Biosimilar is biosimilar

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Contents

- ★ Basic concept
- ★ FDA Approval
- ★ Extrapolation
- ★ Switch & Interchangibility
- ★ Pharmacovigilance & Naming

Biologic

What is a biological product?

- Basic concept

Biologics are a class of drugs that are produced using a living system, such as a microorganism, plant cell, or animal cell.

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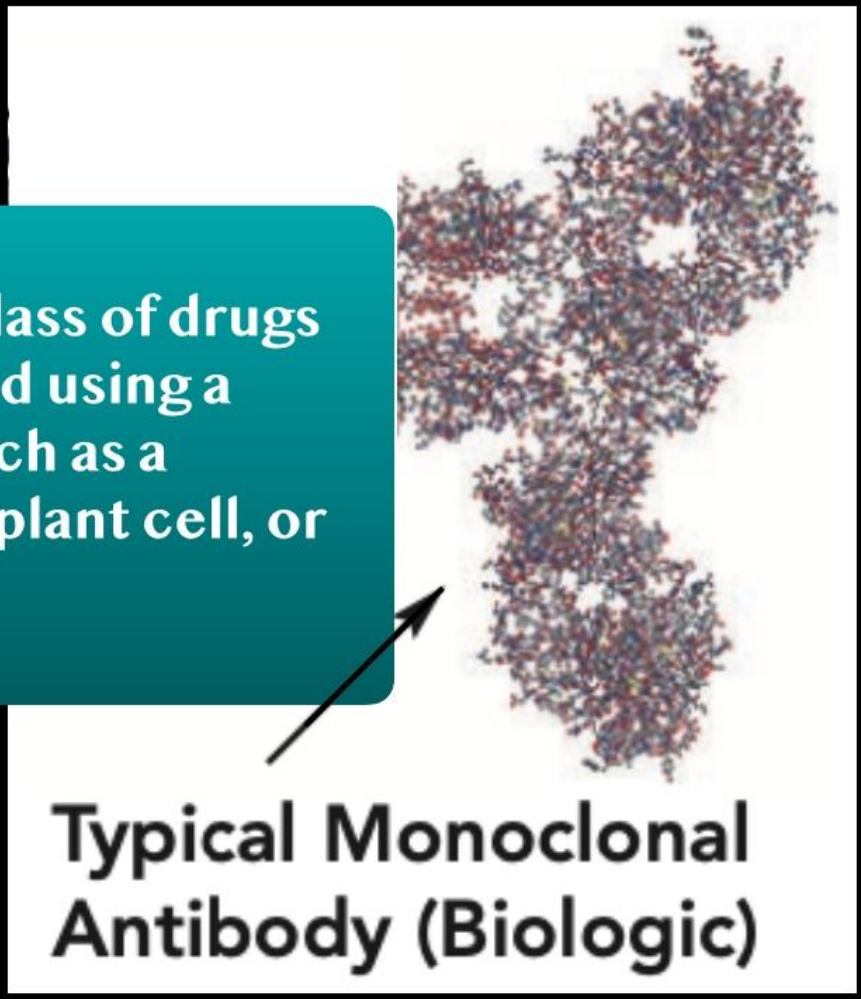

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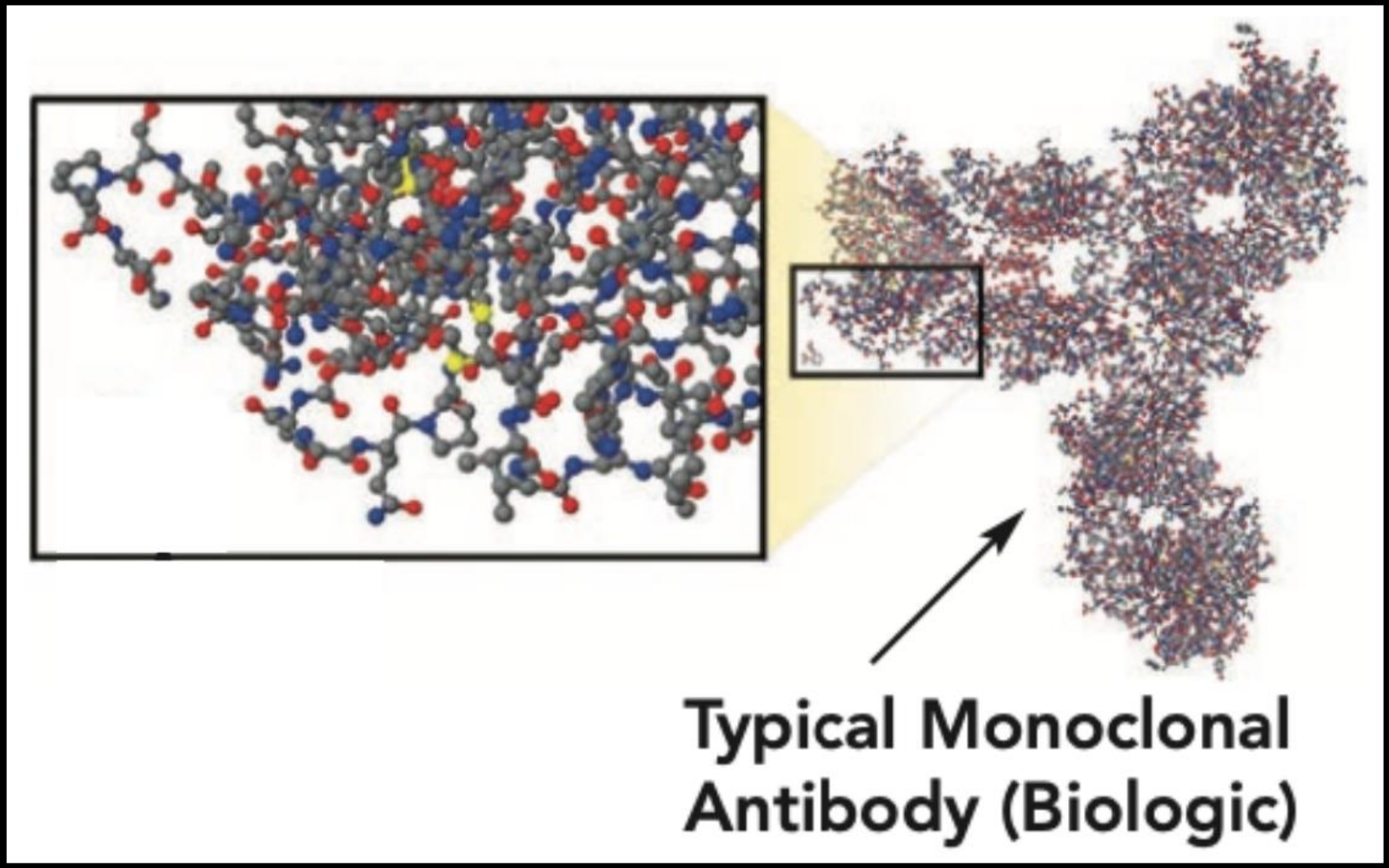

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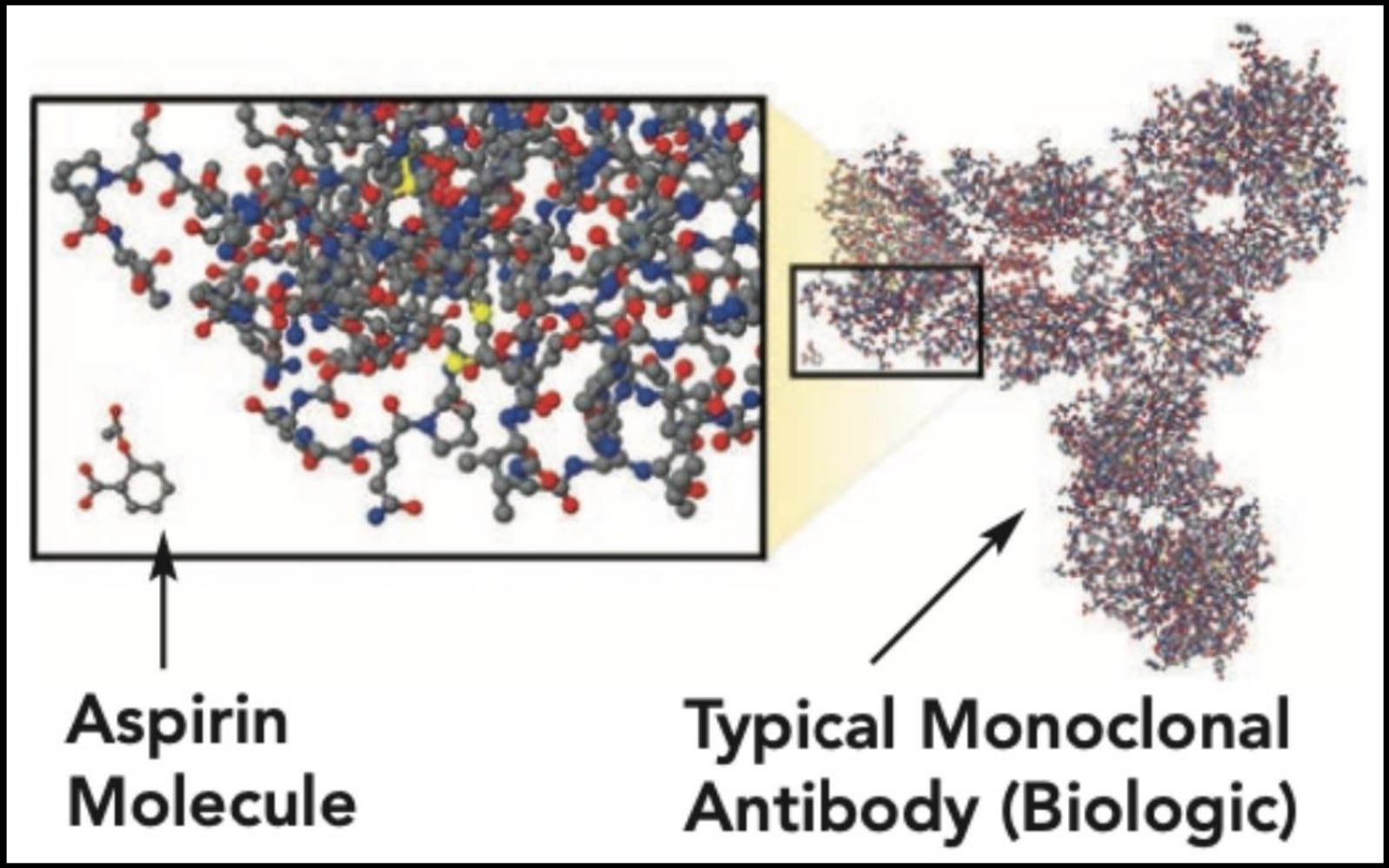

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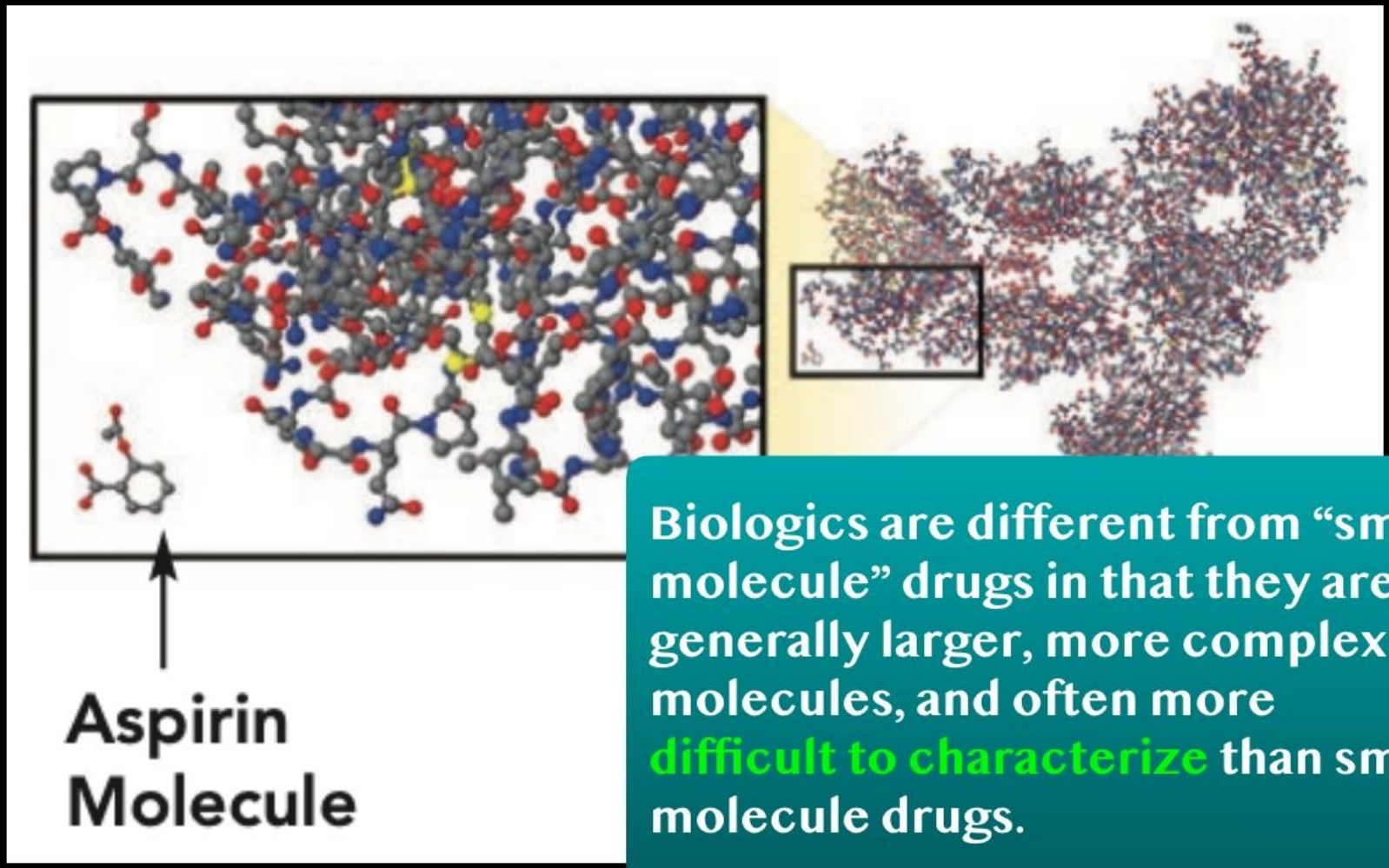
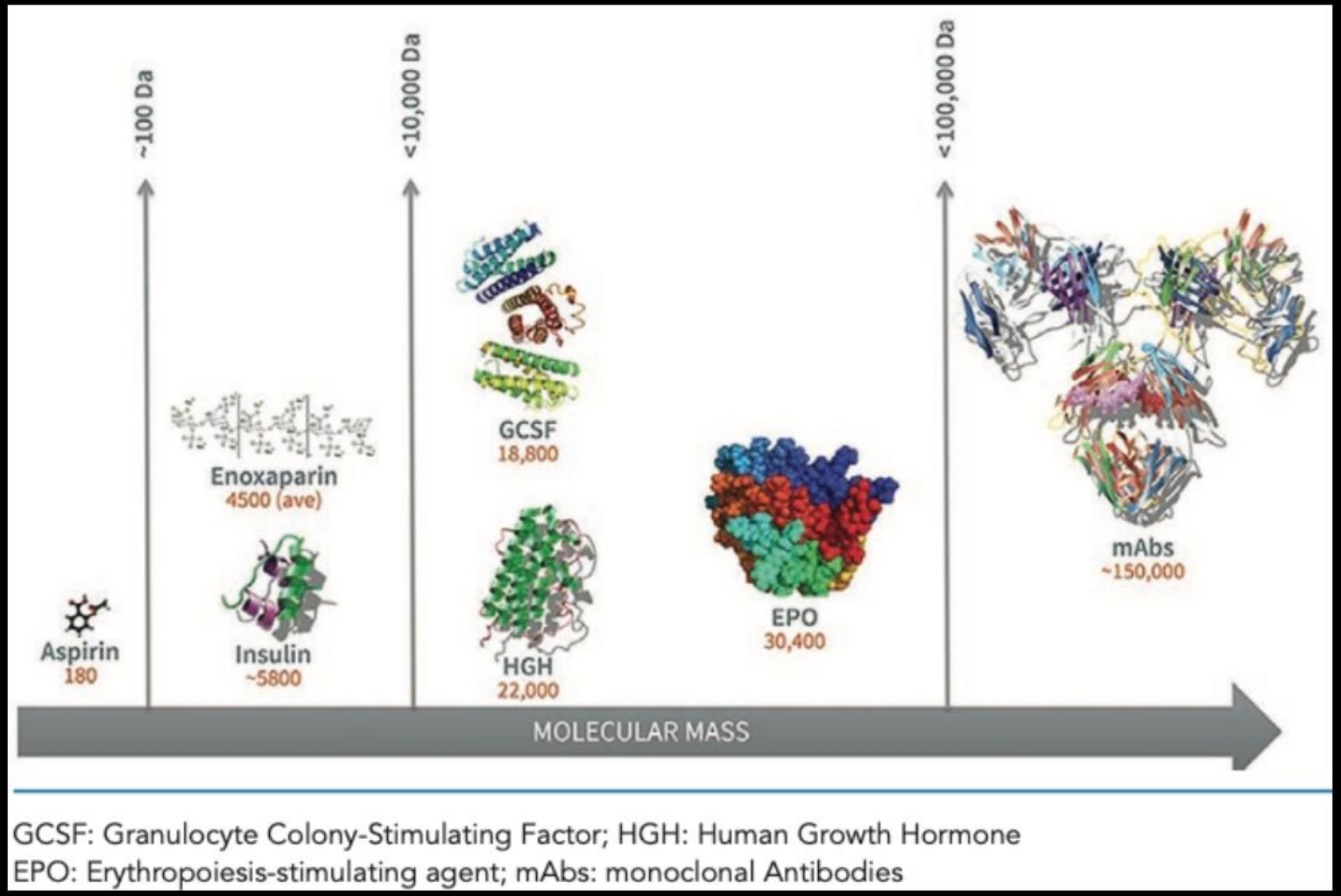


Biologics are different from "small molecule" drugs in that they are generally larger, more complex molecules, and often more difficult to characterize than small molecule drugs.

Biologic

What is a biological product?



GCSF: Granulocyte Colony-Stimulating Factor; HGH: Human Growth Hormone
EPO: Erythropoiesis-stimulating agent; mAbs: monoclonal Antibodies

Biologic

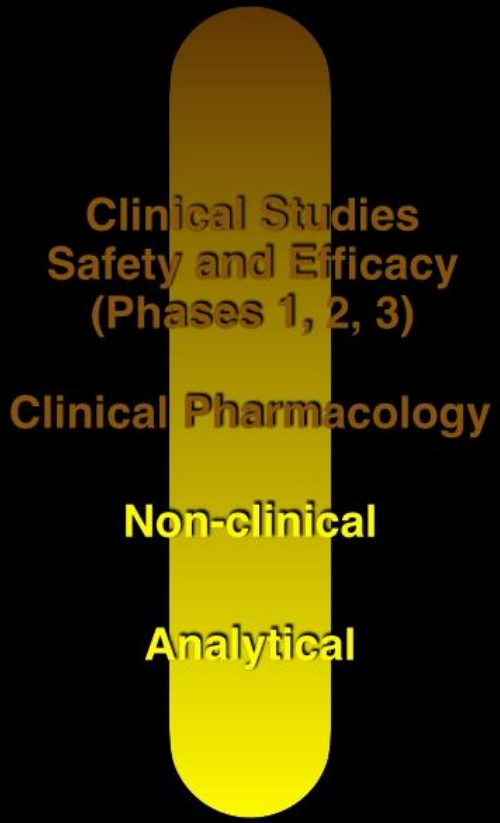
What is a biological product?

- There are many types of biological products approved for use, including
  - monoclonal antibodies (such as bevacizumab)
  - therapeutic proteins (such as filgrastim)
  - vaccines (such as those for influenza and tetanus).
- Biologics are usually administered via injection or infusion.

Biologic: Approval

- A branded biologic is approved in a "standalone" application that must contain all data and information necessary to demonstrate its safety and effectiveness.

Biologic: Approval



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- Generally, the data and information necessary to demonstrate the safety and effectiveness of a branded biologic will include clinical trials for the disease indications being sought by the manufacturer.

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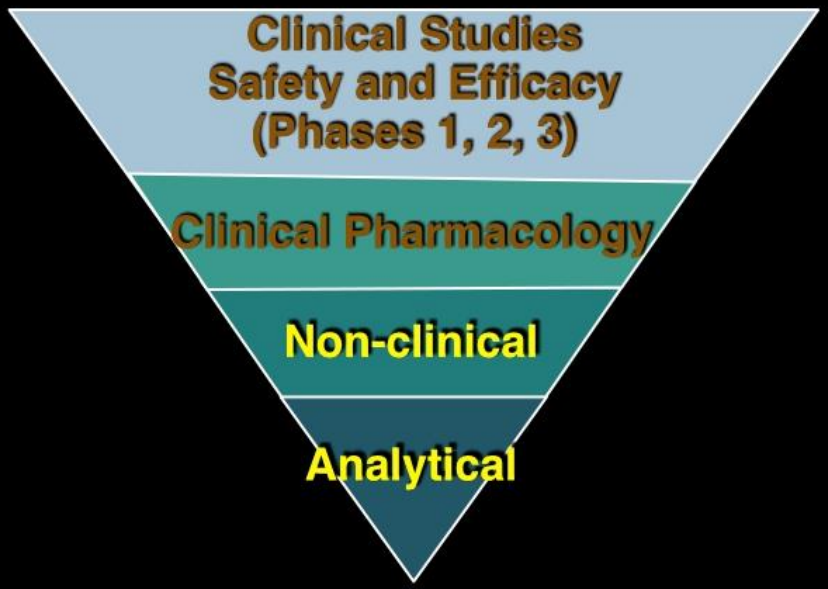

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Biosimilar ?

Biosimilar

Official Definitions of Biosimilars

The European Medicine Agency - A biosimilar is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The United States Food and Drug Administration - A biosimilar is a biological product that is highly similar to a US licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

The World Health Organization - A biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

World Health Organization

Biosimilar

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

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Biosimilar

- A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved biologic.
- A biosimilar is as safe, pure, and potent as the reference product for the indications. There will be no clinically meaningful difference between an original biologic product and a biosimilar.

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- A biosimilar is as safe, pure, and potent as the reference product for the indications. There will be no clinically meaningful difference between an original biologic product and a biosimilar.
- In order to be deemed a biosimilar, the product will have the same mechanism of action (how it works in the body), route of administration (e.g., injection or infusion), dosage form, and strength as its reference product.

Biosimilar: History

- 2006: recombinant human growth factor (Omnitrope) as the 1st biosimilar to receive EMA approval
- 2007: epoetin alfa approved by EMA
- 2009: recombinant human granulocyte colony-stimulating factor approved by EMA

Biosimilar: History

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- 2007: epoetin alfa approved by EMA
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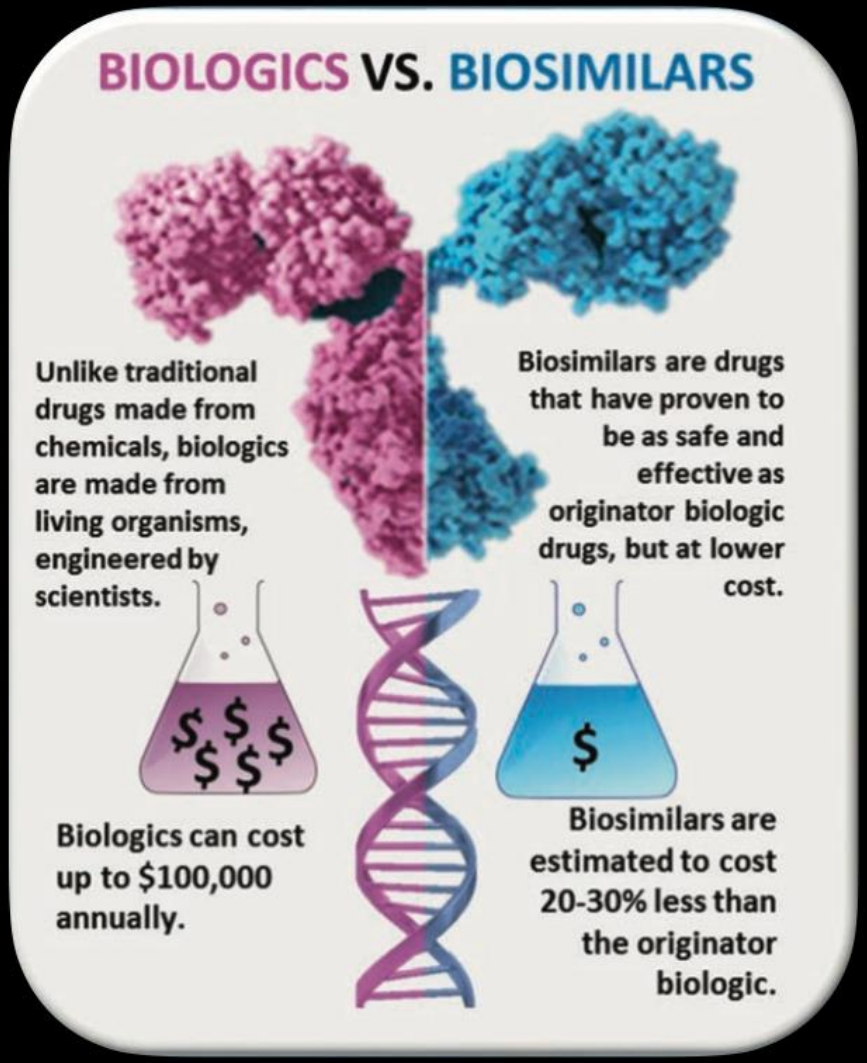
- 2015: recombinant human granulocyte colony-stimulating factor as the 1st biosimilar approved by FDA

Potential problems



Potential problems

Manufacture of biological product

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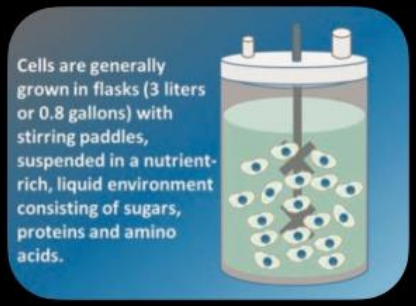

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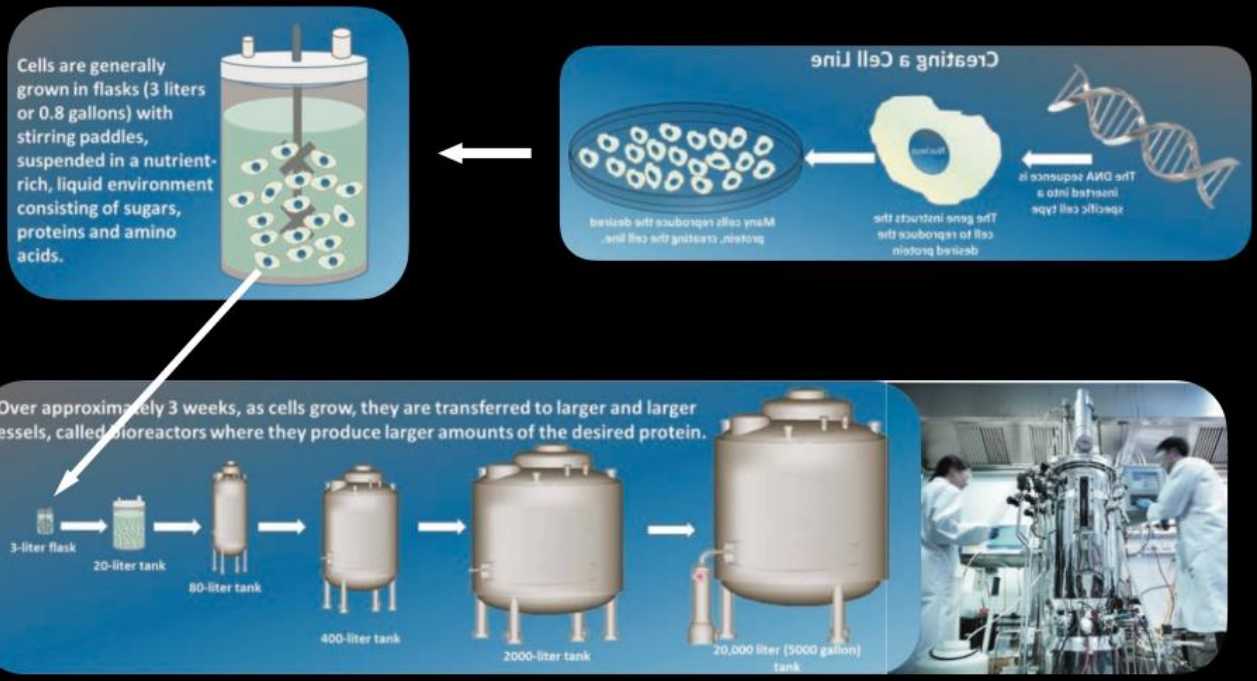

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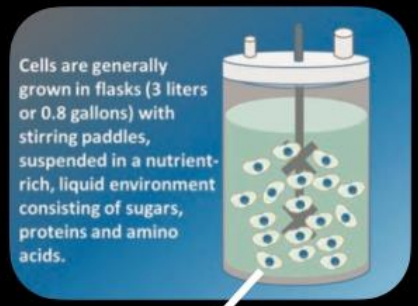

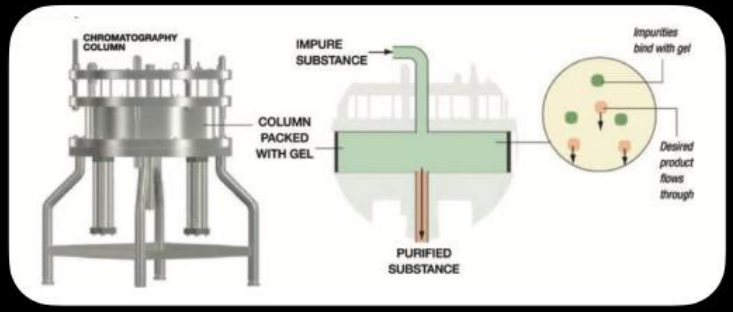

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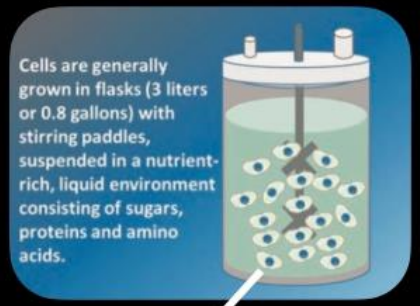
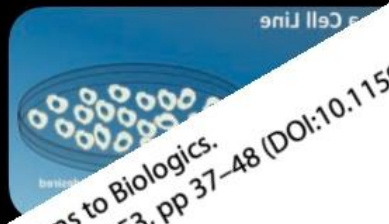


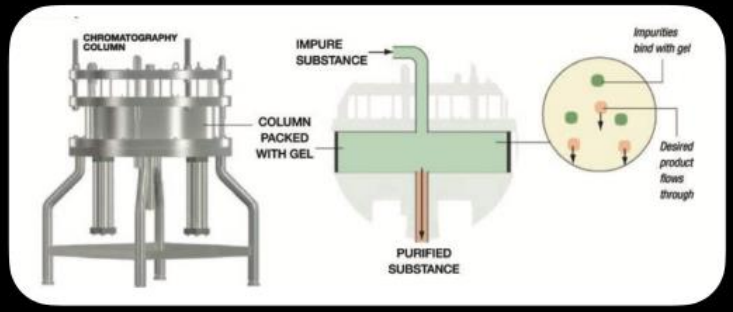


Puig L, Gulliver W (eds): Adverse Reactions to Biologics.
Curr Probl Dermatol. Basel, Karger, 2018, vol 53, pp 37–48 (DOI:10.1159/000478077)

The Immunogenicity of Biologic Therapies

Sandra Garcês[a] · Jocelyne Demengeot[b]

[a]Eli Lilly and Company, Indianapolis, IN, USA; [b]Instituto Gulbenkian de Ciencia, Oeiras, Portugal



Biosimilar

Incyte

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Incyte Announces Global License Agreement with Jiangsu Hengrui Medicine for SHR-1210, an Investigational Anti-PD-1 Monoclonal Antibody

02 September, 2015

Incyte to pay Hengrui $25 million upfront plus the potential for milestone and royalty payments

江蘇恆瑞醫藥

Jiangsu Hengrui Medicine Co,.Ltd

WILMINGTON, Del.--(BUSINESS WIRE)--Sep. 2, 2015-- Incyte Corporation (Nasdaq: INCY) today announced a global license and collaboration agreement with Jiangsu Hengrui Medicine Co., Ltd. for the development and commercialization of SHR-1210, an investigational anti-PD-1 monoclonal antibody. Under the agreement, Incyte will have the exclusive development and commercialization rights to SHR-1210 worldwide, with the exception of Mainland China, Hong Kong, Macau, and Taiwan. SHR-1210 is expected to enter proof-of-concept studies for the treatment of patients with advanced solid tumors in the coming months.

"The addition of this anti-PD-1 candidate to our early stage portfolio reinforces our commitment to cancer patients and further diversifies our clinical development programs," stated Hervé Hoppenot, President and Chief Executive Officer of Incyte. "We continue to make excellent progress in the multiple clinical trials underway across our existing portfolio, including our strategic collaborations."

Piaoyang Sun, Chairman of the Board of Hengrui, added, "Both Incyte and Hengrui are dedicated to cancer immunotherapy and are investigating several relevant biological targets in the area. The addition of SHR-1210 is an excellent fit to Incyte's oncology portfolio, and we are pleased to see Incyte's commitment to this PD-1 program. Combining the expertise and resources of both companies can accelerate the development of SHR-1210."

Terms of the Agreement

Under the terms of the agreement, Incyte will acquire development and commercialization rights to SHR-1210 worldwide, with the exception of Mainland China, Hong Kong, Macau, and Taiwan, in exchange for an upfront payment of $25 million. The terms also include potential milestone payments of up to $770 million to Hengrui, consisting of $90 million for regulatory approval milestones, $530 million for commercial performance milestones, and $150 million based on clinical superiority. The terms also include tiered royalties to Hengrui on net sales of SHR-1210 in Incyte territories. Under the Agreement, Incyte and Hengrui will assume all financial obligations associated with the development and commercialization of SHR-1210 in their respective territories.

About Anti-PD-1 Monoclonal Antibodies

Monoclonal antibodies targeting PD-1 enhance anti-tumoral immunity and are being developed for the treatment of cancer. Many tumor cells express PD-L1, an immunosuppressive PD-1 ligand. Inhibition of the interaction between PD-1 and PD-L1, known as immune checkpoint blockade, can enhance T-cell responses and mediate preclinical antitumor activity.[1]

For this transaction, Incyte was advised by Morgan Lewis, and Hengrui was advised by Wilson Sonsini Goodrich & Rosati.

Biosimilar

Incyte

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江蘇恆瑞醫藥,是國內創新藥企代表,2015年該公司PD-1項目SHR-1210在尚未上市前就有償許可給美國Incyte公司,收益2500萬美元首付外加7.7億美元總額里程金,即當SHR-1210項目每完成一個重要研究進展,Incyte就會從7.7億美元中拿出一定比例作為項目進度款支付。

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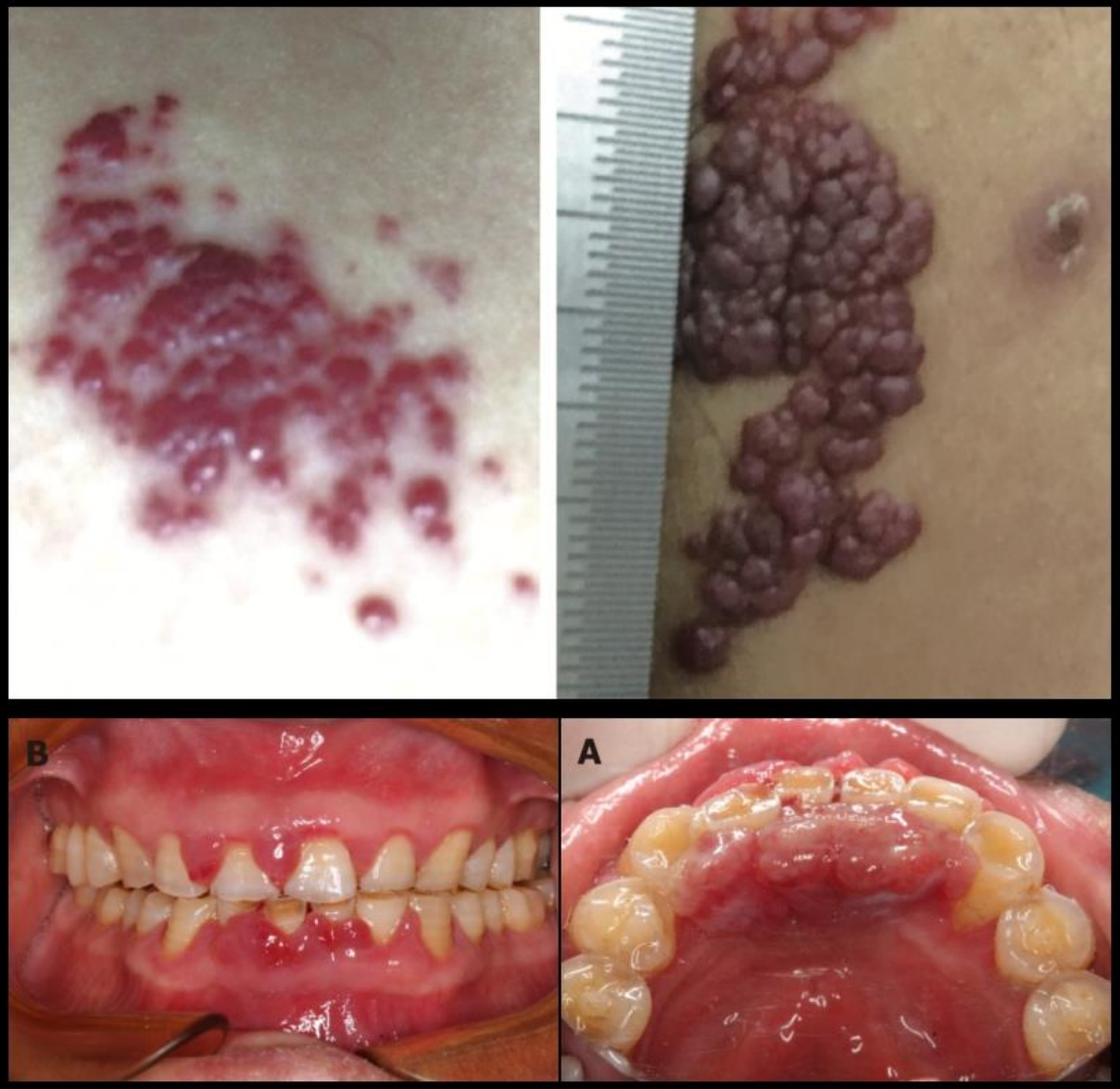
Biosimilar: Immunogenecity



What is the likely rate of biosimilar use in routine clinical practice ?

Nearly half of prescribers (49.0%) use biosimilars in their clinical oncology practice.

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- **Asia-Pacific prescribers: ? %**
- **European prescribers: ? %**
- **UK prescribers: ? %**

What is the likely rate of biosimilar use in routine clinical practice ?

Nearly half of prescribers (49.0%) use biosimilars in their clinical oncology practice.

- **Asia-Pacific prescribers: 56.3%**
- **European prescribers: 46.5%**
- **UK prescribers: 31.3%**

Contents

- ★ Basic concept
- ★ FDA Approval

(1) Biosimilar product is compared to and evaluated against an approved biological medicine, which is also known as …

① **Brand-name biologic**

② **Branded biologic**

③ **Innovator biologic**

④ **Originator**

⑤ **Reference product**

⑥ **All of above**

⑦ **None of above**

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⑤ Reference product

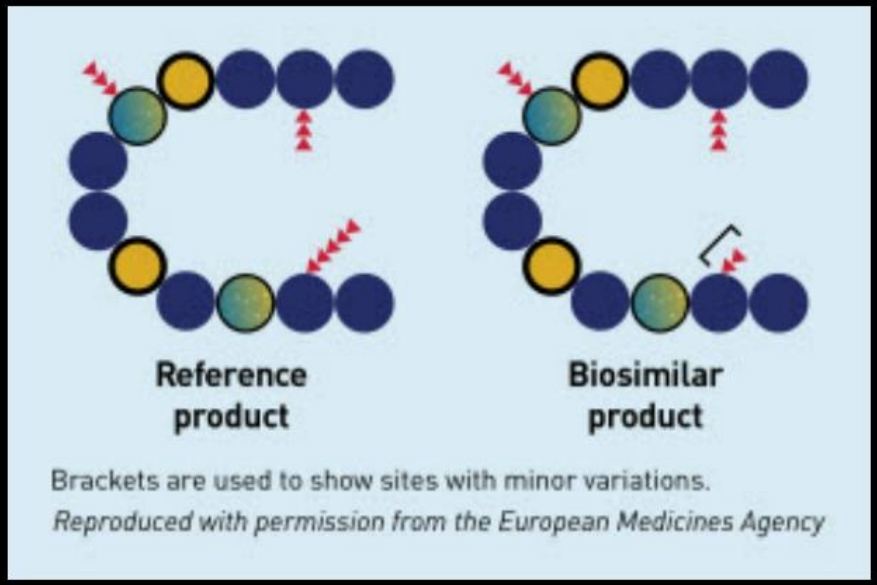
⑥ All of above

⑦ None of above

Minor differences between the reference and biosimilar products

Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable.

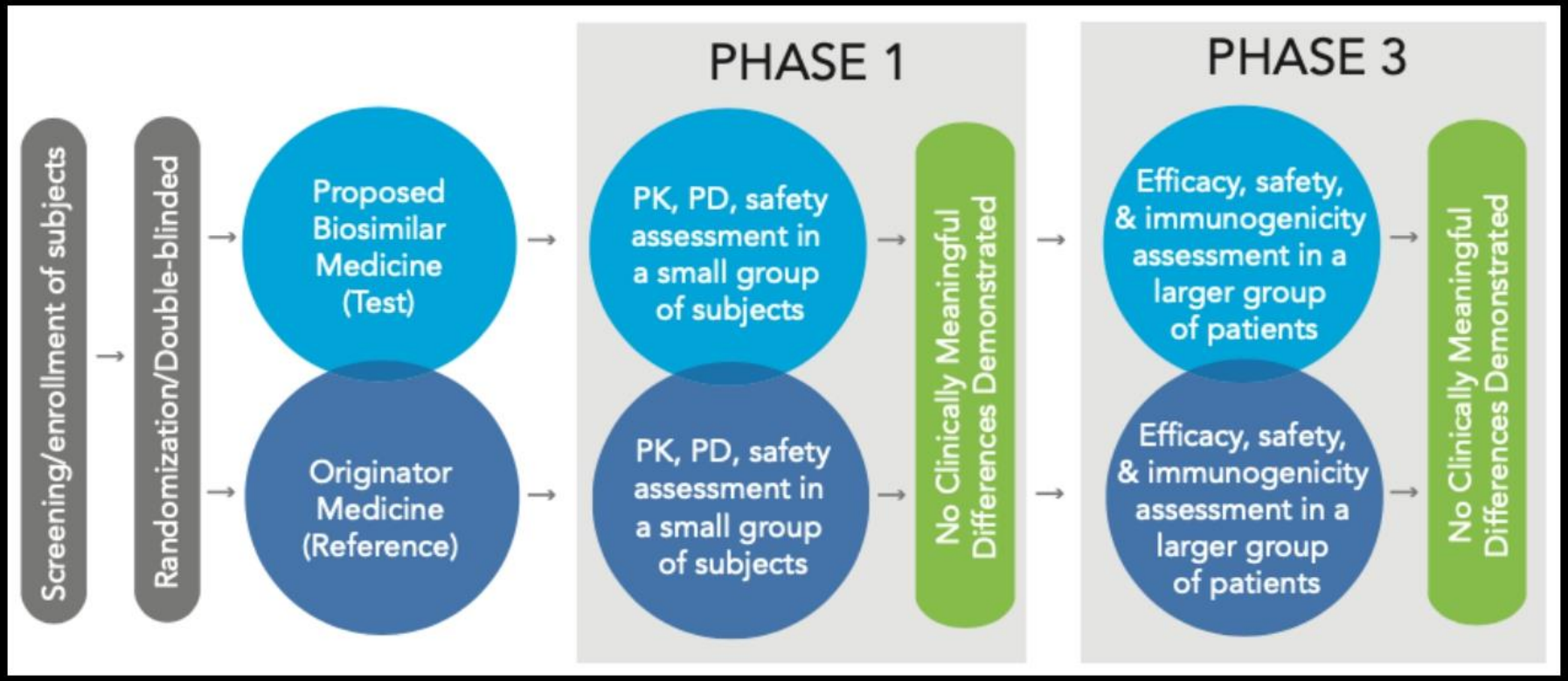
For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product.



No clinical differences between the reference and biosimilar products

- A patient using a biosimilar can expect the **same physical responses** to the biosimilar as they would to the reference product ….
- when these products are **used as intended**.

Biosimilar: Approval



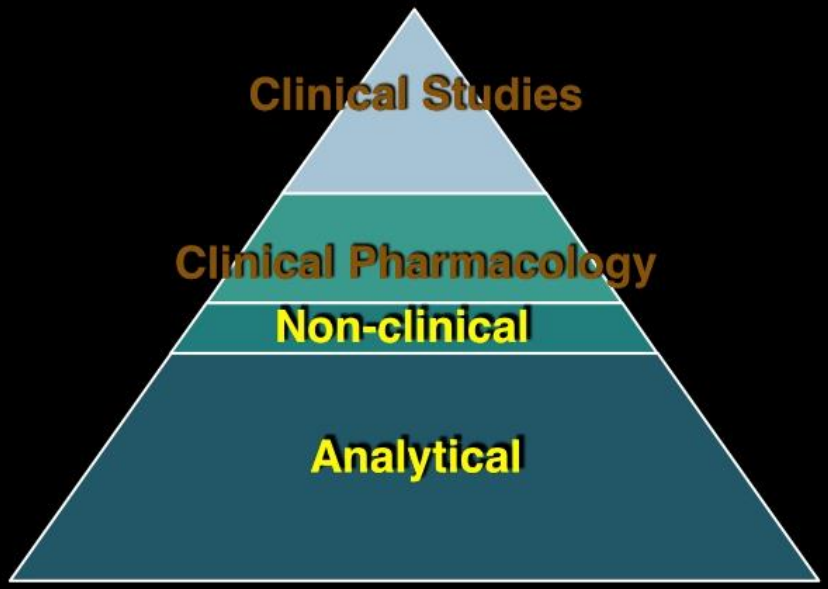
The biosimilar pathway depends on a head-to-head comparison of the proposed biosimilar to a reference product.

Biosimilar: Approval

Not to independently establish the safety and effectiveness of the proposed product. To demonstrate no clinically meaningful differences based on the 'totality of evidence' approach, that is, a comprehensive comparison of the proposed biosimilar and the reference medicine with respect to structure, function, pharmacokinetics, pharmacodynamics, clinical immunogenicity, safety and efficacy.

Biosimilar: Approval

The comparative data are generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies



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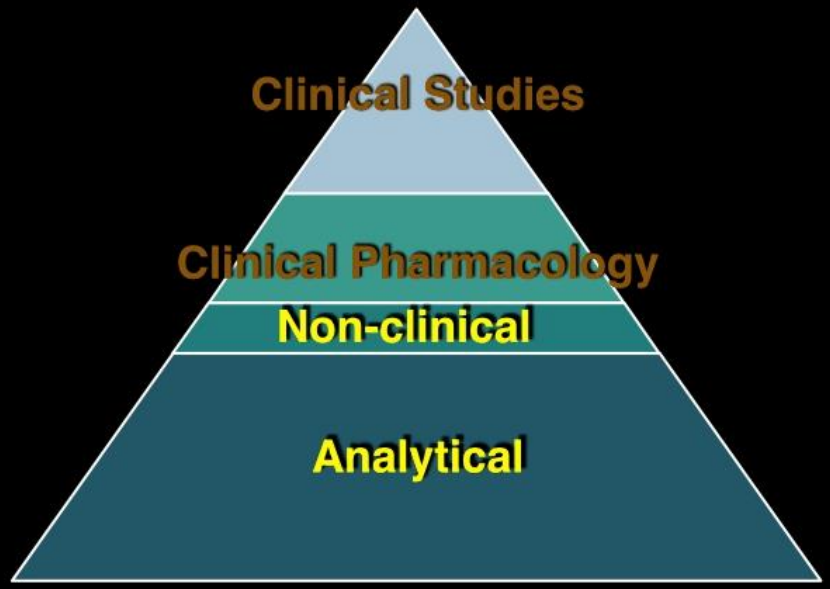
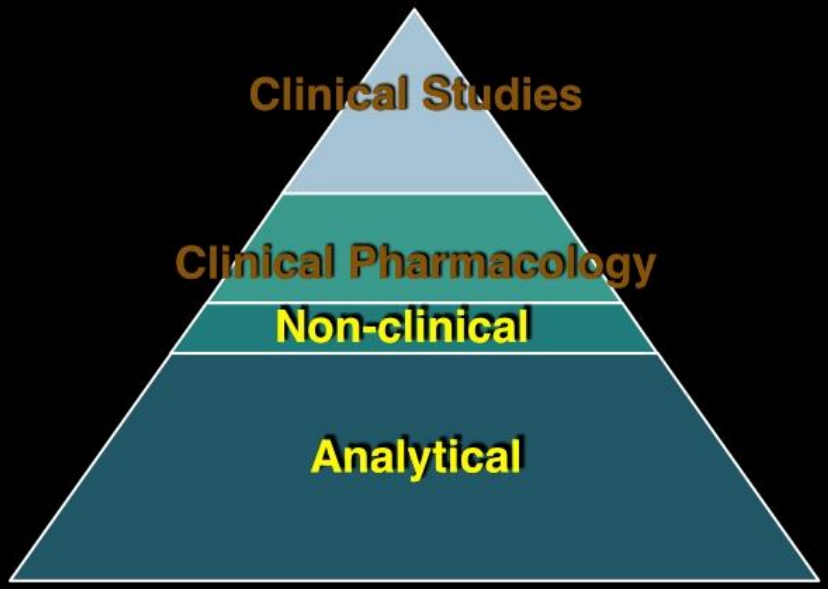


Clinical development is abbreviated and in general consists of:

- 1 Phase I PK/PD study (N~100)
- 1 Phase III (N~600 for oncology, ~400 for RA)

Biosimilar: Approval

1. **Analytical** data showing high similarity
2. Animal studies, including an assessment of toxicity
3. **Clinical** data sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications.



Biosimilar: Approval

- **A manufacturer of proposed biosimilar product may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval.**

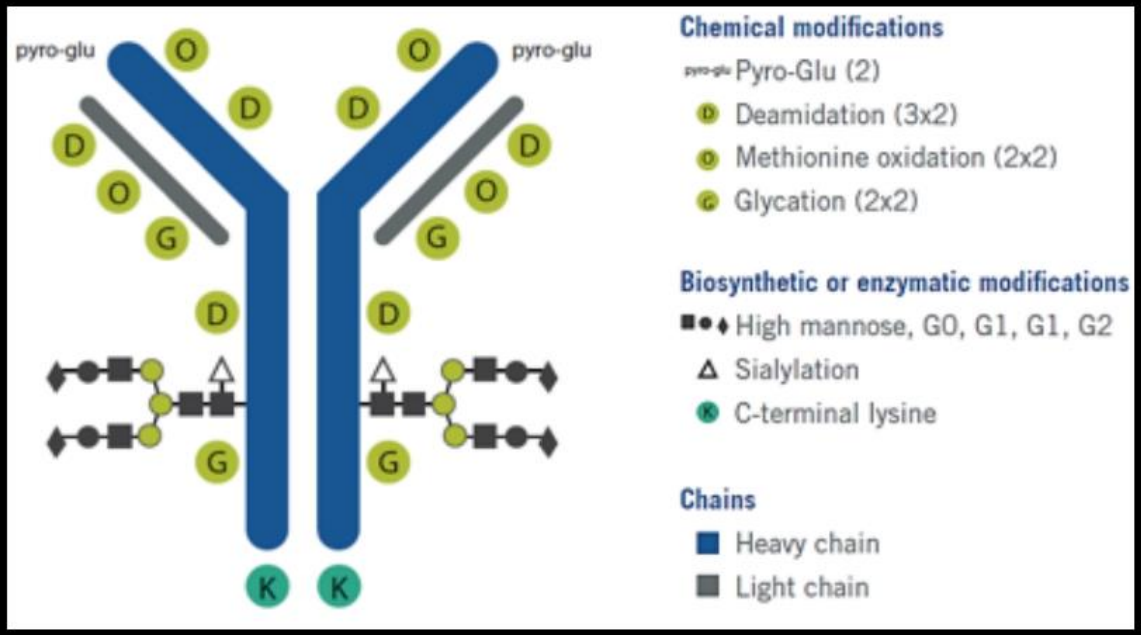
重要性	關鍵品質屬性	臨床相關性與影響
極重要	三級立體結構、ADCC 活性	非常顯著
重要	FcRn 結合力、多醣基	顯著
中等	分子量、不可見微粒	中等
普通	其他非醣基化轉譯後修飾	可接受

ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity; FcRn: neonatal Fc receptor

表一．主管單位對於關鍵品質屬性項目重要性評比

Post-Translational Modifications

- Cleavage
- Glycosylation (present on ≥40% of approved biologics)
- Methylation
- Sialylation
- Methionine oxidation
- Deamidation



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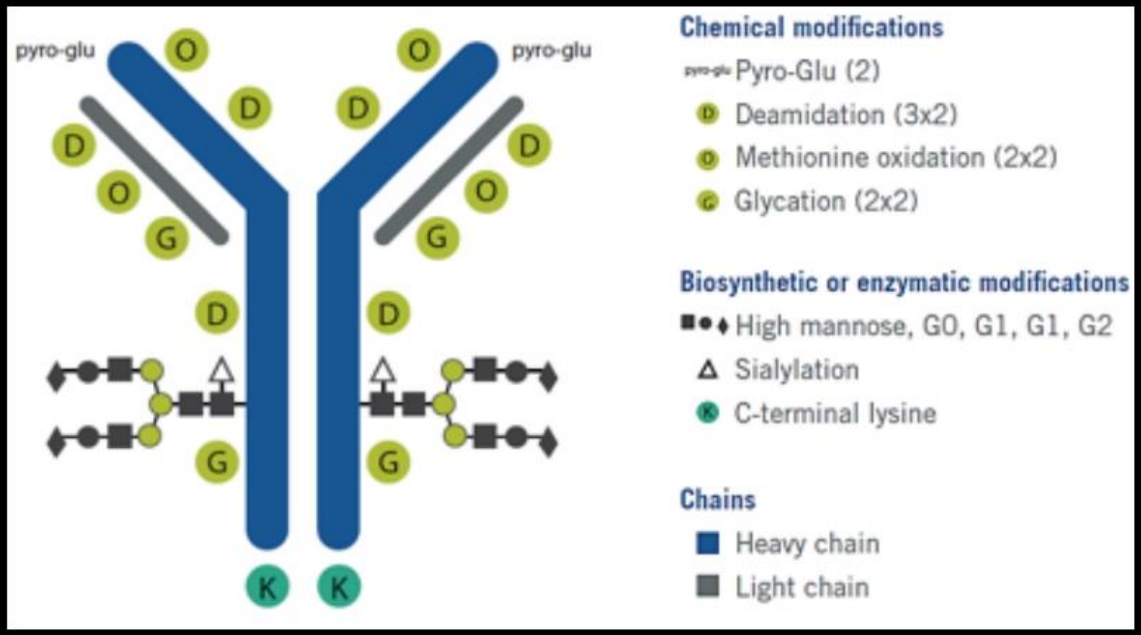

e.g. Higher glycan occupancy in ABP-215 compared to Avastin → may result in higher clearance

(2) Which one of the following is the purpose of clinical data required for approval of a biosimilar product?

① **To show the benefit of the biosimilar product**

② **To show that it is any better than the reference product**

③ **To ensure that any differences have no impact on its quality and safety**

A survey by the European Society for Medical Oncology

(2) Which one of the following is the purpose of clinical data required for approval of a biosimilar product?

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② **To show that it is any better than the reference product**

③ **To ensure that any differences have no impact on its quality and safety**

A survey by the European Society for Medical Oncology

Clinical data required for approval of a biosimilar product

- The goals of a biosimilar development program are different from those of a reference product development program.
- This typically includes assessing
  - **immunogenicity**:
    if it is known that patients have the potential to develop immune responses with adverse outcomes to the reference product, FDA will likely require a more rigorous evaluation of immune responses with the biosimilar.
  - **pharmacokinetics** (exposure)
  - **pharmacodynamics** (response) in some cases
  - a **comparative** clinical study may also be included

Clinical data required for approval of a biosimilar product

- Generally, biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

Clinical data required for approval of a biosimilar product

- Generally, biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

- By focusing on a comparative analysis, biosimilars can be approved without the need to complete the same number of costly clinical trials as the reference product.

What does the phrase 'sensitive indication' mean in terms of biosimilar development?

Less than half (45.2%) of prescribers were able to identify the most appropriate definition of 'sensitive indication'.

Correctly answered by

- **60.0% of Asia-Pacific prescribers**
- **42.1% of European prescribers**

A survey by the European Society for Medical Oncology

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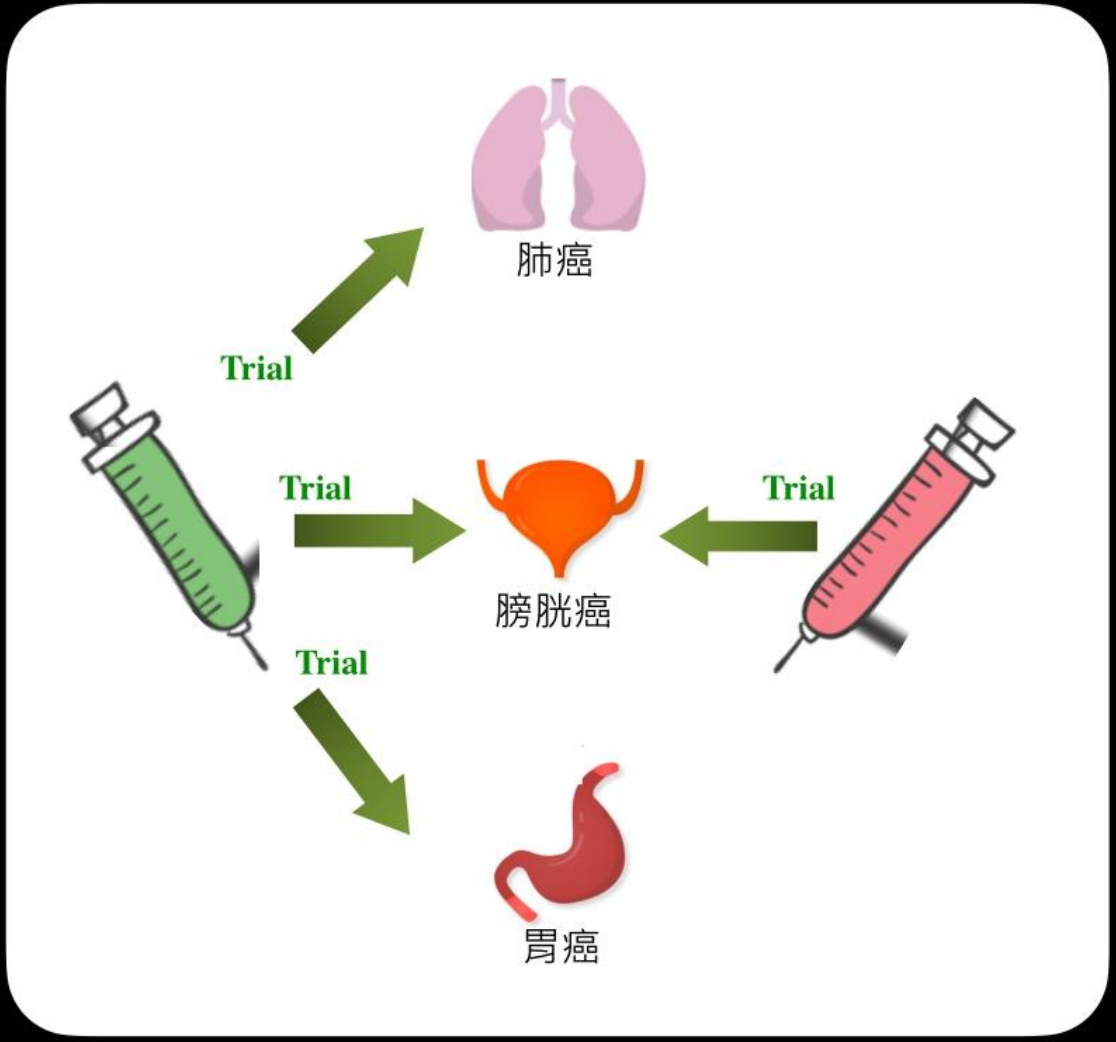
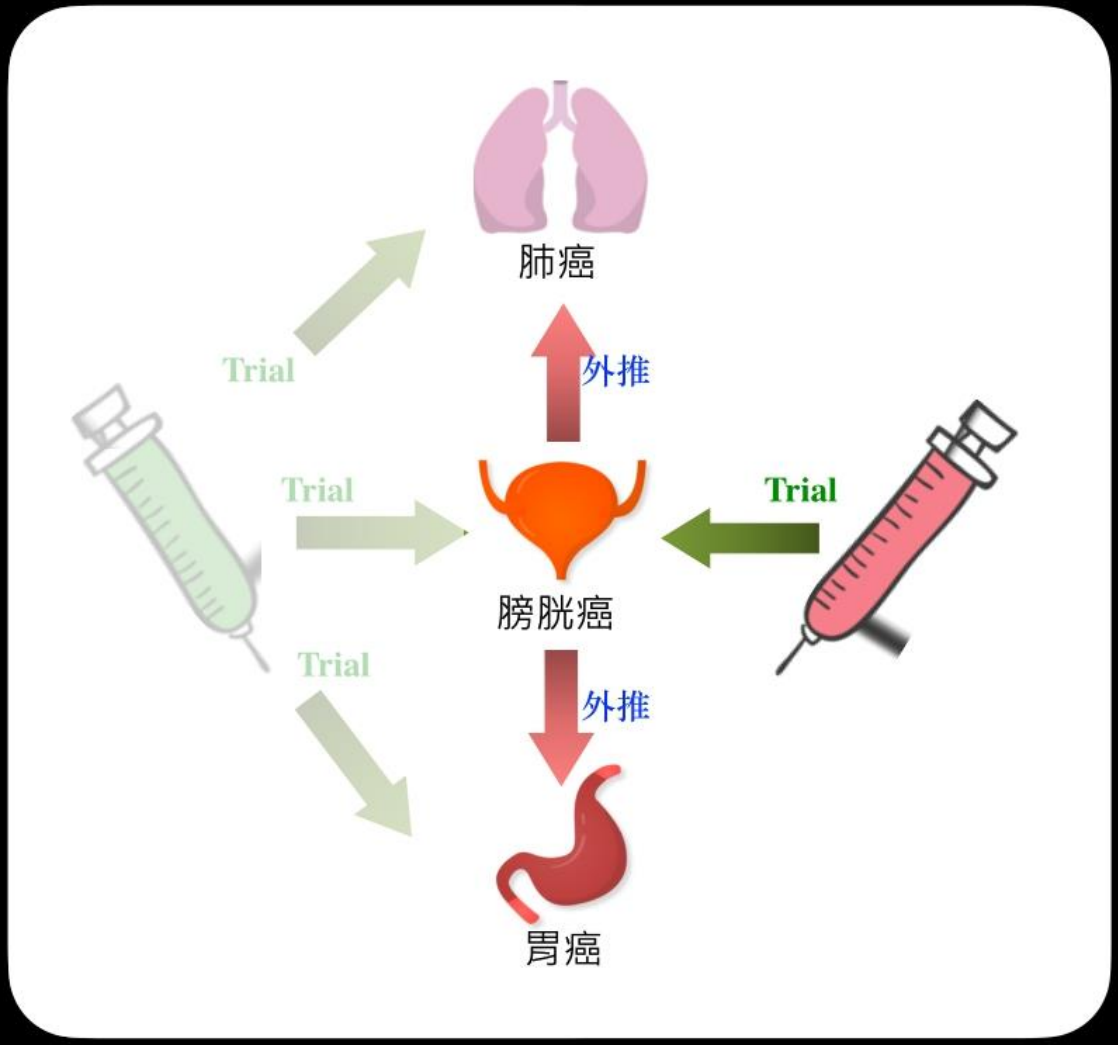
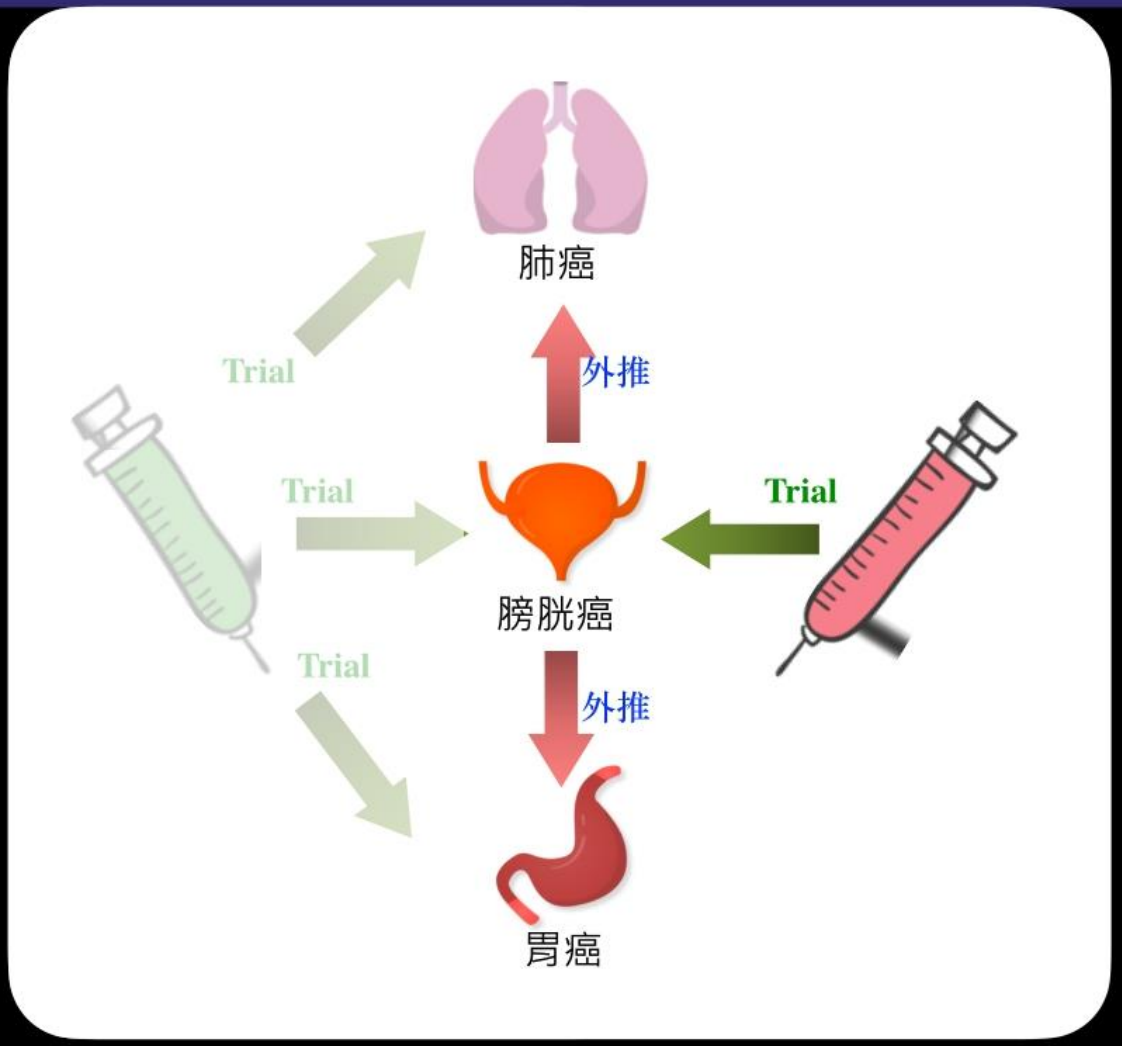
適應症外推



適應症外推



(5) Is it OK?



(5) Which one of the following statement regarding indication is incorrect?

① **Biosimilar products may be approved for all or a subset of the same indications as the reference product.**

② **Biosimilars may have fewer indications than the reference product.**

③ **Biosimilar products only have the indication that is proved by its own clinical trials.**

A survey by the European Society for Medical Oncology

A biosimilar can be approved for an indication that is approved for the reference product even if the biosimilar is not directly studied in that indication.

- If the total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer.

- This concept is called "extrapolation" and is critical to the goals of an abbreviated pathway–improving access and options at a potentially lower cost.

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- If the total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer.

- It is generally unnecessary from a scientific perspective to require a biosimilar manufacturer to conduct clinical trials in all the same disease indications for which the reference product was studied and approved.

Indications of biosimilars

- Biosimilar products may be approved for all or a subset of the same indications as the reference product.
- Biosimilars may have fewer indications than the reference product if, for example, a reference product has unexpired exclusivity for an indication that prevents other manufacturers from obtaining approval for that particular indication.

The scientific justification factors for extrapolation

- The scientific justification factors include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications.

The scientific justification factors for extrapolation

- The scientific justification factors include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications.
- FDA evaluates all of the biosimilar product data to assess whether there are differences between the biosimilar and the reference product that may affect these scientific factors in any of the indications or populations not directly studied by the biosimilar manufacturer.
- If no such differences are identified, approval of the biosimilar for other non-studied indications or populations is generally supported.

The basis of extrapolation

Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population.

The basis of extrapolation

Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population. Extrapolation is based on

1. all available data and information in the biosimilar application,
2. FDA's previous finding of safety and efficacy for other approved indications for the reference product, and
3. knowledge and consideration of various scientific factors for each indication.

FDA works with biosimilar manufacturers during product development to determine what data are needed to support extrapolation.

Contents

- ★ Basic concept
- ★ FDA Approval
- ★ Extrapolation
- ★ Switch & Interchangibility

(7) Can a biosimilar product be used in patients who have previously been treated with the reference product?

① **Yes**

② **No**

(7) Can a biosimilar product be used in patients who have previously been treated with the reference product?

① Yes

② No

(7) Can a biosimilar product be used in patients who have previously been treated with the reference product?

- **Yes, biosimilars can be used in treatment-experienced as well as in treatment-naïve patients.**

Can a biosimilar product be used in patients who have previously been treated with the reference product?

- Yes, biosimilars can be used in treatment-experienced as well as in treatment-naïve patients.

- Before approval of the biosimilar product, FDA may request additional safety information for treatment-experienced patients who undergo a single transition (single switch) from a reference product to a biosimilar product

Interchangeable product

- Interchangeable products are biosimilars that have met additional requirements.
- These requirements include not only showing that the product is expected to produce the same clinical result as the reference product in any given patient, but also that switching back and forth between the reference product and the biosimilar causes the patient no additional risks in terms of safety or effectiveness as using only the reference product.

Interchangeable product: Approval

1. To meet criteria for biosimilar product
2. To produce the same clinical result as the reference product in any given patient
3. For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.

Interchangeable product: Approval

1. To meet criteria for biosimilar product
2. To produce the same clinical result as the reference product in any given patient
3. For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products.

★ Currently there are no interchangeable biosimilars available in the U.S.

Interchangeable product: Substitution

- An interchangeable product may be substituted for the reference product without the involvement of the prescriber, meaning interchangeable biologic can be substituted for the reference product by a pharmacist.

Contents

- ★ Basic concept
- ★ FDA Approval
- ★ Extrapolation
- ★ Switch & Interchangibility
- ★ Pharmacovigilance & Naming

Pharmacovigilance & Naming

- Rare and/or unexpected safety issues often become apparent only after a medicinal product has been on the market
- Using the unique brand name (or INN with unique identifier) for prescriptions and reporting of adverse event ensures transparency and traceability in the post-marketing setting

Pharmacovigilance & Naming

Proprietary names

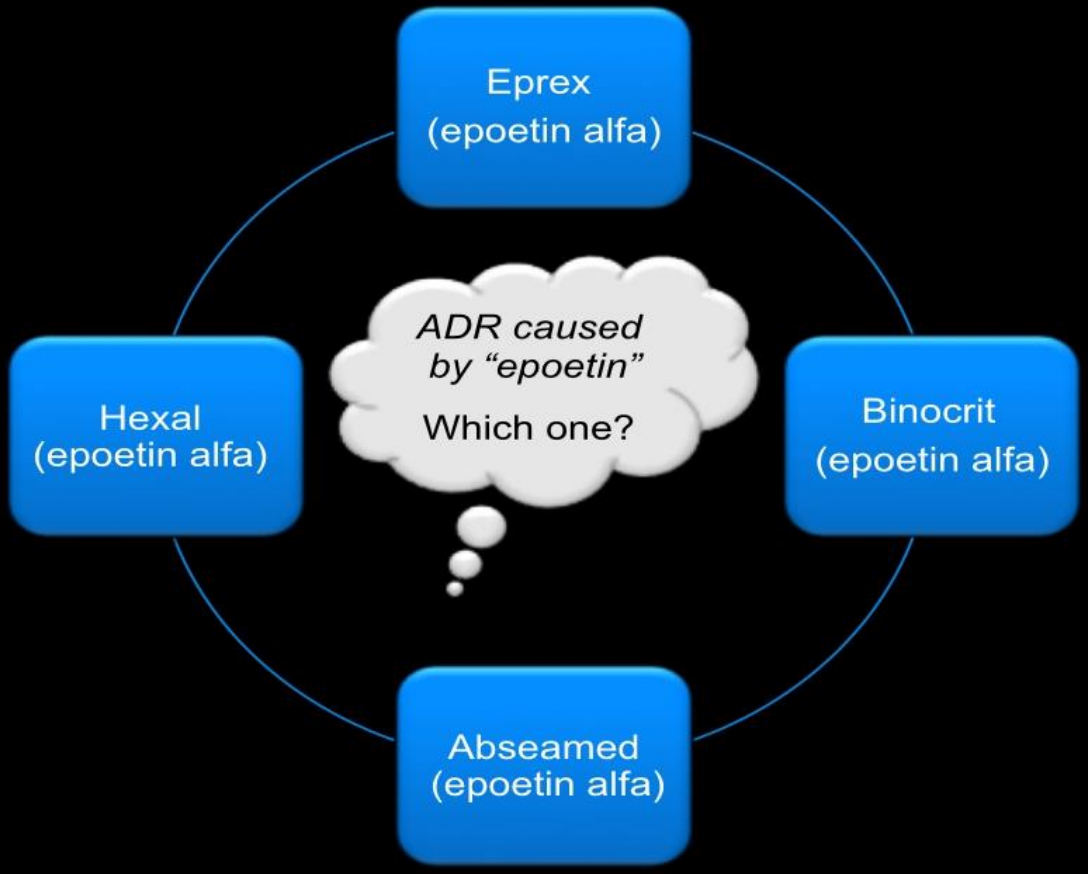
- Tylenol (J&J)
- Panadol (GSK)
- Panodil
- Panamax
- Perdolan
- Calpol
- Doliprane
- Tachipirina
- Ben-u-ron
- Pamol
- Gelocatil

Acetaminophen

International Nonproprietary Name (INN) 國際非專利藥品: WHO給每種藥品的官方非專利性名稱

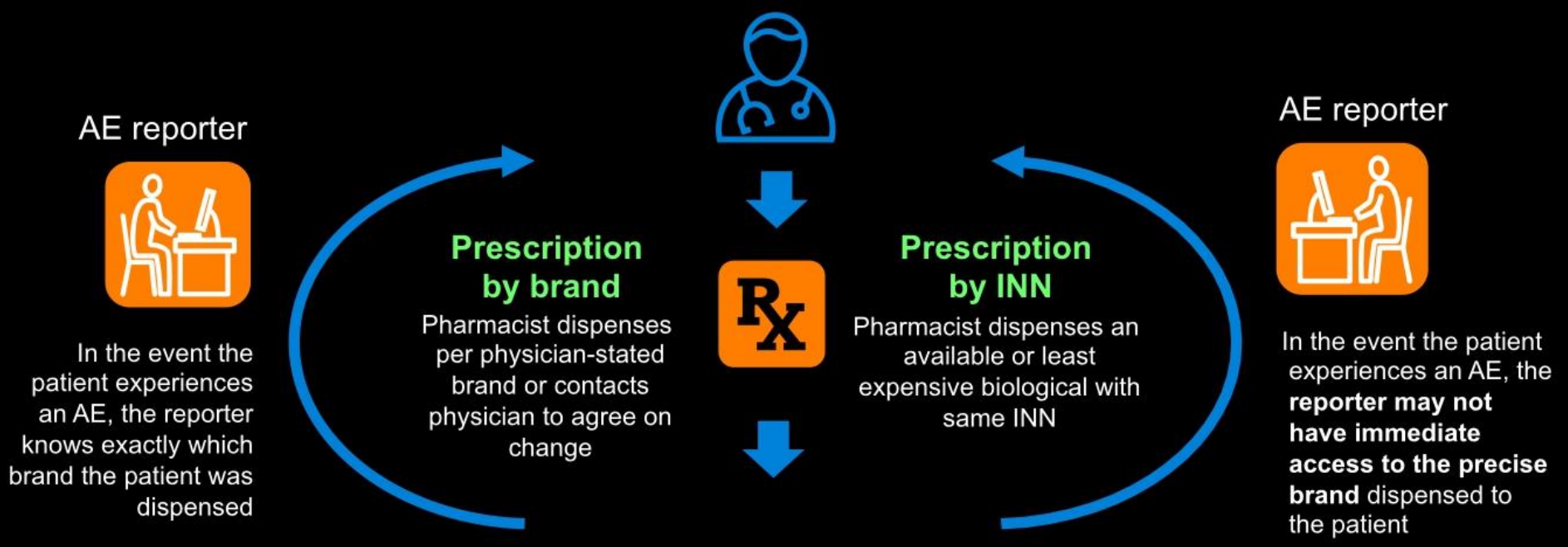
- paracetamol (en)
- paracetamolum (la)
- paracétamol (fr)
- paracetamol (es)
- парацетамол (ru)
- باراسيتامول (ar)
- 对乙酰氨基酚 (zh)

Pharmacovigilance & Naming



Identical names make traceability and product-specific pharmacovigilance impossible.

Pharmacovigilance & Naming



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

Regulatory guidance on biosimilar: Naming and AE reporting	
EMA	☆ Biosimilars are given the **same INN** as the reference product but recommends additional use of trade name to distinguish biotherapeutic products ☆ Brand name and batch number is required for reporting of suspected adverse reactions
FDA	☆ INNs of biologics are given an identifier (four-letter suffix) **unique** to each product ☆ Requires adequate monitoring process to differentiate AEs in the marketplace – but is not specified

Regulatory guidance on biosimilar: Naming and AE reporting

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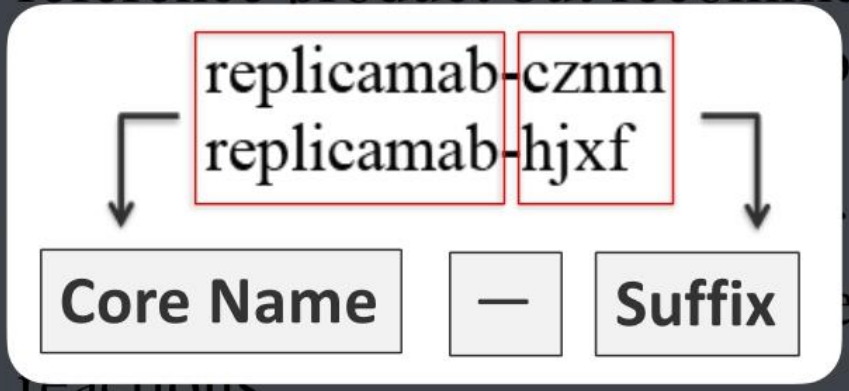
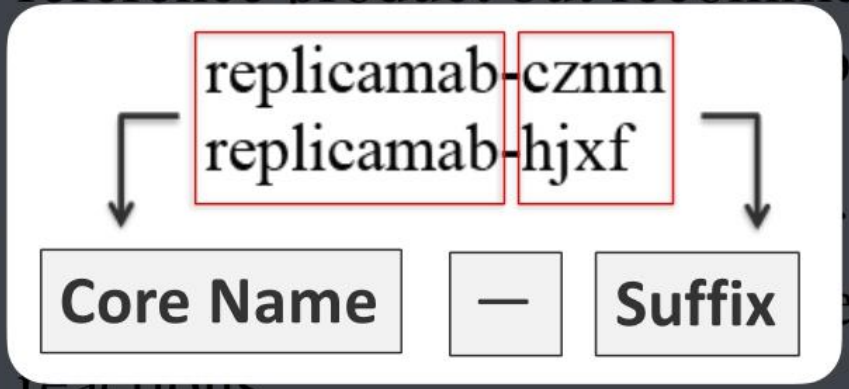


Regulatory guidance on biosimilars: Naming and AE reporting

Proprietary Name	Product (Proper) Name
Humira	Adalimumab
Cyltezo	Adalimumab-adbm
Amjevita	Adalimumab-atto

EMA

- ☆ Biosimilars are given the **same INN** as the reference product but recommends
- ☆ distinguish
- ☆ is required
- erse reactions



FDA

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Regulatory guidance on biosimilar: Naming and AE reporting

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EMA

- ☆ Biosimilars are given the **same INN** as the reference product but recommends
- ☆ is required

replicamab-cznm
replicamab-hjxf

Core Name — **Suffix**

Suffix 應：

- 獨特
- 避免有含意
- 四個小寫字母，其中三個不同
- 不是其他人的專利名
- 和core name間用-連結
- 沒有法規引發的使用問題

Suffix 不應：

- 暗示安全性或療效
- 含數字或符號
- 造成誤導的醫療常用縮寫
- 暗示或包含其他成分名
- 看起來像其他產品名稱
- 暗示其他公司名稱
- 太像FDA用來當範例的名稱

Proprietary Name	Product (Proper) Name
Humira	Adalimumab
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMJEVITA™ safely and effectively. See full prescribing information for AMJEVITA.

AMJEVITA (adalimumab-atto) injection for subcutaneous use.
Initial U.S. Approval: 2016

AMGEVITA® Solution for Injection (adalimumab)
病患用藥說明書

衛部菌疫輸字第 001098 號

含 adalimumab 注射用溶液的預充填針筒
限由醫師使用
本品 AMGEVITA 為 HUMIRA®的生物相似性藥品。

Proprietary Name	Product (Proper) Name
Herceptin	trastuzumab
Trazimera	trastuzumab-qyyp
Ogivri	trastuzumab-dkst
Kanjinti	trastuzumab-anns

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OGIVRI safely and effectively. See full prescribing information for OGIVRI.

OGIVRI (trastuzumab-dkst) for injection, for intravenous use
Initial U.S. Approval: 2017

OGIVRI (trastuzumab-dkst) is biosimilar* to HERCEPTIN (trastuzumab).

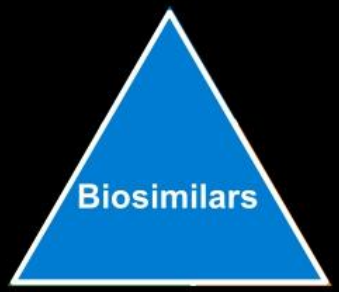
Ogivri® 150 mg
440 mg

衛部菌疫輸字第 001090 號
衛部菌疫輸字第 001089 號
本藥限由醫師使用

本品 **Ogivri** 為 **Herceptin** 的生物相似性藥品。
警語：心肌病變、輸注反應及肺毒性

心肌病變
Trastuzumab 可能會導致無臨床症狀及有臨床症狀之心衰竭 (臨床表徵為鬱血性心衰竭及左心室射出分率<LVEF>降低)。在接受 **trastuzumab** 併用含有 **anthracycline** 化學療法的病患，其左心室功能不全的發生率及嚴重程度最高。
在以 **Ogivri** 治療前及期間應對所有病患評估左心室功能。在有臨床左心室功能顯著降低的情況下，接受輔助治療的病患應停止 **Ogivri** 之治療，對轉移性乳癌病患則應慎重考慮停止 **Ogivri** 之治療。

Summary: Clinical consideration of biologic and biosimilar products



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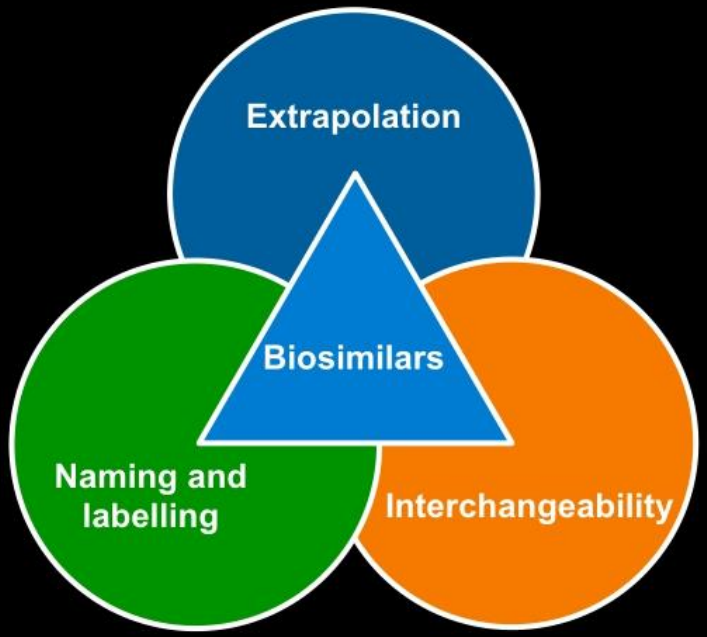

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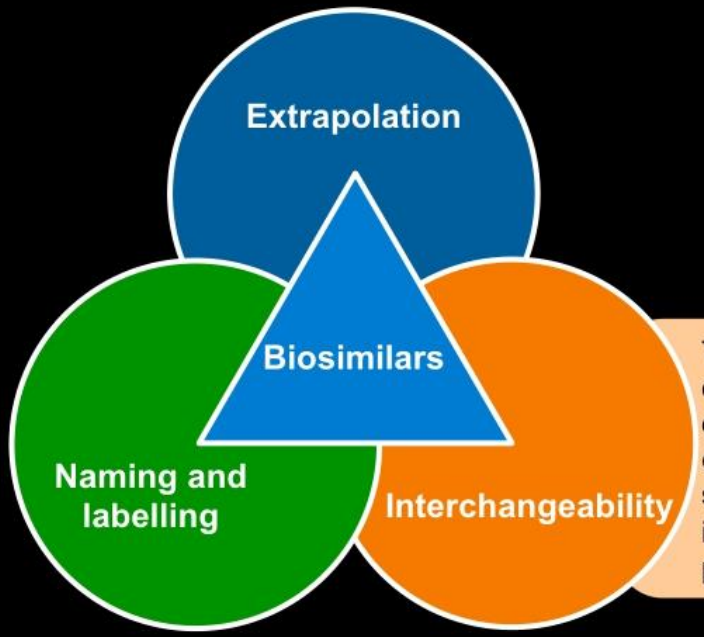
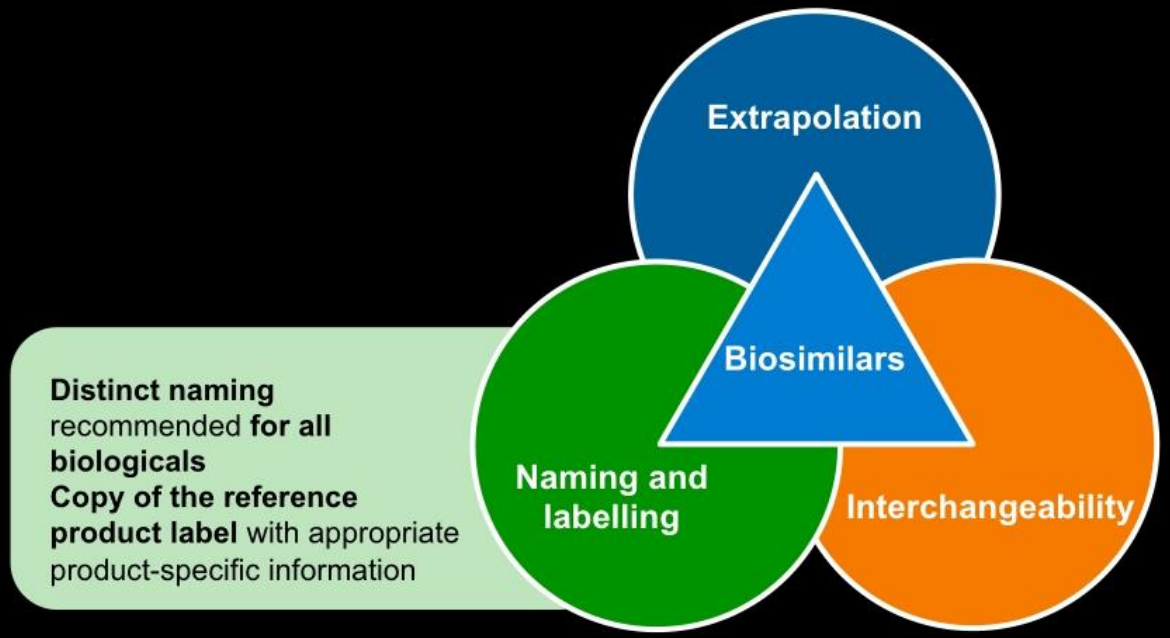


The medical practice of changing one medicine for another that is **expected to achieve the same clinical effect in a given clinical setting and in any patient**, on the initiative or with the agreement of the prescriber

Summary: Clinical consideration of biologic and biosimilar products



Biosimilar is biosimilar

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