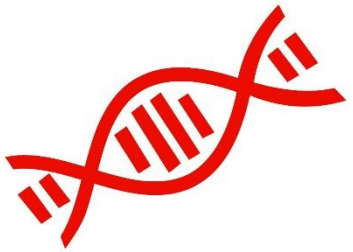


Assistant Professor Wisit Tangkeangsirisin, PhD, Thailand

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

GaBI
Educational
Workshops

24 September 2019, Ankara HiltonSA, Turkey

2nd Turkish Interactive Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

How to handle the pre-existing non-comparable biopharmaceuticals licensed prior to the biosimilar approval pathway: experience from Thailand

Assistant Professor Wisit Tangkeangsirisin, PhD

24 September 2019

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma
Communications
International

How to handle the pre-existing non-comparable biopharmaceuticals licensed prior the biosimilar approval pathway: experience from Thailand

Wisit Tangkeangsirisin, PhD

Faculty of Pharmacy

Silpakorn University, THAILAND

2nd Turkish Interactive Workshop on Regulatory Assessment of Biosimilars

23 September 2019

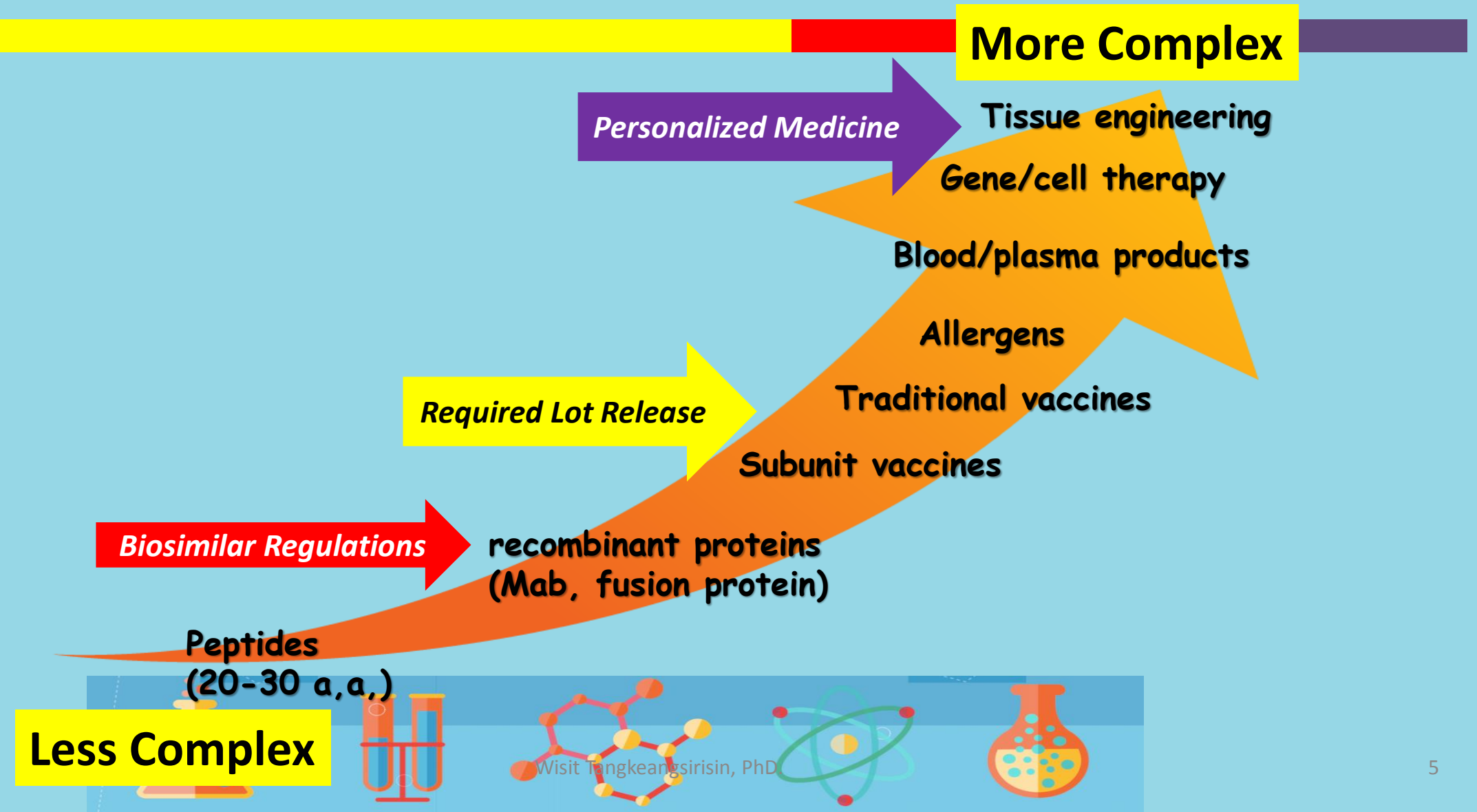
AGENDA

What is Biologicals/Biosimilar?

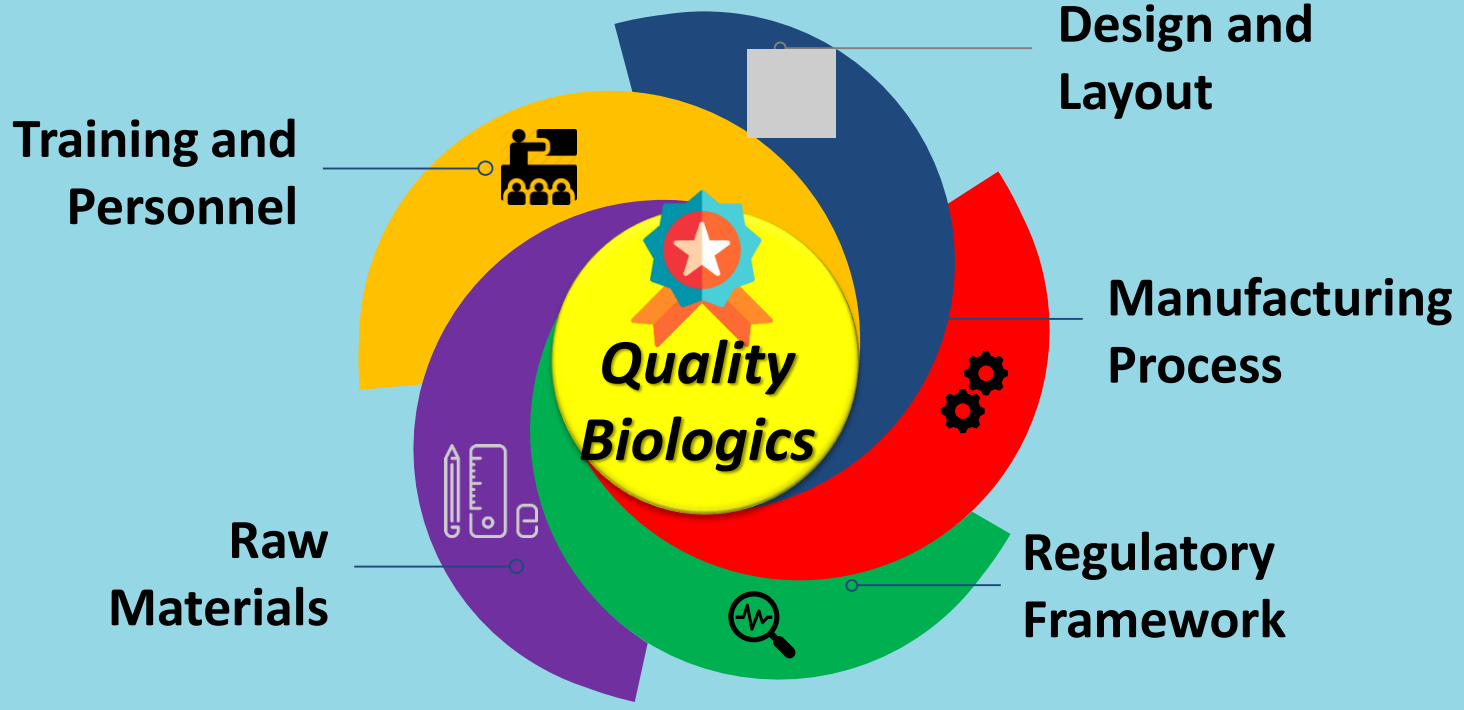
Biosimilar Approval Foundation

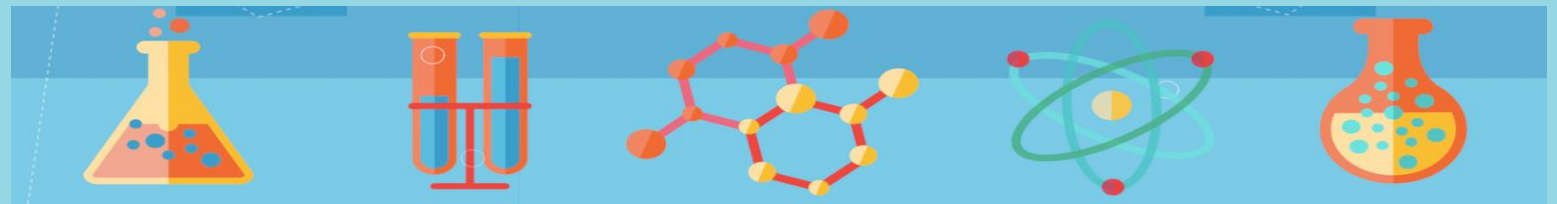
Biosimilar Global, ASEAN and Thailand Regulation

Heterogeneity of Biologicals

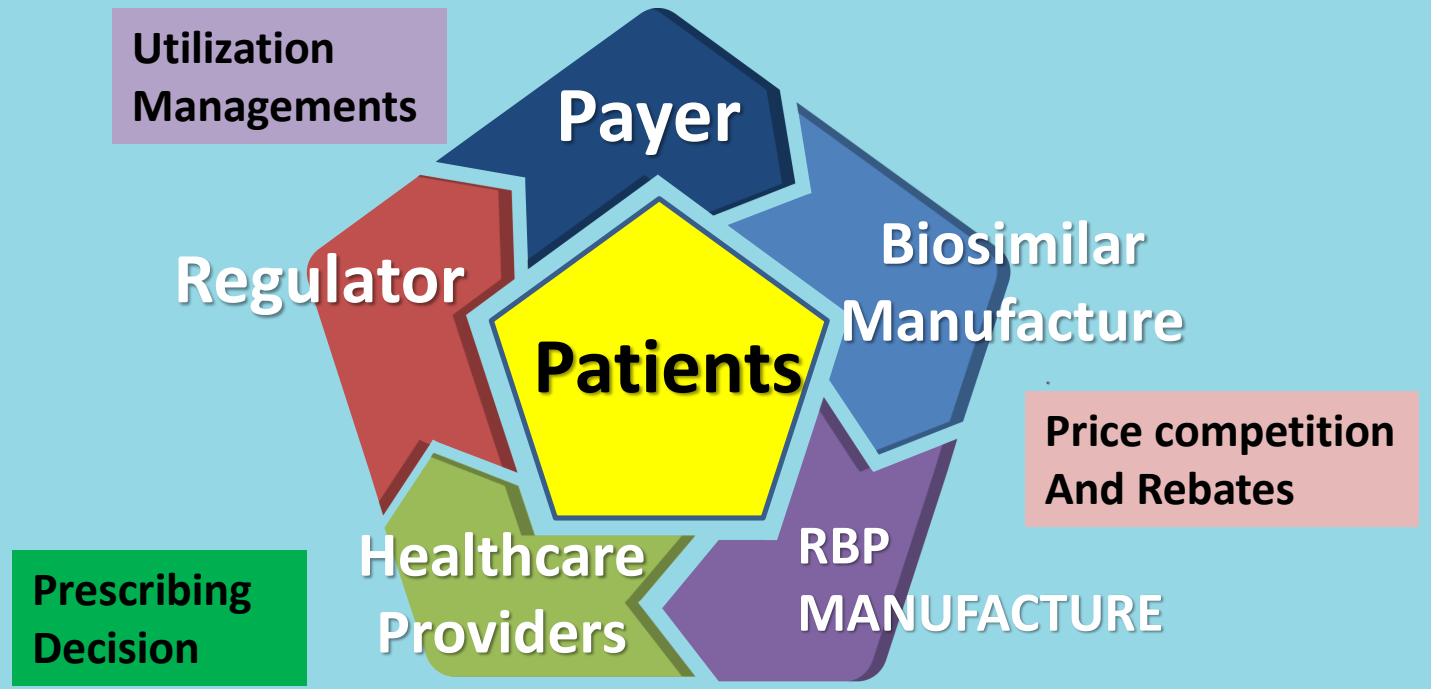


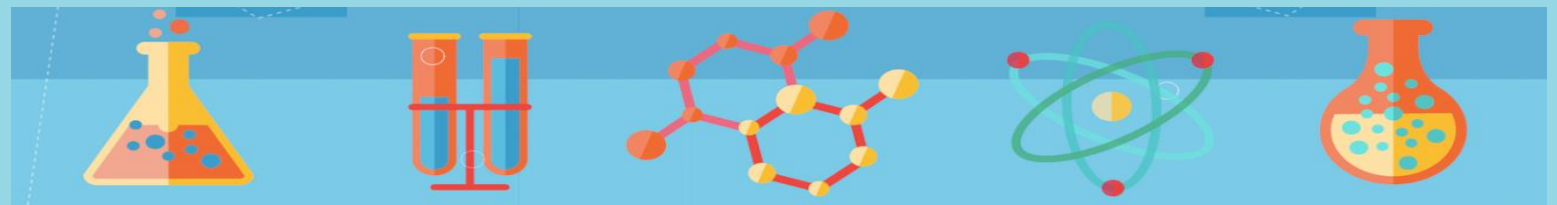
Elements of quality biologicals





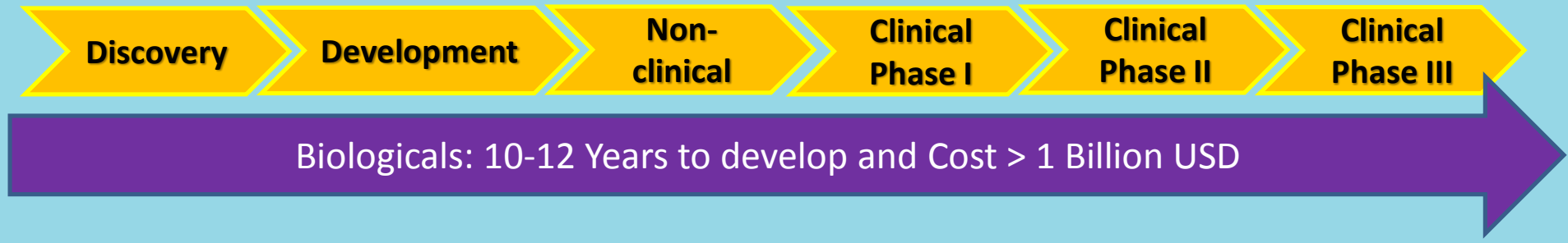
STAKEHOLDERS of Biosimilar





Reduced cost for production of biosimilars

Original Reference Biologic 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/

BIOSIMILAR DEVELOPMENT

Market Challenge Issues

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

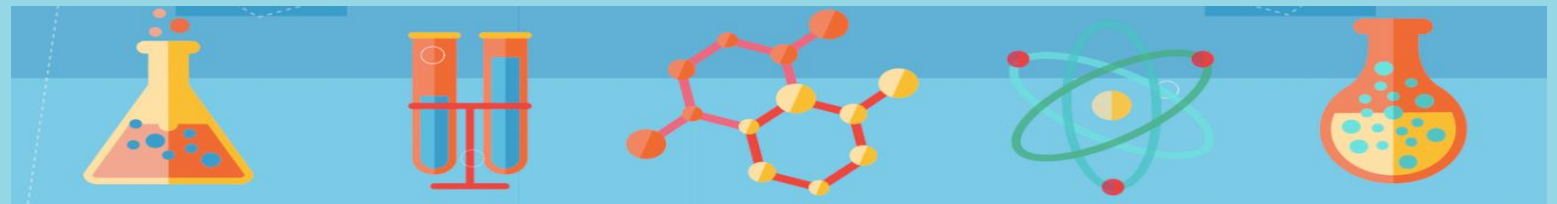
Interchangeability

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

Concern of Biologicals including Biosimilars

- **Quality → impurity, immunogenicity ?**
- **Safety**
  - **Study in Asian Race within the indications ?**
  - **Interchangeability → safety concern in some products ?**
- **Efficacy**
  - **Extrapolation of indication ??**
  - **Do we really need interchangeability study (for all indication)?**

Hype or Facts? Scientific and Logical thinking



BIOSIMILAR GLOBAL REGULATION

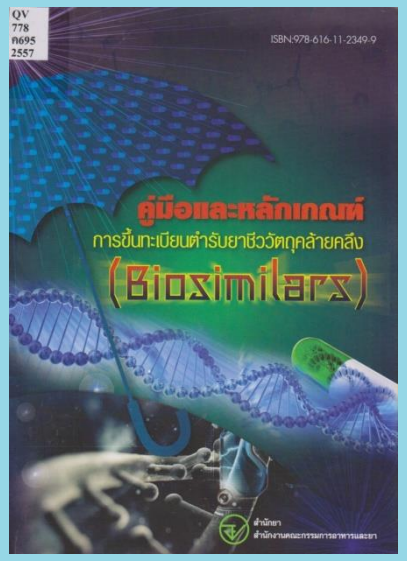
Regulatory Convergence Biosimilars/Biologicals

EMA becomes reference for other Competent Authorities

WHO recommends authorities to approved biosimilar

Thailand Biosimilar Guidelines

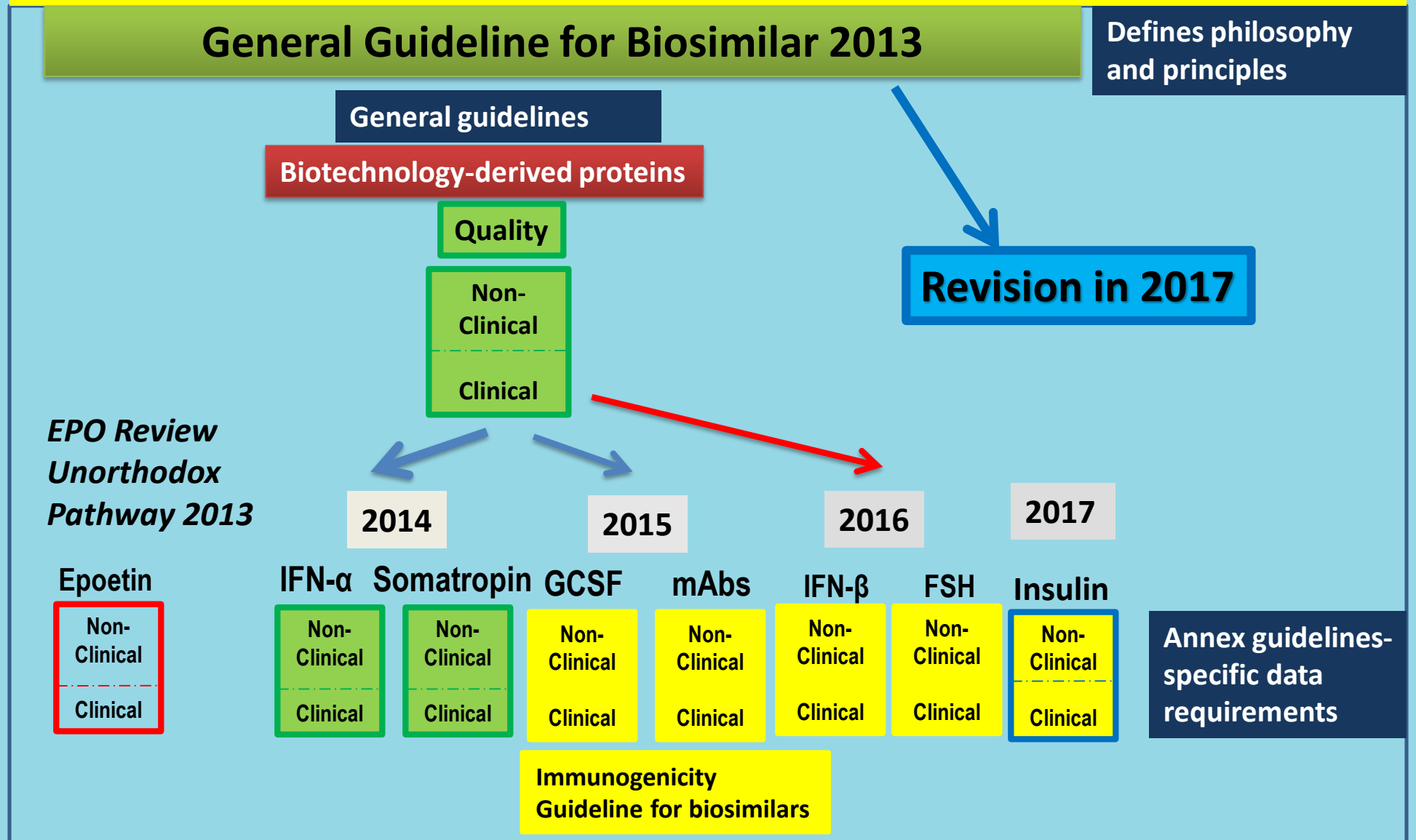
- **Adopted from EMEA Biosimilar Guidelines (Revision 1) 2013**



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 Labeling Issues in Most ASEAN Countries

Approved Biosimilar in Thailand

INN	RBP in Thailand	Biosimilar in Thailand	Non-comparable Biologicals
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

Biologicals in the Real World

Innovator Biologicals

NDA

Stand alone Biologics (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

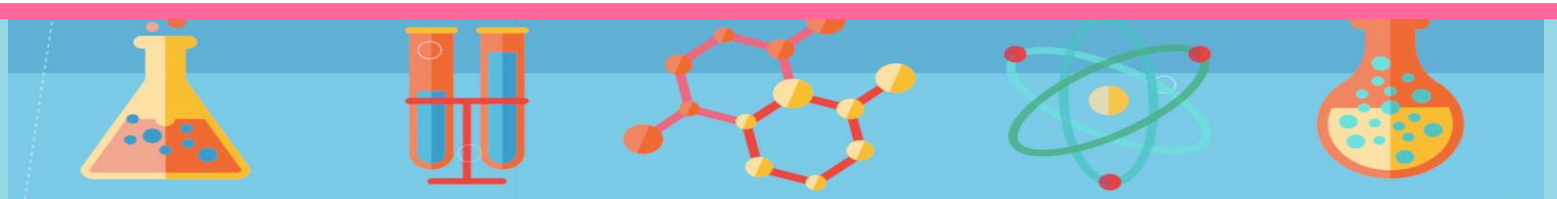
Post ECBS version
ENGLISH ONLY

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

REGULATORY ASSESSMENT OF APPROVED rDNA-DERIVED BIOTHERAPEUTICS

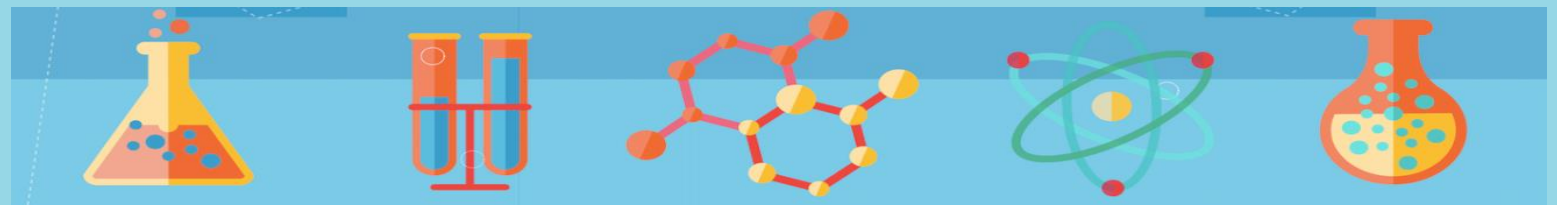
PROPOSED ADDENDUM TO: WHO TRS 987, Annex 4.

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)



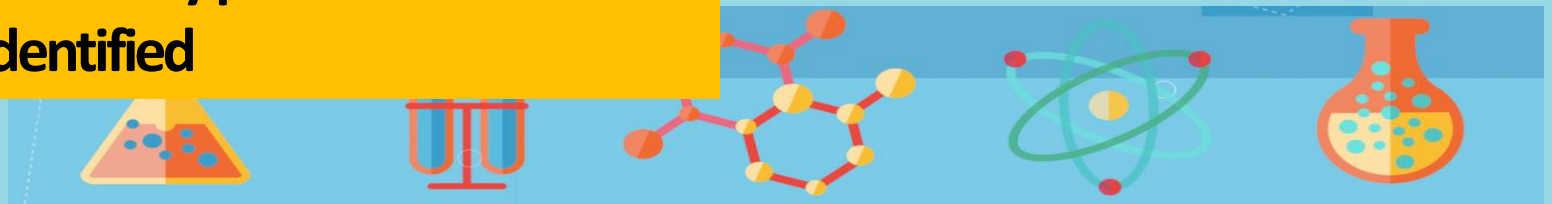
Four Options

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

2. Withdraw from the market immediately

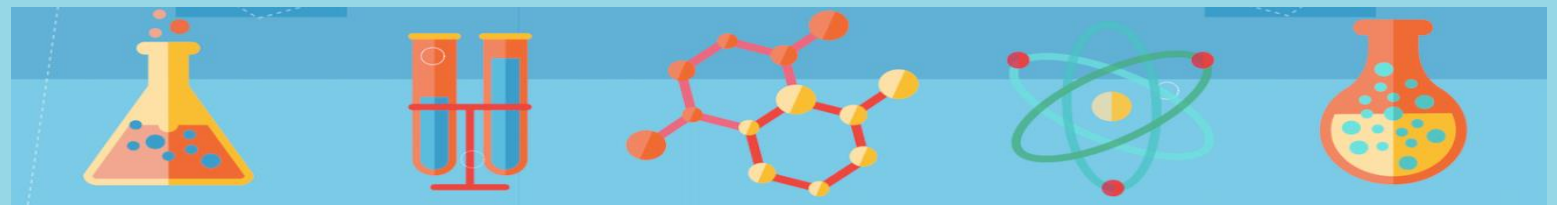
3. Withdraw only when a safety or efficacy problem has been identified

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 license. (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

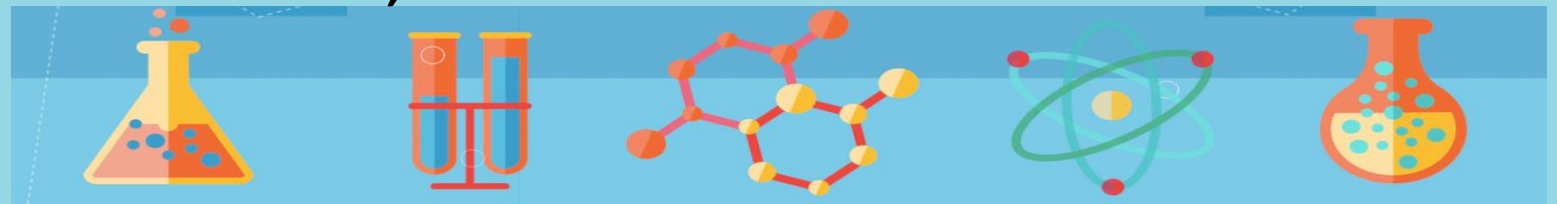
EPOETIN PRCA Solutions

Legal Actions

- Revised Regulations
  - 2009 ASEAN Harmonization / ICH
  - 2013 Biosimilar Registration Pathway
- New EPO registration will be submitted as either New Biologics 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

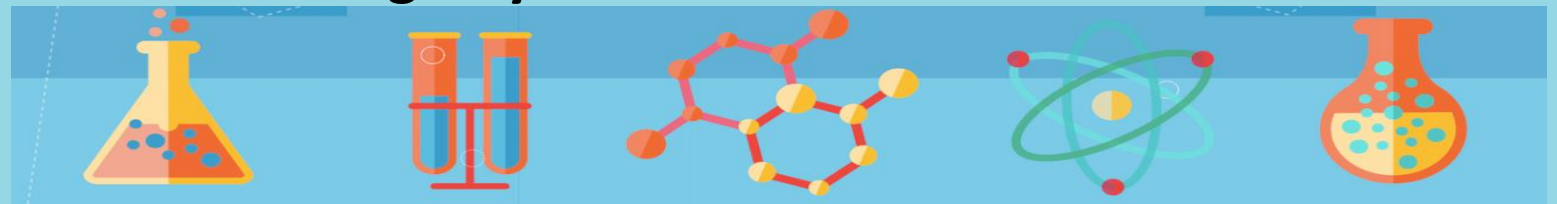
- Product of interest
  - New drug, High alert drug

Cohort event monitoring

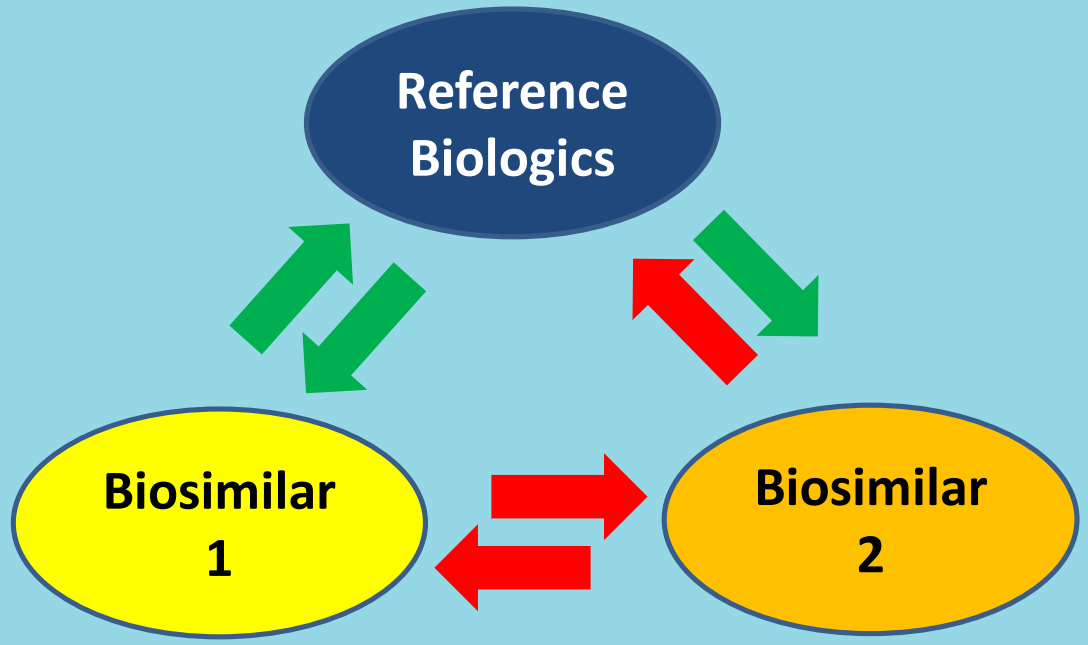
- Anti-TB drugs (New drug, New regimen)
- Epoetin

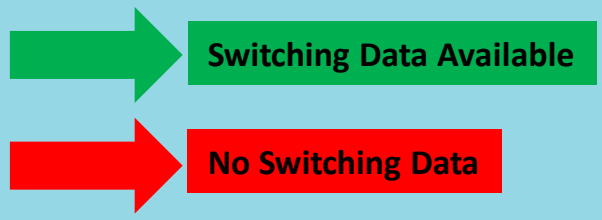
Registry

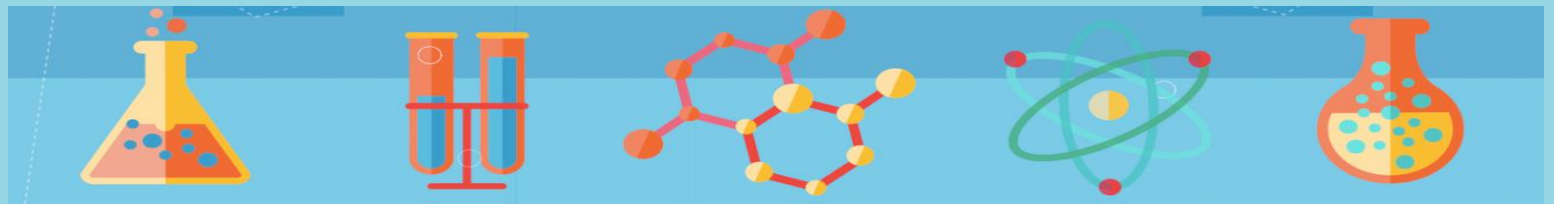
- Thai EPO registry



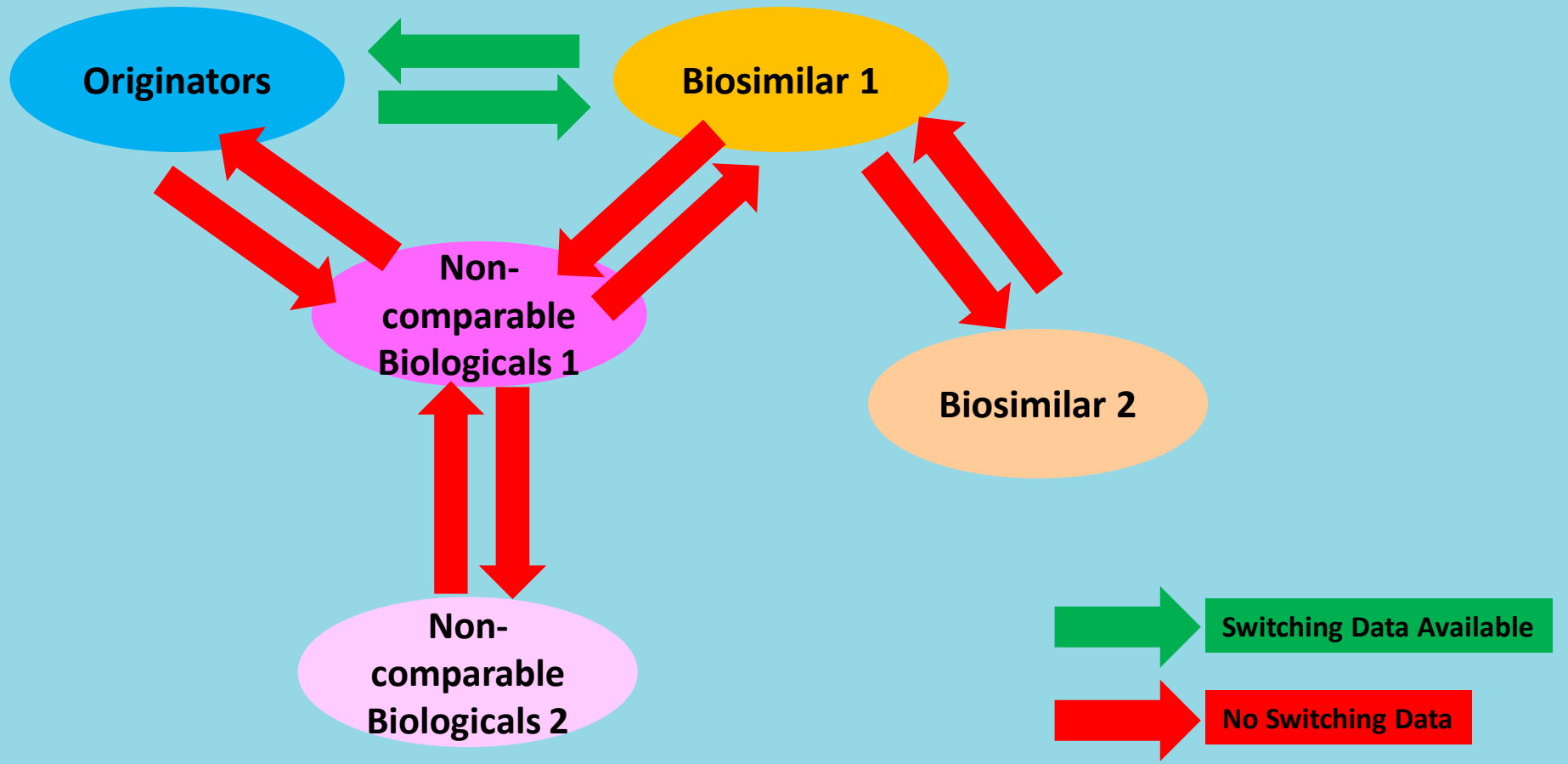
Switching study model in real world situation







Real World of Switching on Biopharmaceuticals



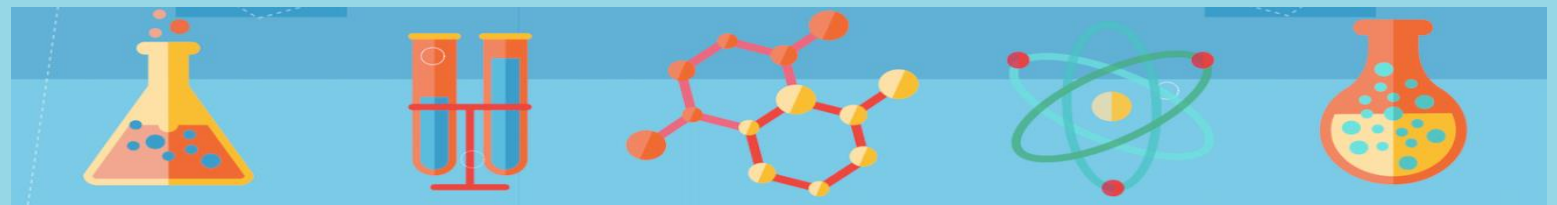
Interchangeability Model

Chemical

Originators → ***Switching/ Automatic Substitution*** → **Generics** ✓

Generics → ***Switching/ Automatic Substitution*** → **Originators** ✓

Routine Pharmacovigilance
Routine Quality Monitoring



Interchangeability Model

Biologics

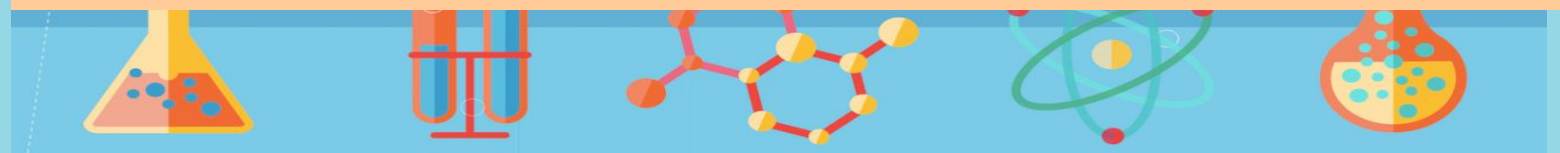
Originators → *Switching/ Automatic Substitution* → **Biosimilars** → ?

Originators → *Switching + Patient Awareness Scientific Evidence Case-by-case basis* → **Biosimilars** ✓

Routine Pharmacovigilance

Originators → *Switching + Patient Awareness Scientific Evidence Case-by-case basis* → **Non Comparable Biologics** ✓

Routine Pharmacovigilance
Risk Management
Stepwise Evaluation

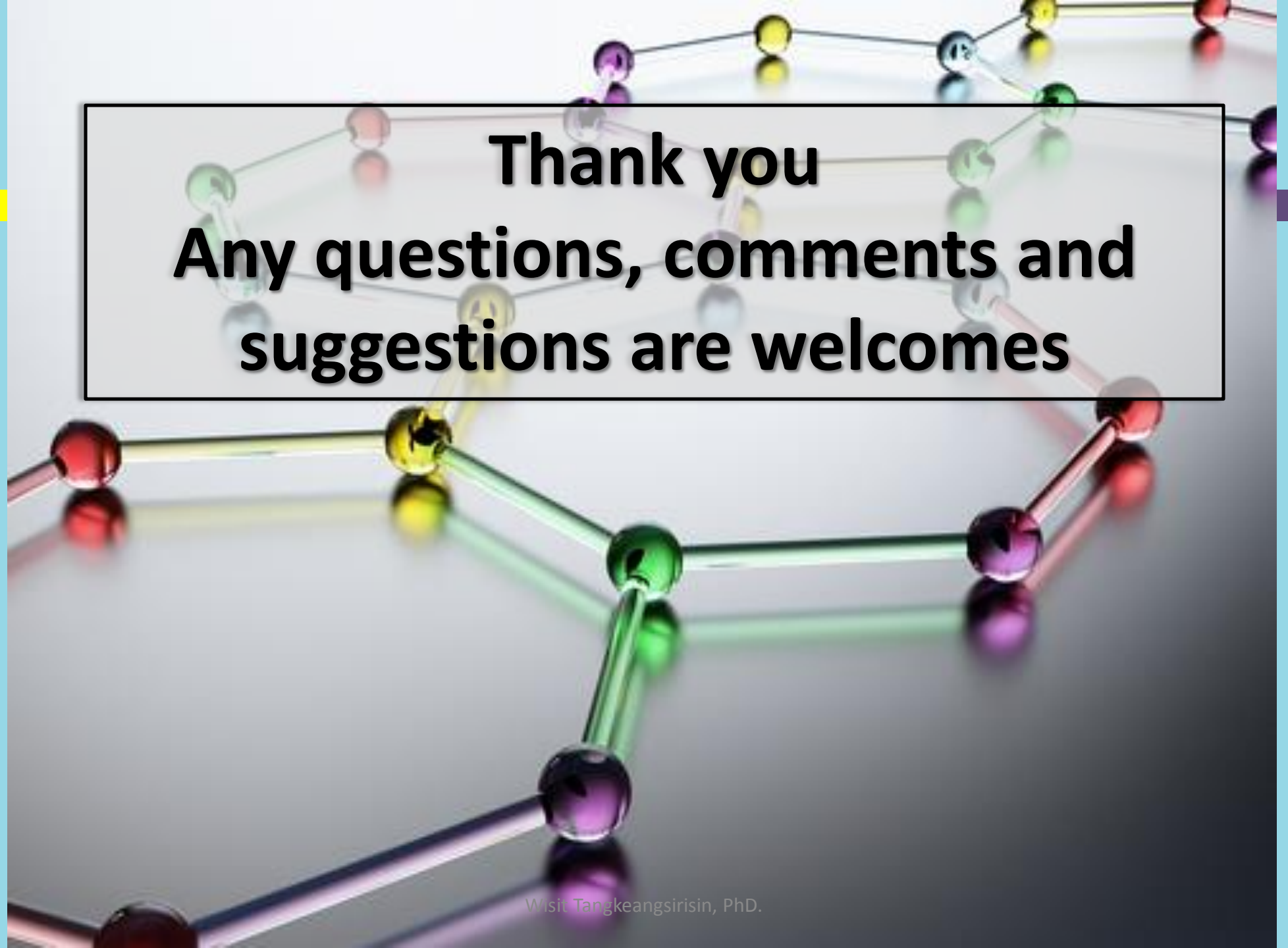


Take Home Message

Biosimilar is now the global trend

Non-comparable Biologicals should be re-evaluated for their safety and efficacy by submission missing data

Routine Pharmacovigilance and risk management plan should be implemented to ensure the safety and efficacy of all biologicals



Thank you
Any questions, comments and suggestions are welcomes