



生物相似性藥品(Biosimilar Products)之審查及管理機制

從醫院藥品管理觀點談Biosimilar Products 之臨床使用實務考量

臺大藥學專業學院 沈麗娟

Oct. 12th, 2017

1953-1984



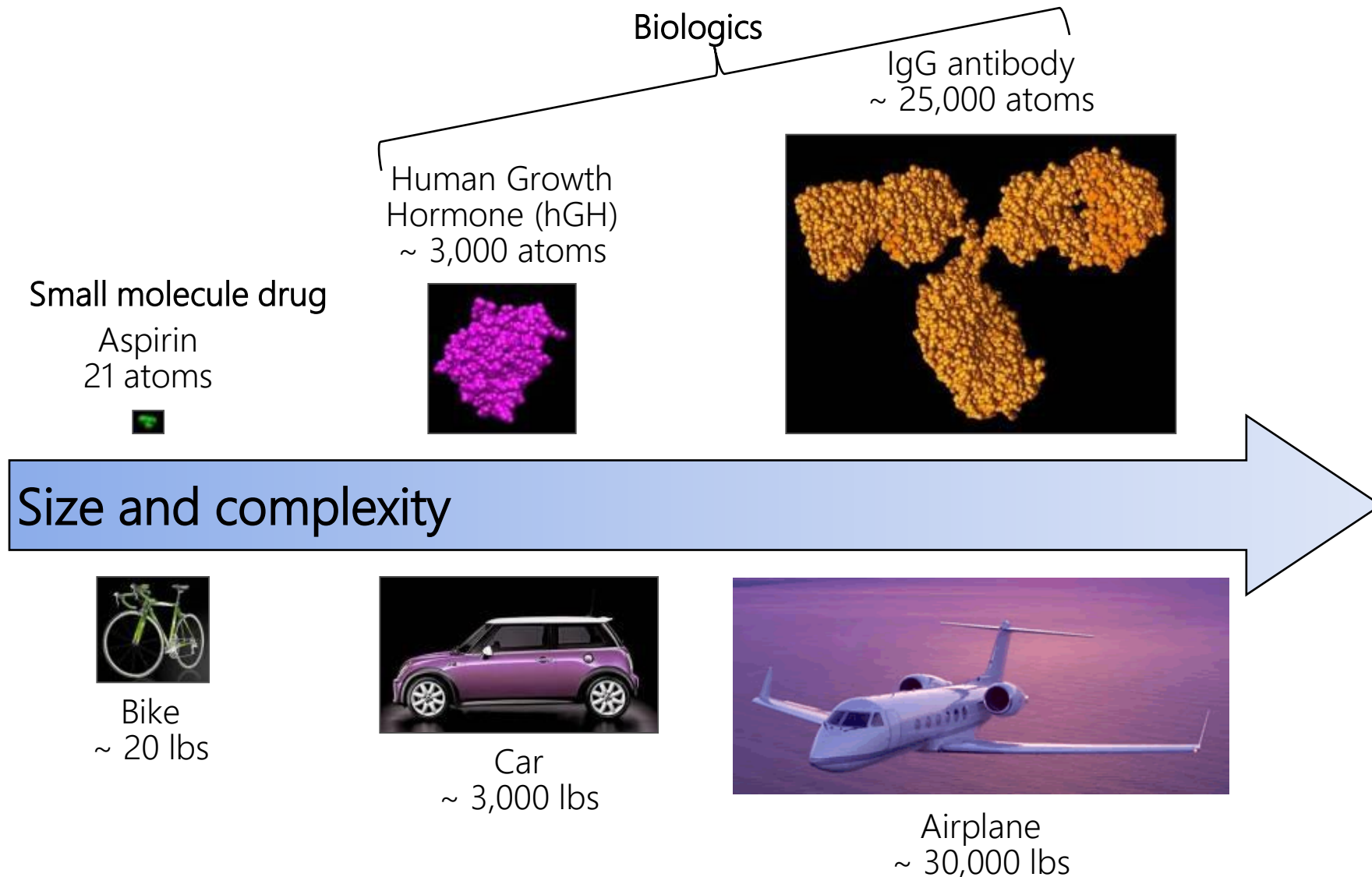
1984-2014



2014-



Biologics are much more complex than chemically-synthesised small molecule drugs



Differences between biosimilars and generics



Biosimilar (biologic)

Generic (small molecule drug)

Manufacturing

Produced in living systems

Produced via chemical synthesis

Similarity to originator

"Similar" to its originator product (not identical copy)

Identical copy of its originator product

Clinical data requirement

Phase I PK/PD study (N ~100) and Phase III study (N ~several hundreds)




Small clinical trial in healthy volunteers (Phase I)

In contrast to generics, a biosimilar is **never** an exact copy of the originator product

THE REAL WORLD CASE

Infliximab (Remicade vs. Remsima)

Remicade vs. Remsima – Indication Extrapolation?

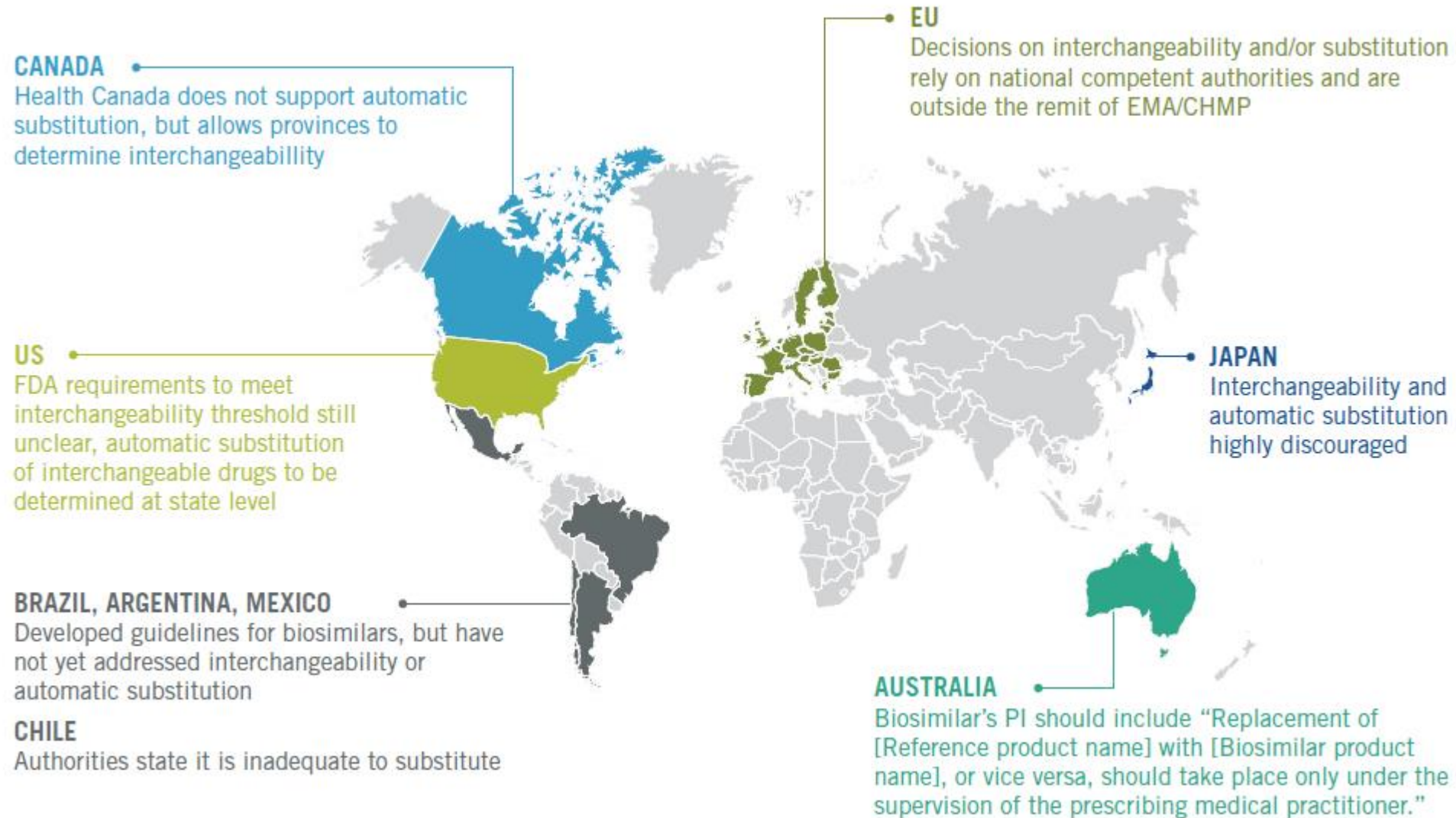
		Remicade (originator)	Remsima (biosimilar)
Indication	FDA 	Crohn's Disease Pediatric Crohn's Disease Ulcerative Colitis Rheumatoid Arthritis in combination with methotrexate Ankylosing Spondylitis Psoriatic Arthritis Plaque Psoriasis Pediatric Ulcerative Colitis	Crohn's Disease Pediatric Crohn's Disease Ulcerative Colitis Rheumatoid Arthritis in combination with methotrexate Ankylosing Spondylitis Psoriatic Arthritis Plaque Psoriasis
	EMA 	Same as FDA	FDA indications + Pediatric Ulcerative Colitis
	TFDA 	Crohn's Disease Pediatric Crohn's Disease Ulcerative Colitis Pediatric Ulcerative Colitis	Crohn's Disease Pediatric Crohn's Disease Ulcerative Colitis Pediatric Ulcerative Colitis
Studies		All disease types of indications	Rheumatoid Arthritis Ankylosing Spondylitis

Originator and Biosimilar

	REMICADE 類克凍晶注射劑	REMSIMA 類希瑪
健保代碼	KC00980255	KC01035255
成份	Infliximab	
成份含量	100 mg	
健保價	15,302元	13,007元
起訖	106.05.01~迄今	106.10.01~迄今
藥品分類	一般學名藥	NA
發證日期	104/09/01	105/12/22
許可證字號	衛部菌疫輸字第000980號	衛部菌疫輸字第001035號
適應症	1、成人克隆氏症 2、小兒克隆氏症 3、成人潰瘍性結腸炎 4、小兒潰瘍性結腸炎	1、成人克隆氏症 2、小兒克隆氏症 3、成人潰瘍性結腸炎 4、小兒潰瘍性結腸炎
限制項目	02輸入 1D須執行風險管理計畫 5I免除銜接性臨床試驗	02輸入 1D須執行風險管理計畫 1EPhase IV Study 5F免除銜接性試驗
備註		Remsima是具有生物相似性的藥品(仿單)

Global **interchangeability** and **substitution** practices

2016 snapshot



US/FDA – ‘Interchangeable’ product designation for biosimilars

- FDA views biosimilarity and interchangeability as **distinct concepts** and accordingly classifies biosimilar products as ‘biosimilar’ or ‘interchangeable’.
- To meet the additional FDA standard of interchangeability, provided data must:
 1. Demonstrate **biosimilarity**;
 2. Demonstrate that the biological product can be expected to produce the **same clinical result** as the reference product in any given patient;
 3. Demonstrate, for a product administered **more than once**, that the risk in terms of safety or diminished efficacy of **alternating/switching** between the biosimilar and the reference product is not greater than the risk of using the reference product.
- FDA has not yet defined the weight of evidence required to fulfil these requirements; **a draft guidance** on the scientific assessment of interchangeability is **expected in 2017**.
- To date, **no biosimilars** have been approved with an ‘interchangeable’ designation.

NAMING/LABELING/PHARMAOVIGILANCE

Current naming policies pose a challenge for pharmacovigilance

Example: Epoetin medicinal products approved by the EMA

Type of authorisation:

Originator biologic

Biosimilar

List of epoetin products
(brand name [INN])
available on the market
at a given year

1998

- Eprex (epoetin alfa)
- NeoRecormon (epoetin beta)

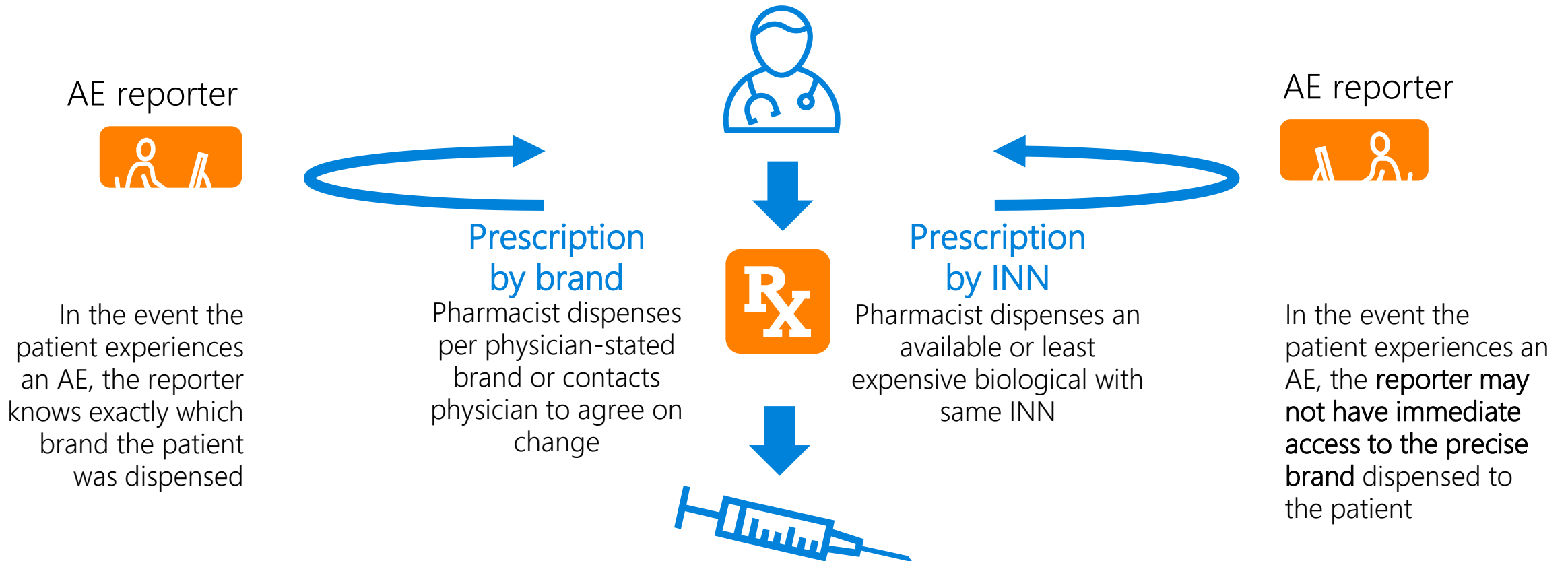
2001

- Aranesp (darbepoetin alfa)
- Eprex (epoetin alfa)
- NeoRecormon (epoetin beta)

2016

- Aranesp (darbepoetin alfa)
- Biopoin (epoetin theta)
- Eporatio (epoetin theta)
- Eprex (epoetin alfa)
- Mircera (peg-epoetin beta)
- NeoRecormon (epoetin beta)
- Abseamed (epoetin alfa)
- Binocrit (epoetin alfa)
- Epoetin alfa Hexal (epoetin alfa)
- Retacrit (epoetin zeta)
- Silapo (epoetin zeta)

Current naming policies pose a challenge for pharmacovigilance



Prescribers must be able to track accurately which particular biologic was given to a patient to allow for adequate pharmacovigilance

INN Naming

	Guideline/Issue date	Proposed Naming	Example
FDA	Nonproprietary Naming of Biological Products/ Jan. 2017	Proper name: core name plus the designated suffix (4 lowercase letters) attached with a hyphen	Infliximab (core name) - dyyb
EMA		Same INN with the originator	Infliximab
WHO	Biological Qualifier An INN Proposal/ Oct. 2015	An alphabetical code assigned at random	Infliximab dyyb?

FDA Labeling for Biosimilar Product

- Incorporate relevant information from the reference product labeling (safety and efficacy) with appropriate product-specific modifications
- Data from comparative clinical study is not relevant to support the efficacy and safety of biosimilar product
- When to use the biosimilar product name
 - Information specific to the biosimilar product
 - e.g. Indication and usage, dosage and administration, dosage forms and strengths, description, how supplied/storage and handling
 - Directive statements and recommendations
 - e.g. Boxed warning, contraindications, warnings and precautions, drug interactions

Labeling for Biosimilar
Products

Guidance for Industry

March 2016
Labeling

DRAFT GUIDANCE

FDA Labeling for Biosimilar Product (cont'd)

- When to use the reference product name
 - Clinical studies or data derived from studies with the reference product
 - e.g. Adverse reactions, clinical studies
 - Biosimilarity statement
- When to use the core name
 - The overall risk-benefit profile of the reference product is relevant to the biosimilar product and thus it would be appropriate to use the core name
 - e.g. boxed warning, contraindications, warnings and precautions, adverse reactions
- When to use more than one product name
 - The product identification approaches are used to accurately convey information

Labeling in FDA & TW

	FDA	TFDA
Indication & Usage	Inflectra (Biosimilar product name)	Remsima & Infliximab (Biosimilar product name)
Dosage & Administration		
Contraindications		Infliximab
Description [#]		Infliximab
How supplied/storage & Handling		Remsima
Dosage forms & Strengths [#]	Infliximab-dyyb	Infliximab
Warnings & Precautions	Inflectra & Infliximab	Remsima & Infliximab
Drug Interactions		
Adverse Reactions	Infliximab	Infliximab
Clinical Studies		

[#] Only FDA has this item

ASHP: Strategies for managing generic drugs

- The use of high-quality generic equivalents is encouraged in order to provide the **best possible care at an affordable cost**.
- Use of generic drugs that have been deemed **bioequivalent** by FDA does not require review or approval by the P&T committee, although a review of all new medications for **key safety issues** (e.g., lookalike, sound-alike concerns) should be conducted to **prevent medication errors**.
- For some medication with a **narrow therapeutic range**, a more thorough evaluation of the bioequivalency data and approval of experts or the P&T committee should be considered **before implementing a generic substitution**.
- These policies and procedures should include the following points:
 - The pharmacist is responsible for selecting from available generic equivalents those drugs to be dispensed pursuant to a prescriber's order for a particular medication.
 - The prescriber has the option, at the time of prescribing, to specify the brand or supplier of the drug to be dispensed for that particular medication order **if considered clinically justified**.
 - The prescriber's decision should be based on pharmacologic or therapeutic considerations (or both) relative to that patient.

**Table 1 Considerations for P&T Committee Members
Evaluating Biosimilars for Formulary Inclusion^{1–4,6–9,12–14,17,24}**

Clinical Considerations

- Indications
- Evaluation of efficacy and safety using available data
- Immunogenicity

Product Considerations

- Nomenclature
- Manufacturing and supply chain considerations
- Packaging, labeling, and storage

Institutional Considerations

- Substitutions and interchangeability
- Therapeutic interchange
- Transition of care
- Pharmacovigilance
- Cost
- Reimbursement
- Provider and patient education
- Information technology

Table 2 American Society of Health-System Pharmacists (ASHP) Policy Guidelines on Approval of Biosimilar Medications³⁰

- Encourage the development of safe and effective biosimilars to make such medications more affordable and accessible.
- Encourage research on the effectiveness, safety, and interchangeability of biosimilar medications.
- Support legislation and regulations to allow FDA approvals of biosimilars.
- Support legislation and regulation to allow FDA approval of biosimilar medications that are determined to be interchangeable and may be substituted for the reference product without intervention of the prescriber.
- Oppose implementation of any state laws regarding biosimilar interchangeability prior to finalization of FDA guidance.
- Oppose any state legislation that would require a pharmacist to notify a prescriber when a biosimilar designated as interchangeable is dispensed.
- Require post-marketing surveillance for all biosimilar medications to ensure their continued safety, efficacy, purity, quality, identity, and strength.
- Advocate for adequate reimbursement for biosimilar medications that are designated as interchangeable.
- Develop and promote ASHP-directed education of pharmacists about biosimilar medications and their appropriate use within hospitals and health systems.
- Advocate and encourage pharmacist evaluation and the application of the formulary system before biosimilar medications are used in hospitals and health systems.

Summary

- Biologics are complex molecules produced in living cells
- Biosimilars are copies of approved biologics
 - Biosimilar \neq originator product
- Biosimilar approval is based on the 'Totality of evidence' approach
- Key areas of consideration for biosimilars
 - Extrapolation of indication
 - Interchangeability/substitution
 - Naming and labelling, pharmacovigilance
- Pharmacovigilance is critical for biologics, especially biosimilars
- Global regulatory frameworks are still being developed/evolving

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目錄
02 前言
04 臺大藥學之今
06 藥學之未來
08 藥學之過去
10 藥學之現在
12 藥學之未來
14 藥學之未來
16 藥學之未來

Thank you

臺大藥學專業學院

School of Pharmacy, National Taiwan University

發行人 新紀章 吳維豐 梁啟銘 李德義
編輯顧問 薛捷雲
執行編輯 何穎芳 張嘉銓 朱淑英
發行單位 臺大藥學專業學院
臺大藥學校友會
中華景康藥學基金會
臺大藥學系北美校友會
設計 HOUU DESIGN
地址 臺北市林森南路33號
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BACKUP SLIDE

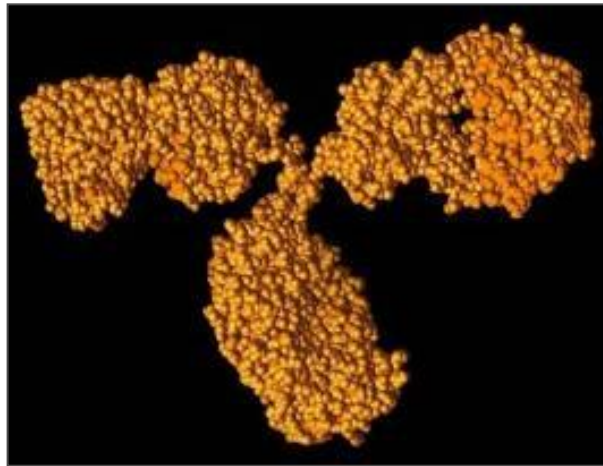
Bevacizumab

Brand Name	Avastin (originator)	Mvasi (biosimilar)
	bevacizumab	bevacizumab-awwb
Company	Roche	Amgen
Indication	Taiwan mCRC, non-squamous NSCLC, GBM, OC , BC	FDA mCRC, non-squamous NSCLC, GBM, mRCC, CC
Studies	mCRC, non-squamous NSCLC, GBM, OC , BC	NSCLC

mCRC: metastatic colorectal cancer
 NSCLC: non-small cell lung cancer
 GBM: glioblastoma
 OC: ovarian cancer
 BC: breast cancer
 mRCC: metastatic renal cell carcinoma
 CC: carcinoma of the cervix

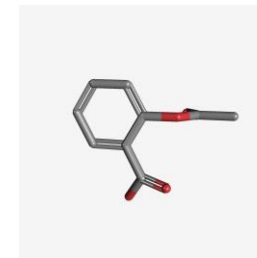
Biologics are produced in living cells

Biologics:
produced in living cells



- Produced by living cells in a complex biotechnological process
- Example: Large complex molecules

Small molecule drugs:
chemically synthesised

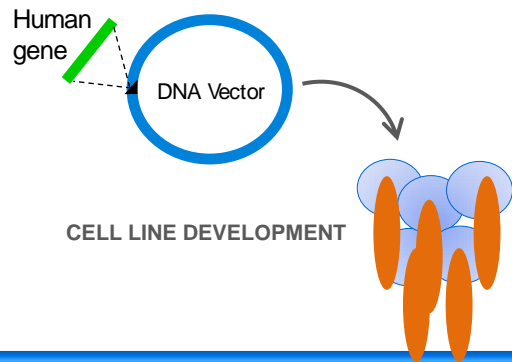


- Synthesised through a series of chemical reactions
- Manufacturing process can be reproduced to yield an identical end product (i.e. a generic)
- Example: Aspirin

How are biologics made – a complex

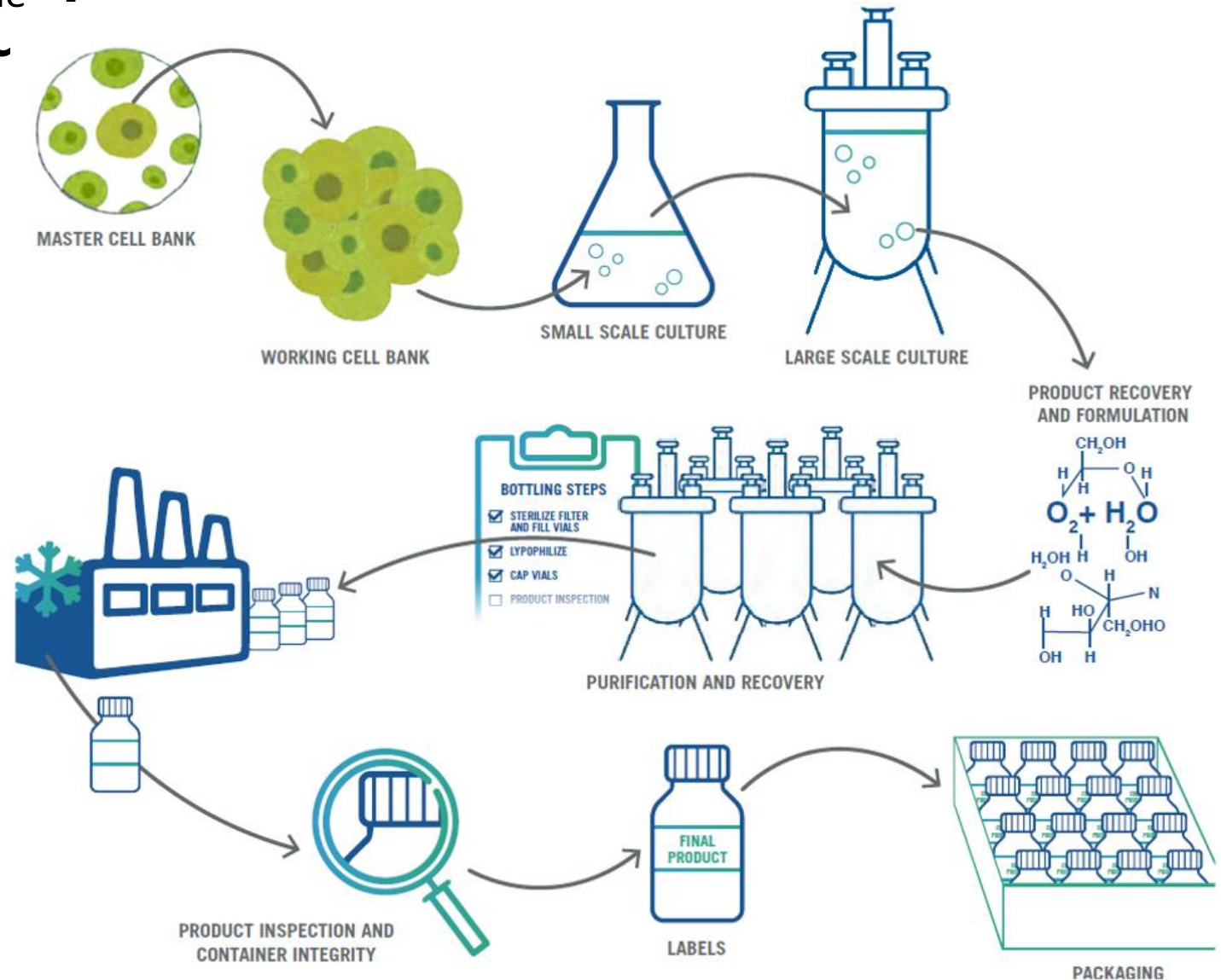
- Biologics (i.e. therapeutic proteins) are made from living cells
- Each step in the process is tailored/optimised for the specific therapeutic protein
- Due to their complex manufacturing process, biologics have an inherent variability which needs to be tightly controlled

manufacture



CELL LINE DEVELOPMENT

The product is dependent on the process



What is a biosimilar?

- A copy of an existing biologic that has already been approved
- Biosimilar must be similar to its originator product in terms of:
 - Quality characteristics
 - Biological activity
 - Safety and efficacy
- Similarity is established in a comprehensive comparability exercise
- Biosimilars are not the same as generics:
 - Generics are simpler and considered identical to their originator drugs
 - Biosimilars are complex and NOT identical to their originator products
- The biosimilar manufacturer has to re-create the entire manufacturing process, starting with an independent cell line
- Biologics, particularly mAbs, have many quality attributes
 - Those that may affect safety and efficacy are called “critical quality attributes”
 - CQAs need to be exactly matched to the originator product

Specific factors to be considered in the clinical development of a biosimilar candidate

Aspects of development	Biosimilar candidate	Originator product
Clinical design	• Comparative vs originator (normally equivalence)	• Superiority vs standard of care (SoC*)
Patient population	• Sensitive and homogeneous (patients are <i>models</i>)	• Any
Study endpoints	• Sensitive • Clinically validated PD markers	• Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)
Safety	• Similar safety profile to originator	• Acceptable benefit/risk profile versus SoC*
Immunogenicity	• Similar immunogenicity profile to originator	• Acceptable benefit/risk profile versus SoC*
Extrapolation to additional indications	• Possible if justified	• Not allowed; clinical trials required in each indication

* In some cases SoC may not exist

INDICATION EXTRAPOLATION

Remicade vs. Remsima – Clinical studies

- Clinical sensitivity
 - Pivotal comparability study
 - 606 patients with RA who previously failed MTX
 - Remicade or Remsima at wk 0, 2, and 6; every 8 weeks thereafter in combination with MTX
 - The use of MTX may confound a conclusion that Remicade \approx Remsima
 - Not reflect the outcomes in PsA, CD, UC, or Pso: infliximab monotherapy
- Clinical sensitivity
 - Ankylosing spondylitis (僵直性脊椎炎) study (pharmacokinetic study)
 - Efficacy: Remicade \approx Remsima
 - Approval for AS should not imply that extrapolation from RA to AS for future biosimilars is appropriate
 - RA has been identified as having the lowest placebo-adjusted response to infliximab and Pso the highest

Remicade vs. Remsima – Mechanism of action

- Mechanism of action
 - MAB is different from cytokines and hormones
 - Fc and Fab participate in various biological activities
 - Antigen neutralization: Fab only
 - Antibody-dependent cell-mediated cytotoxicity (ADCC): Fab along with Fc
 - Herceptin:
 - HER2 receptor binding: Fab only
 - ADCC: Fab + Fc

Remicade vs. Remsima – Mechanism of action

- Mechanism of action
 - In RA: mainly neutralization of soluble and trans-membrane TNF-alpha
 - In CD: signaling through membrane-associated forms of TNF-alpha and Fcγ receptor (trigger apoptosis or ADCC)
 - CT-P13
 - Reduced binding in vitro to FcγRIIIa and to NK cells isolated from healthy donors and CD patients
 - Specific glycosylation residues present in the Fc region after binding to the Fc region affect binding to the Fc receptor and thereby ADCC

Remicade vs. Remsima – Mechanism of action

- Mechanism of action
 - Health Canada: not approve CD or UC indication
 - Differences in the ability of CT-P13 to induce ADCC could not be ruled out
 - ADCC can not be ruled out as a mechanism of action in the inflammatory bowel diseases

Remicade vs. Remsima – Mechanism of action

- Immunogenicity
 - FDA & WHO: investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events
 - RA study: MTX suppresses the formation of anti-drug antibodies to infliximab
 - Patients with AS historically exhibited a lower incidence of anti-drug antibodies to infliximab than patients with Pso, CD, or UC

Remicade vs. Remsima – Mechanism of action

- Site of action
 - Infliximab is active in various tissues and organ systems
 - Drug levels in serum may not be an adequate surrogate for drug level in target tissues
 - All relevant target tissues have not been evaluated by the comparative studies in RA and AS

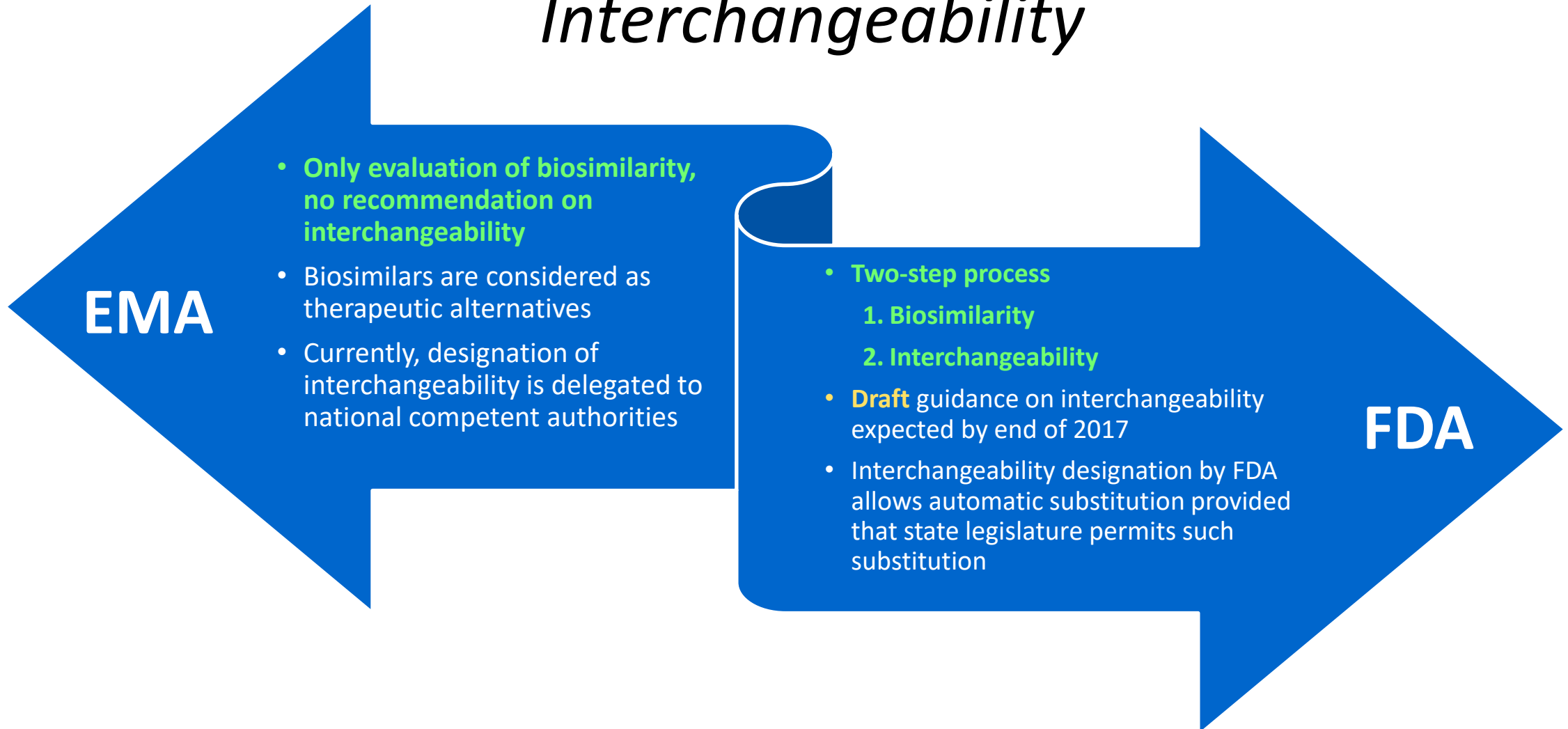
CT-P13 vs. Infliximab

- Pathophysiology of disease
 - RA, AS, PsA, CD, UC, and Pso are distinct conditions
 - TNF-alpha
 - Implicated in all of them
 - The contribution to disease progression depends on receptor interactions and cooperating pathway in specific tissues
 - In body as soluble form and trans-membrance form, and the interaction with receptors TNFR1 and TNFR2
 - These disease do not share a single, common, pathophysiology

INTERCHANGEABILITY

Differences in regulatory approaches in the EU and US

Interchangeability



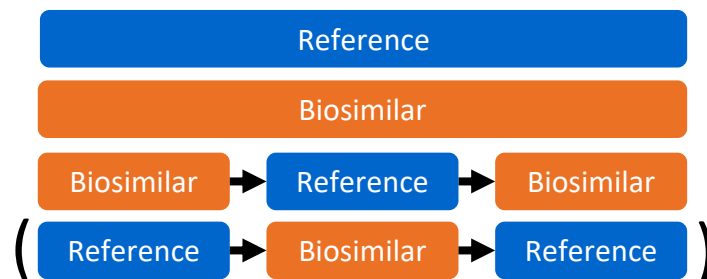
US/FDA – ‘Interchangeable’ product designation for biosimilars

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- To date, **no biosimilars** have been approved with an ‘interchangeable’ designation.

What would a study investigating interchangeability of biosimilars look like?

Cross-over studies address the safety and efficacy of switching

Addition of **parallel** switching arm(s) to registration study



Supplementary switching study following registration study



Extension switching study following registration study



- At least two switches are required to establish comparable efficacy and safety of alternating between reference product and biosimilar (i.e. interchangeability).
- Switching may be incorporated into the clinical development programme as a supplementary or extension study following the registration study.

Different categories that approved by FDA

Product Designation	Application Type	Application Pathway	Clinical Studies Required	
Drug Food, Drug, and Cosmetic Act	New Drug Application (NDA)	505(b)1	Yes, full evaluation of safety and efficacy	
		505(b)2	Yes, however, studies do not have to be done by the application sponsor	
	Abbreviated New Drug Application (ANDA)	505(j)	No, but must demonstrate bioequivalence	Generic medication
Biologic Public Health Services Act	Biologics License Application	351(a)	Yes, full evaluation of purity, safety and potency	Biologic products
	Biosimilar Application	351(k)	Yes, but abbreviated process	biosimilar

Approved based on detailed structural and functional characterization and clinical trial information

NDA 505(b)2: For Drugs with new indications, new formulation, prodrugs of an existing drug, new combination, etc.