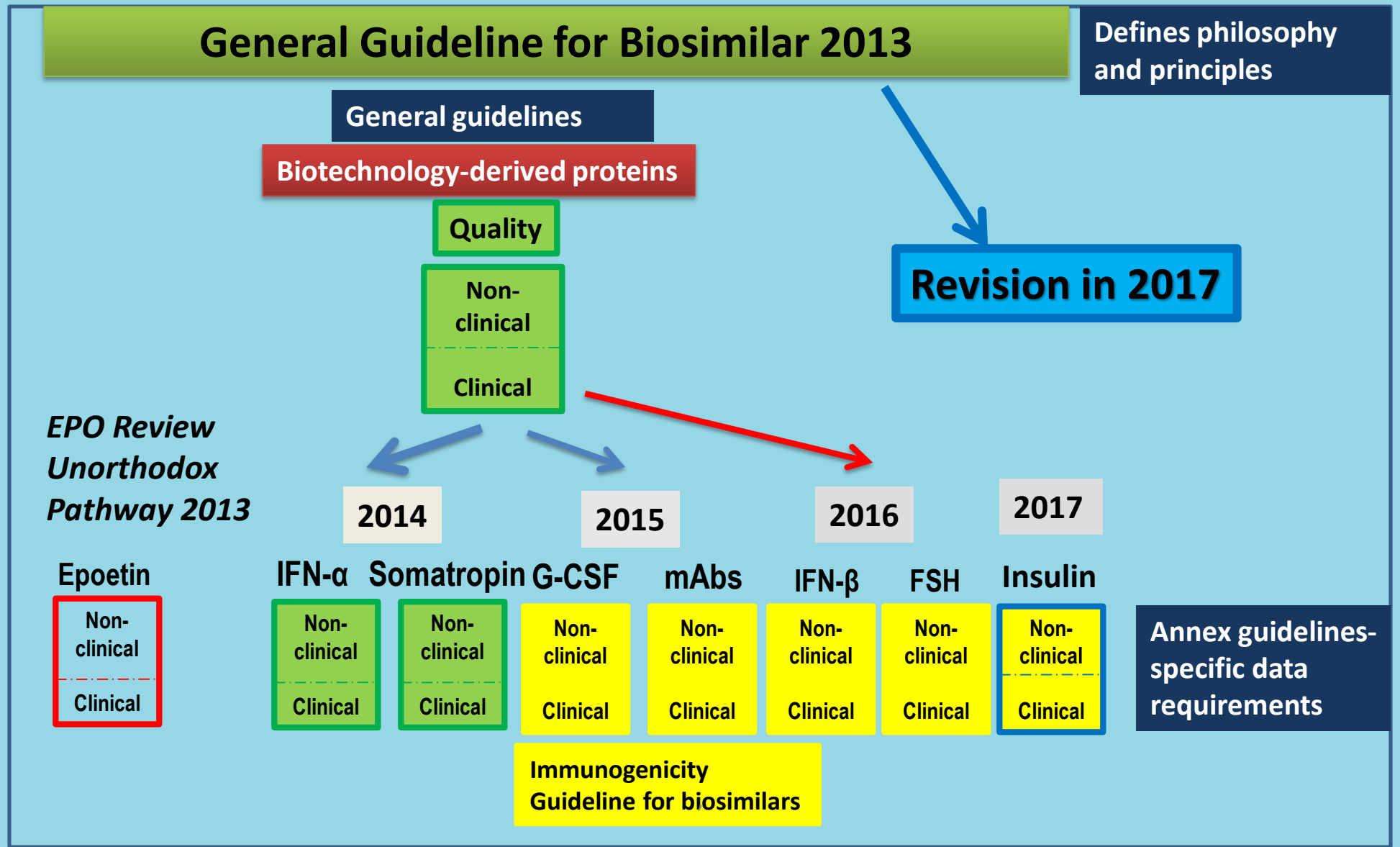
- **Adopted from EMEA Biosimilar Guidelines (Revision 1) 2013**



Revision

Revision in 2017

Current Thailand Biosimilar Guidelines



Different regulatory requirement for biosimilars in Asian countries

Adapted from Curr Rheumatol Rep. 2017;19:47.

	China	*India*	*Japan*	*Korea*	*Taiwan*	*Thailand*
Interchangeability	Not provided	Not provided	Not allowed	Not provided	Not provided	Not provided
Automatic Substitution	Not mentioned	Not mentioned	Not allowed	Not allowed	Not allowed	Not mentioned
Indication Extrapolation	Allow	Allow	Allow on Provision	Allow on Provision	Allow on Provision	Allow on Provision
Reference Product	Registered in China in clinical study	Registered in India with provision	Registered in Japan with provision	Registered in Korea with provision	Authorized in Taiwan	Authorized in Thailand
Others		Single arm study may be acceptable				

No Naming and labelling Issues in Most ASEAN Countries

Approved Biosimilar in Thailand

INN	RBP in Thailand	Biosimilar in Thailand	Non-comparable Biologics
Epoetin alpha	√	Binocrit*	>10
Filgrastim	√	Zarzio, Nivestim	few
Infliximab	√	Remsima*	×
Rituximab	√	Truxima, xx	×
Trastuzumab	√	Ogivri, Herzuma	×
Adalimumab	-	xx	×
Bevacizumab	√	Mvasi	×

* Approved before Biosimilar GL in place ♥ Under internal revise

Biologicals in the Real World

Innovator Biologicals

NDA

Stand alone Biologicals (Non-comparable biologicals)

- Abbreviated Dossier (stringency is vary)
- Some data depend on Innovator's Data

Biosimilars

Biosimilar registration

Type of Biopharmaceuticals in the Global Market (including Thailand)

Innovator Biopharmaceuticals	Similar Biotherapeutic Products (Biosimilar)	Non-comparable Biopharmaceuticals
• Novel Product • Patent Protection • Fully Regulatory Dossier	• Highly similar to innovators that has been authorized • Approved by biosimilar regulatory pathway	• Not approved in accordant with WHO SBP/ Biosimilar Guidance • Should not be approved as generic

World Health Organization

Post ECBS version
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 12 to 16 October 2015

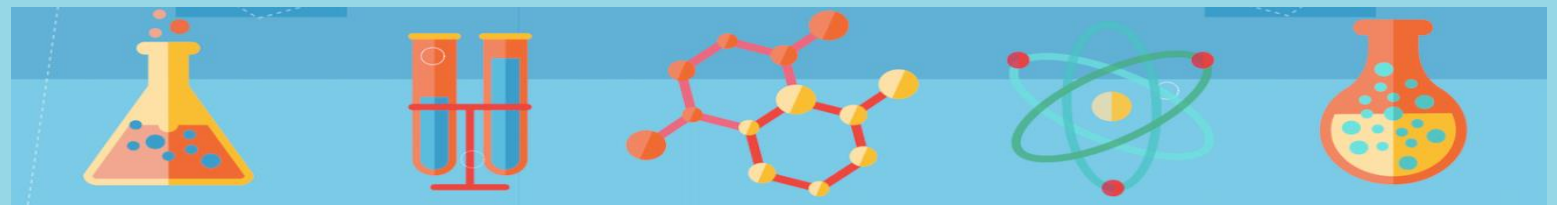
REGULATORY ASSESSMENT OF APPROVED rDNA-DERIVED BIOTHERAPEUTICS

PROPOSED ADDENDUM TO: WHO TRS 987, Annex 4.

Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology

What should be done with these already licensed products?

- To develop approaches ***to evaluating these already licensed products according to current guidelines or for phasing them out*** in a reasonable period of time
- WHO guidance on Regulatory Assessment of Approved rDNA-Derived Biotherapeutics (2015)



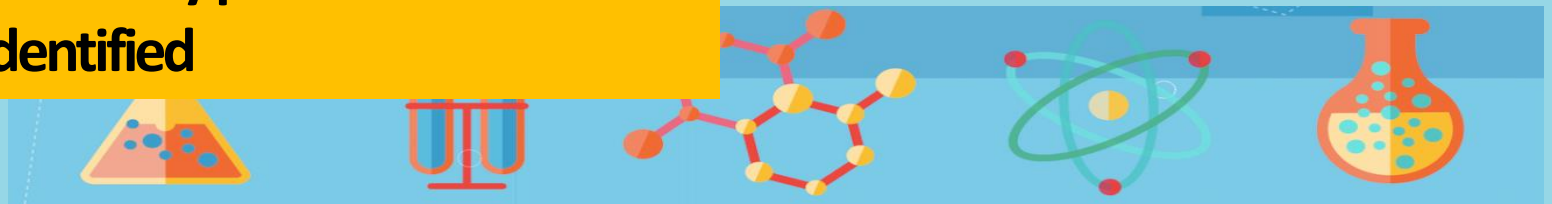
Four Options

1. Leave on the market and strengthen post market surveillance to identify possible adverse effects associated with use;

2. Withdraw from the market immediately

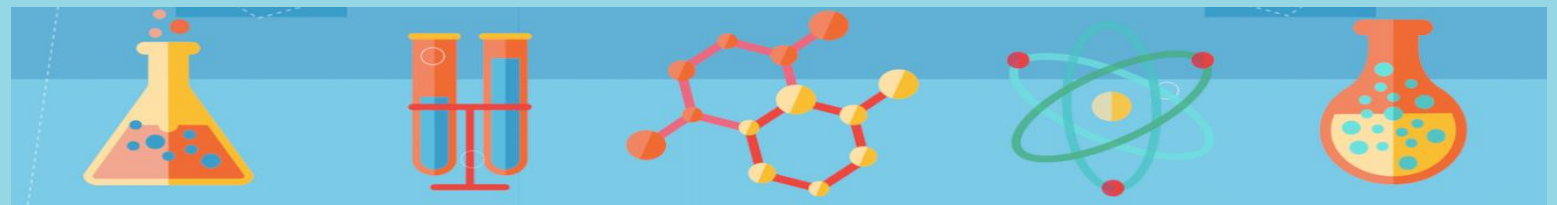
3. Withdraw only when a safety or efficacy problem has been identified

4. Leave on the market for a specified period, during which time manufacturers would be required to submit appropriate missing data and a 'risk management plan' for regulatory evaluation to support the continuation of the licence. (stepwise assessment)



EPO cases in Thailand

- What are the issues about EPOETIN in Thailand?
  - 15 brands of EPO-alpha and 1 brand of EPO-beta have been licensed in Thailand
  - Access to Epoetin by UC patients due to the low price



see commentary on page 11

Kidney International (2011) **80,** 88–92; doi:10.1038/ki.2011.68;
published online 23 March 2011

Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies

Kearkiat Praditpornsilpa[1], Khajohn Tiranathanagul[1], Pawinee Kupatawintu[2], Saengsuree Jootar[3], Tanin Intragumtornchai[4], Kriang Tungsanga[1], Tanyarat Teerapornlertratt[5], Dusit Lumlertkul[6], Natavudh Townamchai[1], Paweena Susantitaphong[1], Pisut Katavetin[1], Talerngsak Kanjanabuch[1], Yingyos Avihingsanon[1] and Somchai Eiam-Ong[1]

- **… 30 patients with chronic kidney disease treated by SC injection with biosimilar r-HuEpo and who developed a sudden loss of efficacy.**
- **Sera from 23 of these patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts.**
- **However, we can clearly state that repeated subcutaneous injections of biosimilar agents could result in the development of anti-r-HuEpo-associated PRCA.**

EDITOR'S NOTE:
Biosimilar is a term applied to subsequent versions of biopharmaceutical products that have been approved by the regulatory authorities of a given country. The pathway for approval is thus specific for that country, and because of regulatory differences, the biosimilar classification may not apply in other countries.

Reality about EPOETIN in Thailand

16 EPOETIN brands has been registered in Thailand.

Not a single brand registered as BIOSIMILAR

EPOETIN switching has been commonly done in Thailand.

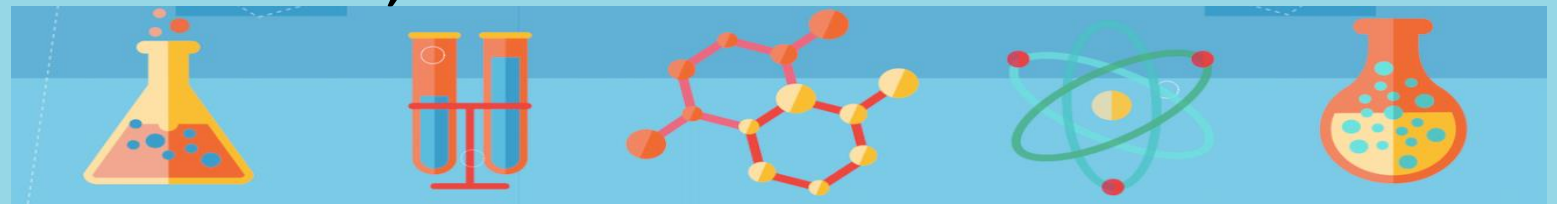
EPOETIN PRCA Solutions

Legal Actions

- Revised Regulations
  - 2009 ASEAN Harmonization / ICH
  - 2013 Biosimilar Registration Pathway
- New EPO registration will be submitted as either New Biologicals or Biosimilar
- Reassessment process for the registered EPO (EPO review)
- Pharmacovigilance

Non-legal Actions

- Dear Dr. Letter, Alert Letter



Possible causes for high reporting PRCA in Thailand

- Products?
- Quality?
- Formulation?
- Storage and Handling?
- Route of Administration?
- Interchangeability of Products?
- Genetic?
- ?????

Active Surveillance Methods

Intensive (hospital) Monitoring

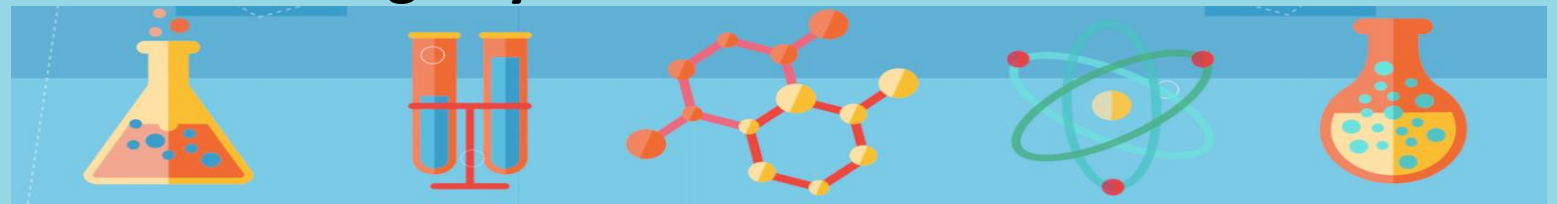
- Product of interest
  - New drug, High alert drug

Cohort event monitoring

- Anti-TB drugs (New drug, New regimen)
- Epoetin

Registry

- Thai EPO registry



Take Home Message

Biosimilar is now the global trend

Relevant Clinical Comparability Study Design with sensitive biomarker and population will provide scientific evidence for Extrapolation of Indication

Biosimilar provides more access to patients even in developed countries

Interchangeability, Market Perception and Real-world situation are challenging issues