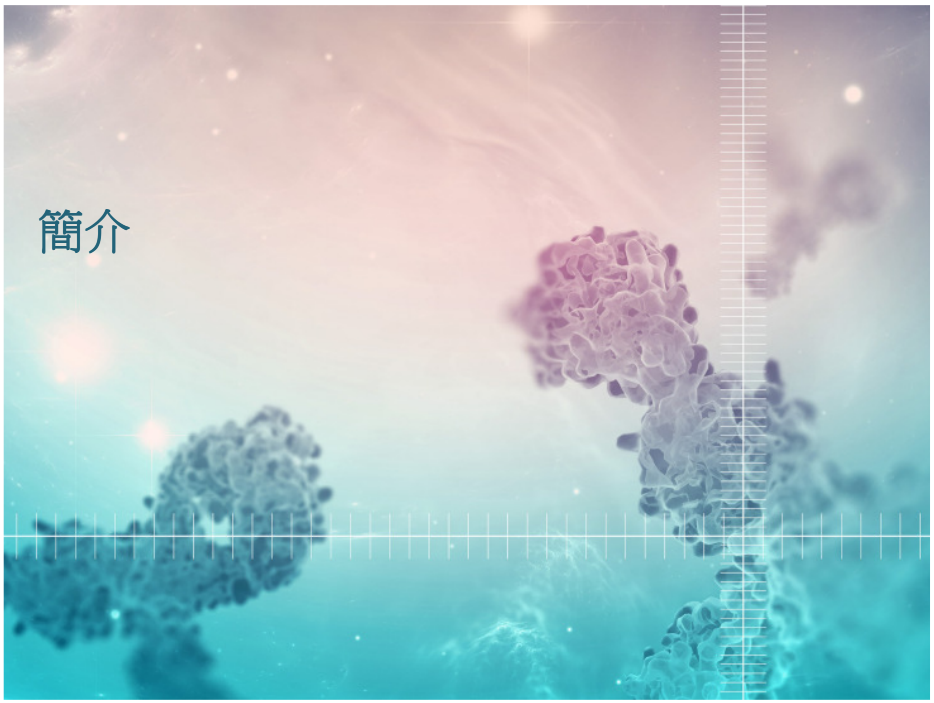
概要

- 簡介
- 生物製藥概述
- 必要的臨床數據
- 免疫原性
- 外推指示
- 互換性
- 非醫療切換
- 結論

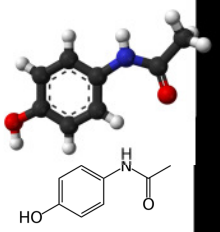


何謂生物藥品(BioPharmaceuticals)

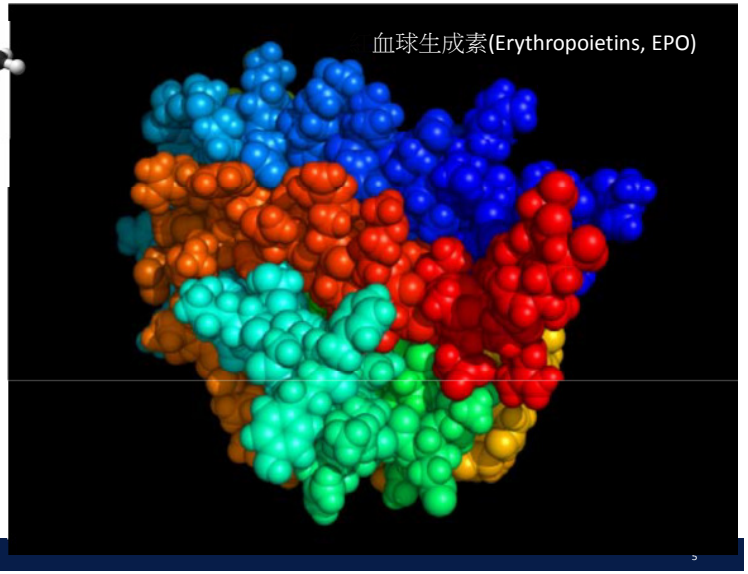
- 生物藥品由生物細胞製造, 非化學合成的蛋白質。現時治療風濕病的生物製劑(Biologic)是生物藥品的一種。

- 以下是一些例子:
- • **干擾素**(Interferons, IFN)
- • **胰島素**(Insulins)
- • **單株抗體**(Monoclonal Antibodies)
- • **血液因子**(Blood Factors)
- • **生長賀爾蒙**(Growth Hormones, GH)
- • **白介素**(Interleukins)
- • **疫苗**(Therapeutic Vaccines)

小分子藥物vs 生物藥品



acetaminophen



小分子藥物 vs 生物藥物

項目	小分子藥物 (化學合成藥物)	生物藥物 (蛋白質藥物)
製造方式	化學合成	生物細胞製造
分子量大小	數百Dalton	數千至數十萬Dalton
物理化學特性	單純/單一	複雜/多樣
檢測鑑定	純度容易測定	純度較難測定
免疫反應	可能性低	可能性高
服藥方式	多樣性(口服/注射等等)	大多為注射
保存方法	大多為常溫	大多為低溫
生物性雜質	可能性低/無	可能性高

生何謂生物仿製藥物(biosimilar)

- 生物仿製藥是由非原廠生產的,與原裝生物製劑(innovator)幾乎相同的副本。
- 生物仿製藥需要通過醫療監管部門批准,然後在產品的專利到期後開始製造。

為什麼有生物仿製藥(biosimilar)的出現?

- 藥廠研發出新藥後，為保護其知識產權，會申請藥物專利權
- 專利並非永久，年限一過，其他藥廠便能自行配製同一藥物，是為仿製藥物。

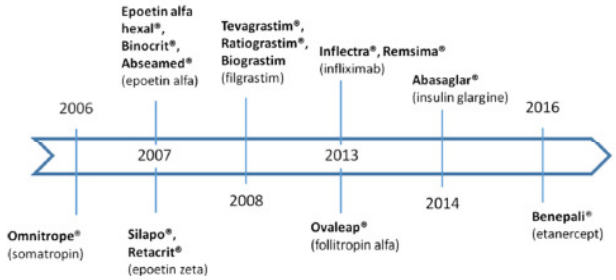
- 近幾年，將陸續有許多生物製劑專利到期，對生物仿製藥來說商機無限
- 全球亦有許多生技公司及藥廠已陸續投入生物仿製藥研發與製造。

- 生物仿製藥因為成本較低, 價格較低, 可能造福更多的患者。

生物仿製藥如何得到認可?

- 分析與參考生物製品在非臨床和臨床上的
  - 相似性
  - 安全性
  - 有效性
- 全面的風險效益分析
- 例子: Remsima

Fig. 1 Timeline of the first biosimilars in each class approved by the European Union



Curr Rheumatol Rep (2016) 18: 50

生物仿製藥的優點和缺點

優點	缺點
藥物成本較低	現階段，生物仿製藥仍處於起步階段。
加入競爭，減少專利藥物的壟斷行為	生物仿製藥不能完全替換生物製劑 兩者的可替換性及相似性仍有待更多數據支持
	需緊密監察藥物安全

生物仿製藥關鍵問題

- **生物仿製藥**並**不是**原生**生物製**劑
- 生物仿製藥雖然與參考生物製劑相似, 並不意味著互換性
- 生物仿製藥與參考生物製劑的相似度成為生物仿製藥的關鍵

原生生物製藥的製造　與　生物仿製藥的發展

原生生物製劑的製造

原生生物製劑製造商:

- 通過既定的控制和驗收參數，調整藥物的製造過程[1]
- 充分掌握有關產品的知識和製作流程[2]

≠

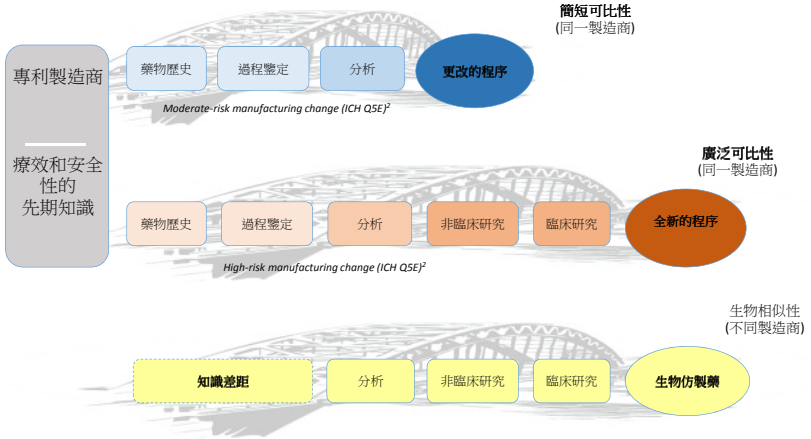
生物仿製藥的製造

其他製造商:

- 從已發表原生生物製劑的資料與數據分析，逆向設計出生物仿製藥
- 沒有原生藥物的相關知識與製造過程的資訊
- 需要更多的數據和信息，以建立生物相似性[2]

1. ICH Q5E Comparability of Biotechnological/Biological Products: Guidance for Changes in Their Manufacturing Process. June 2005; 2. Adapted from: FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Feb 2012

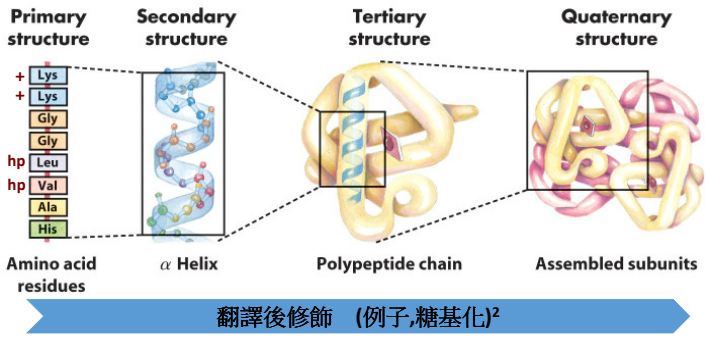
原生生物製藥的製造　與　生物仿製藥的發展[1]



所需要的數據取決於殘留物的不確定性

1. Image reproduced with permission from Lee JF Current Medical Research & Opinion Vol. 28, No. 6, 2012, 1053–1058; 2. ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

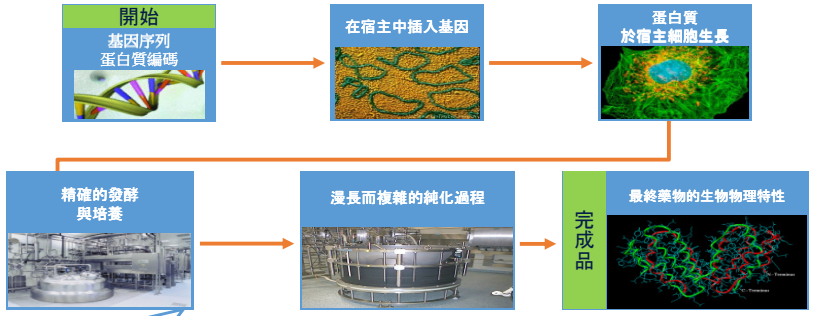
蛋白質結構和翻譯後修飾



- 生物產品的製造，由簡單的氨基酸排列開始，慢慢發展到三維(3D)結構，有時更與其他結構結合而成。

1. Image reproduced with permission from: Kozlowski. FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology 2012. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/advisorycommitteeforpharmaceuticalsciencesandclinicalpharmacology/ucm315764.pdf; 2. Sekhon & Saluja. Biosimilars 2011;1:1–11; 3. Jefferis. J Immunol Res. 2016. Epub ahead of print.

生物製劑的生產流程



影響分子性質的因素:

- 生物反應器的狀態[1,2,5] (時間, 酸鹼值,溫度, 含氧量/乳酸堆積[6]), 培養媒界[1,2]

常被影響的性質:

- 糖基化特徵[1-5], 帶電荷的物質[2,5],聚集物[2]

影響藥物性質的因素:

- 宿主細胞DNA和蛋白質的去除過程[2,5]
- 碎片 和聚集物的去除過程[2]
- 蛋白質的濃度[2]

1. Mellstedt et al. Ann Oncol 2008;19:411–9; 2. Kozlowski & Swann. Adv Drug Deliv Rev 2006;58:707–22; 3. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 4 WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 5. Lee. Curr Med Res Opin 2012;28:1053–8. 6. Williams J. Bioreactor selection. http://people.clarkson.edu/~wwilcox/Design/reactbio.pdf. Accessed May 2016

嚴緊的製作監控

- 生物仿製藥有獨特的生物活性及免疫性，這些都是深受蛋白質結構及修飾過程影響。
- 任何製作過程的改變
  - 如宿主細胞變動，DNA質體修改，培養基配方更改，培養溫度或pH值不同，製程放大等
- 均有可能導致蛋白質結構的改變
  - 如序列改變，轉譯後修飾(PTM)的改變, 如醣基化或磷酸化等
- 進而影響其活性及效用。
- 因此必須嚴緊監察所使用的生物來源及製作過程。

1. Kozlowski and Swann. Adv Drug Deliv Rev 2006;58:707–72; 2. Dörner et al. Ann Rheum Dis 2013;72:322–8; 3. Goldsmith. Nephrol Dial Transplant 2006;21(Suppl 5):v1–3; 4. Shacter. Drug Met Reviews 2000;32:307–26; 5. Primer. Recombinant Protein Characterization. Agilent Technologies 2011, available at https://www.agilent.com/cs/library/primers/Public/5990-8561EN_LO.pdf

一些可能在製作過程出現的化學反應(參考)

糖基化	• 導致結構變化，影響在藥物動力學的功效，免疫原性和清除性[2,3]
分裂	• 激活作用[3]
氧化	• 綁定，功能，免疫原性和聚合[4]
油脂連接	• 薄膜定位[3]
磷酸化	• 蛋白激活或抑制[3]
帶電亞型	• 功能和穩定性，免疫原性[5]

生物製藥 製造過程－摘要

- 製造過程可導致蛋白質結構產生變化而影響最終藥物的功效[1,2–5]
- 眾多因素可以影響分子/藥物的性質[1,6–10]
- 生物仿製藥的過程不同於生物製藥的過程[11,12]

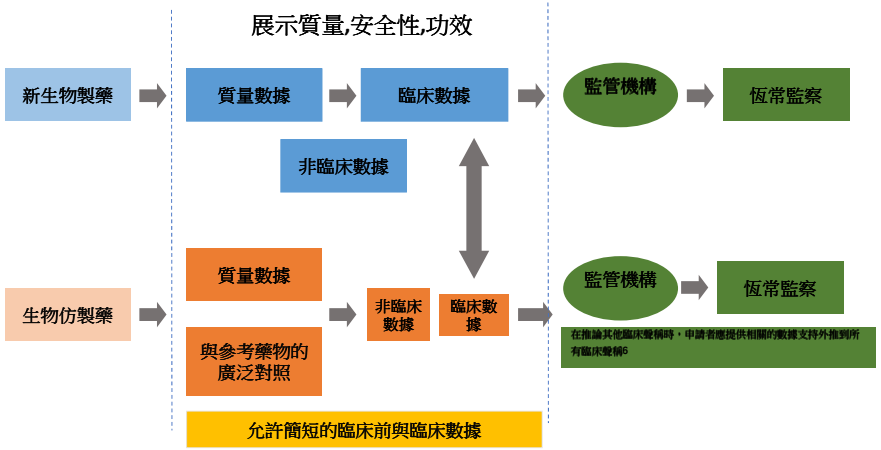
1. Kozlowski and Swann. Adv Drug Deliv Rev 2006;58:707–72; 2. Dörner et al. Ann Rheum Dis 2013;72:322–8; 3. Goldsmith. Nephrol Dial Transplant 2006;21(Suppl 5):v1–3; 4. Shacter. Drug Met Reviews 2000;32:307–26; 5. Primer. Recombinant Protein Characterization. Agilent Technologies 2011, available at https://www.agilent.com/cs/library/primers/Public/5990-8561EN_LO.pdf; 6. Ho et al. Pharm Bioprocess 2013;1:71–87; 7. Mellstedt et al. Ann Oncol 2008;19:411–9; 8. US HHS/FDA. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry, April 2015; 9. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 10. Lee. Curr Med Res Opin 2012;28:1053–8; 11. Adapted from: FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Feb 2012; 12. ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

臨床數據的基本原理

- 目的在於展示生物仿製藥與參考藥的的相似度[1–3]
- 所需要的臨床對比研究的數量與程序取決於:
  - 對生物相似性的剩餘不確定性程度[1,2,3]
  - 對比參考藥物的安全性考量[1,2,3]
  - 病人人數[1,3]

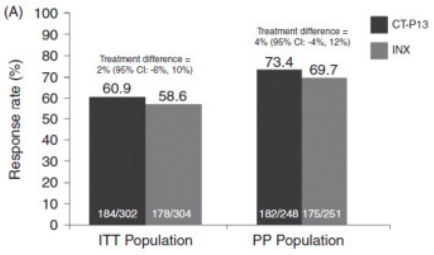
1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 2. EMA CHMP Guideline on Similar Biological Medicinal Products, Oct 2014; 3. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009;

建立生物相似性的流程[1–5]



Adapted from:
1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product. HHS FDA/CDER/CBER, Apr 2015; 2. FDA Guidance for Industry. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. HHS FDA/CDER/CBER, Apr 2015; 3. EMA CHMP Guideline on Similar Biological Medicinal Products, Oct 2014; 4. Health Canada. Guideline for Sponsors. Information and Submission Requirements for Subsequent Entry Biologics (SEBs), Mar 2010; 5. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 6. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study



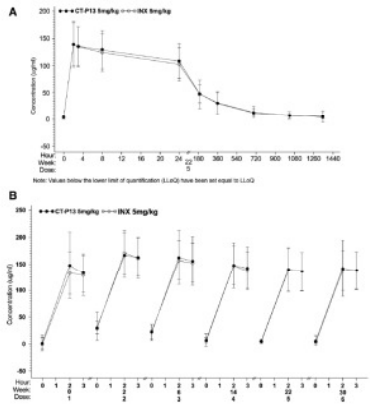
Yoo DH, *et al. Ann Rheum Dis* 2013;**72**:1613–1620.

Table 3 Treatment-emergent adverse events (TEAEs) reported as related in at least 1% of patients in either treatment group, no (%)

Related TEAEs reported in at least 1% of patients in either treatment group	CT-P13 3 mg/kg (N=301)*	INX 3 mg/kg (N=301)*	Total (N=602)
Alanine aminotransferase increased	12 (4.0)	11 (3.7)	23 (3.8)
Aspartate aminotransferase increased	8 (2.7)	8 (2.7)	16 (2.7)
γ-Glutamyltransferase increased	2 (0.7)	3 (1.0)	5 (0.8)
Latent tuberculosis	13 (4.3)	14 (4.7)	27 (4.5)
Upper respiratory tract infection	4 (1.3)	4 (1.3)	8 (1.3)
Urinary tract infection	4 (1.3)	7 (2.3)	11 (1.8)
Bronchitis	4 (1.3)	4 (1.3)	8 (1.3)
Nasopharyngitis	6 (2.0)	4 (1.3)	10 (1.7)
Gastroenteritis	2 (0.7)	3 (1.0)	5 (0.8)
Herpes zoster	1 (0.3)	3 (1.0)	4 (0.7)
Rhinitis	0	3 (1.0)	3 (0.5)
Tuberculosis	3 (1.0)	0	3 (0.5)
Infusion-related reaction	20 (6.6)	25 (8.3)	45 (7.5)
Anaemia	2 (0.7)	3 (1.0)	5 (0.8)
Neutropenia	3 (1.0)	2 (0.7)	5 (0.8)
Leucopenia	1 (0.3)	3 (1.0)	4 (0.7)
Headache	4 (1.3)	6 (2.0)	10 (1.7)
Pyrexia	0	3 (1.0)	4 (0.7)
Rash	1 (0.3)	4 (1.3)	5 (0.8)
Nausea	1 (0.3)	3 (1.0)	4 (0.7)
Flare in RA activity	7 (2.3)	4 (1.3)	11 (1.8)
Bone pain	3 (1.0)	0	6 (1.0)
Hypertension	5 (1.7)	3 (1.0)	8 (1.3)

The total number of treatment-emergent adverse events count included all related patient events. At each level of summarisation, a patient was counted once if he or she reported one or more related events. Only the most severe event was counted.
*Patients who received at least one (full or partial) dose of CT-P13 were included in the CT-P13 group for safety analyses, irrespective of their randomisation.
INX, innovator infliximab; RA, rheumatoid arthritis.

A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study



Park W, *et al. Ann Rheum Dis* 2013;**72**:1605–1612.

Table 4 Related treatment-emergent adverse events reported in at least 1% of patients in either treatment group, no (%)

	CT-P13 5 mg/kg (N=128)	INX 5 mg/kg (N=122)	Total (N=250)
Alanine aminotransferase increased	14 (10.9)	13 (10.7)	27 (10.8)
Aspartate aminotransferase increased	12 (9.4)	10 (8.2)	22 (8.8)
γ-glutamyltransferase increased	4 (3.1)	5 (4.1)	9 (3.6)
Latent tuberculosis*	5 (3.9)	4 (3.3)	9 (3.6)
Upper respiratory tract infection	3 (2.3)	2 (1.6)	5 (2.0)
Nasopharyngitis	3 (2.3)	2 (1.6)	5 (2.0)
Pharyngitis	2 (1.6)	3 (2.5)	5 (2.0)
Urinary tract infection	5 (3.9)	0	5 (2.0)
Bacteriuria	0	2 (1.6)	2 (0.8)
Tonsillitis	0	2 (1.6)	2 (0.8)
Tuberculosis	2 (1.6)	1 (0.8)	3 (1.2)
Infusion-related reaction	5 (3.9)	6 (4.9)	11 (4.4)
Serum creatinine phosphokinase increased	4 (3.1)	1 (0.8)	5 (2.0)
Neutropenia	2 (1.6)	2 (1.6)	4 (1.6)
Leukopenia	0	2 (1.6)	2 (0.8)
Pyrexia	2 (1.6)	1 (0.8)	3 (1.2)
Headache	3 (2.3)	1 (0.8)	4 (1.6)
Rash	0	3 (2.5)	3 (1.2)
Urticaria	0	2 (1.6)	2 (0.8)
Nausea	1 (0.8)	2 (1.6)	3 (1.2)

免疫原性

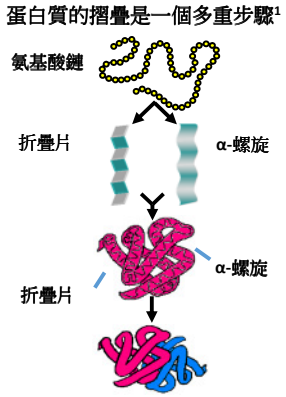
- 免疫原性：一個分子可以引發細胞介導免疫反應的能力[1]
- 免疫原性的發生率[1,2]:
  - 於不同研究有著廣泛的差異
  - 受諸多因素影響，不可能完全從分析和非臨床數據預測

影響免疫原性的因素[1,2]	
與病人有關的因素	**與治療有關的因素**
病人特徵	劑量與治療時間
基因差異	用藥途徑
免疫系統原整性	制定和儲存
病情	生物治療: • 序列和結構* • 糖基化等翻譯後修飾 • 宿主細胞 • 污染物/雜質
額外的未知因素	

*在天然蛋白質結構中，越多序列變異，通常會有更多疫原性

1. Schellekens. Clin Ther 2002;24:1720–36; 2. Schellekens. Nat Rev Drug Discov 2002;1:457–62; 3. Chamberlain. Biosimilars 2014;4:23–43

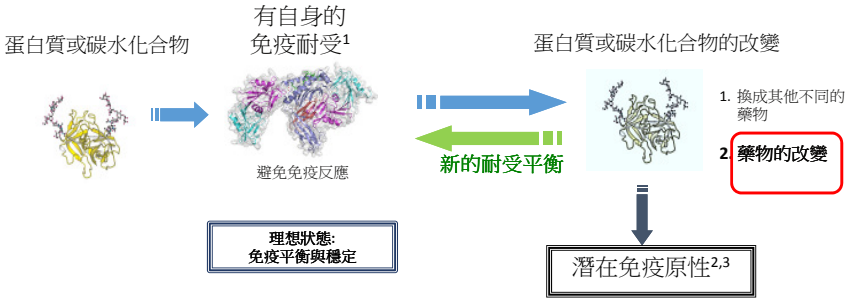
蛋白質特性影響免疫原性



- 翻譯後修飾，摺疊與形狀的細少改變足以影響免疫原性[2,3]

1. UMass. Workshops, Short Courses and Seminars 2015 https://www.umass.edu; 2. Scott et al. J Clin Pharmacol 2015;55:S123–32; 3. Chamberlain. Biosimilars 2014;4:23–43

免疫原性的潛在結果



1. National Inst. Allergy and Infect. Dis Accessed 3/22/2016. http://www.niaid.nih.gov/topics/immuneSystem/Pages/immuneTolerance.aspx. Image reproduced with permission; 2. Shankar et al. AAPS 2014;16:658–73; 3. Scott et al. The journal of Clinical Pharmacology DOI:I 002/jcph.339

免疫原性

- 免疫原性數據是行使生物相似性的必要部份[3]
  - 動物實驗，結構性及功能性數據都不能充分預測免疫原性[4]
  - 因此，至少要有一個臨床研究來比較基準製品與參考製品的免疫原性。[4]
- 額外的長期免疫原性和安全性數據可能需要後期觀察[5]

1. Schellekens. Nat Rev Drug Discov 2002;1:457–62; 2. Schellekens. Clin Ther 2002;24:1720–36; 3. EMA CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, Dec 2014; 4. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 5. EMA CHMP Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use, May 2012;

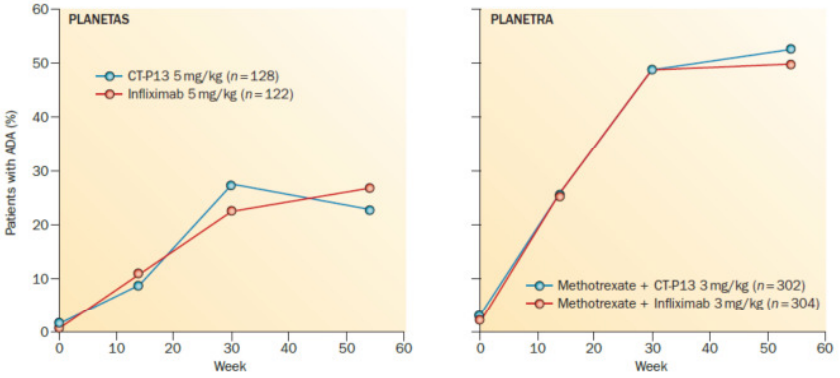


Figure 3 | ADA induction after treatment with infliximab or CT-P13. Comparative induction of ADAs against reference infliximab and CT-P13 in patients with ankylosing spondylitis (left) and rheumatoid arthritis (right) during two clinical studies (PLANETAS and PLANETRA, respectively).[14,15,32] ADAs were assessed by electrochemical-luminescent immunoassay technology (Meso Scale Discovery). Abbreviation: ADA, antidrug antibody.

Dörner. T. & Kav. J. *Nat. Rev. Rheumatol.* **11**. 713–724 (2015):

生物仿製藥外推指示原則概要

- **如果有充分的科學根據**， 我們可以推斷一種藥物應用於不同病症都會有相似治療效果 [1–4]
  - 藥物外推指示只能於該藥物已獲許可的條件下使用[1]

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as an Active Substance: Non-Clinical and Clinical Issues

FDA

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

World Health Organization

Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)

emea

Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as an Active Substance: Non-Clinical and Clinical Issues

1. FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. HHS FDA/CDER/CBER, April 2015; 2. EMA CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Dec 2014; 3. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 4. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012

生物仿製藥使用外推法原則概要 (1) 藥物動力學

- 科學根據應涉及以下問題：
  1. **不同治療指示下的作用機制**
  2. 藥物在不同病人組別的**藥物動力學和體內分佈**[1]
  3. 測試指示應為檢測臨床安全性和有效性差異**最敏感的**（包括免疫原性）[1,3]
  4. 每個使用情況下**所預計的安全性差異**[1–4]

1. FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. HHS FDA/CDER/CBER, April 2015; 2. EMA CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Feb 2006; 3 WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 4. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012; 5. FDA Draft Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Feb 2012

單克隆抗體特別注意事項 (mAbs)

- 複雜的生物治療藥物[1–3]
- 顯著的免疫原性潛力[1,2–5]
- 常有多於一個作用機制；
  很多機制仍未能被完全識別或理解[1,2,8–11]
- 針對一組複雜疾病[8,11]
  - 尚未完全理解發病機制

1. Miletich et al. mAbs 2011;3:318–25; 2. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012; 3. Brinks. GaBI J 2013;2:188–93; 4. EMA CHMP Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use, May 2012; 5. Brinks et al. Pharm Res 2011;28:2379–85; 6. FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. HHS FDA/CDER/CBER, April 2015; 7. WHO Guidelines on Evaluation of Similar Biotherapeutic Products. Geneva: WHO, 19–23 Oct, 2009; 8. Tracey et al. Pharmacol Ther 2008;117:244–79; 9. Vos et al. Inflamm Bowel Dis 2012;18:401–8; 10. Vos et al. Gastroenterology 2011;140:221–30; 11. Peake et al. Inflamm Bowel Dis 2013;19:1546–55;

摘要：外推指示

- 有科學根據下可作外推指示，並只能於該藥物已獲許可的條件下使用[1]
- 科學根據應涉及:
  - 不同治療指示下的**作用機制** [1–4]
  - 測試指示應為檢測臨床安全性和有效性差異最敏感的（包括免疫原性）[1,3]
  - 每個使用情況下所預計的安全性差異[1–4]
- 使用複雜的生物製劑需特別注意，如單克隆抗體有顯著的免疫原性潛力[5–9]，有多於一個作用機制[5,6,10-13]， 並且針對一組複雜疾病

FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. HHS FDA/CDER/CBER, April 2015; 2. EMA CHMP Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, Feb 2006; 3. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 4. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012; 5. Miletich et al. mAbs 2011;3:318–25; 6. EMA CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May 2012; 7. Brinks. GaBI J 2013;2:188–93; 8. EMA CHMP Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use, May 2012; 9. Brinks et al. Pharm Res 2011;28:2379–85; 10. Tracey et al. Pharmacol Ther 2008;117:244–79; 11. Vos et al. Inflamm Bowel Dis 2012;18:401–8; 12. Vos et al. Gastroenterology 2011;140:221–30; 13. Peake et al. Inflamm Bowel Dis 2013;19:1546–55;

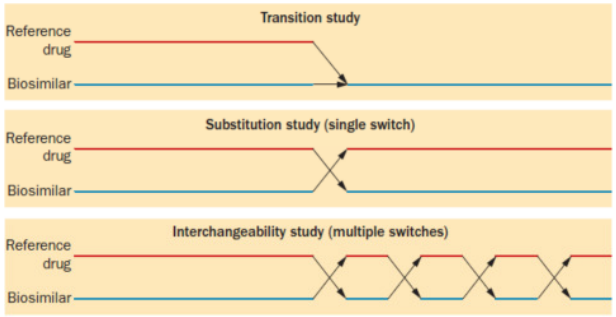


Figure 4 | Study design to compare the efficacy of reference drugs and biosimilars. Switching, as has been carried out in clinical trials of some biosimilars, is compared with substitution involving single or multiple switches, as potential study designs to support the FDA designation of interchangeability. Switch studies are not required for approval by the EMA.

非醫療切換

- 非醫療切換是指患者轉換生物製劑後，能承受該藥物，及對其有良好反應[1–3]
- 進行非醫療切換的原因大多數是因為:
  - 减少成本/支出[1–3]
  - 患者的意願[6]
- 非醫療切換可以有以下種類:
  - 轉換同一類別的生物製劑[2,6]
  - 從生物製劑轉換至相關的生物仿製藥[7]

	醫療切換	非醫療切換
定義	切換藥物的原因是為了優化治療	切換藥物的原因與臨床需要無關 而是因為患者的經濟需要/意願， 或採購政策[2–6]
何時切換?	第一種藥物失效後	患者病情穩定後[2,6]
多重切換	通常會繼續使用切換後的藥物	切換藥物後仍有機會再次切換至其他藥物

1. Rubin et al. ECCO 2015, P354; 2. Gibofsky et al. AMCP 2015, Poster; 3. Liu et al. ISPOR 2015, PHS26;
4. Morgan et al. Open Medicine 2009;3:131–9; 5. Declerck. GaBi J 2012;1:13–6; 6. Van Assche et al. Gut 2012;61:229–34;
7. CADTH. Rapid Response Report, February 2015, https://www.cadth.ca/

Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study

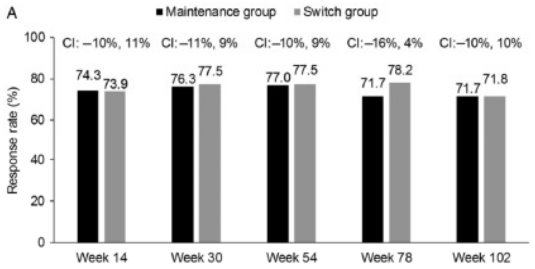


Table 2 Proportion of patients with RA who were positive for ADAs and NAbs in the main study and the extension study (safety population)

	Patients positive for ADAs and NAbs (n, %)		
Time point	Maintenance group* (n=159)	Switch group† (n=143)	p Value
Main study period			
Week 14 ADAs	33 (20.8)	30 (21.0)	1.00
NAbs	33 (100.0)	29 (96.7)	
Week 30 ADAs	73 (45.9)	63 (44.1)	0.82
NAbs	72 (98.6)	63 (100.0)	
Week 54 ADAs	78 (49.1)	69 (48.3)	0.91
NAbs	78 (100.0)	65 (94.2)	
Extension study period			
Week 78 ADAs	71 (44.7)	66 (46.2)	0.82
NAbs	71 (100.0)	64 (97.0)	
Week 102 ADAs	64 (40.3)	64 (44.8)	0.48
NAbs	64 (100.0)	64 (100.0)	
ADA persistency (n/N‡, %)			
Sustained ADAs	73/91 (80.2)	74/92 (80.4)	1.00
Transient ADAs	18/91 (19.8)	18/92 (19.6)	1.00

Yoo DH, *et al. Ann Rheum Dis* 2016;**0**:1–9. doi:10.1136/annrheumdis-2015-208786

Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study

Won Park,[1] Dae Hyun Yoo,[2] Pedro Miranda,[3] Marek Brzosko,[4] Piotr Wiland,[5] Sergio Gutierrez-Ureña,[6] Helena Mikazane,[7] Yeon-Ah Lee,[8] Svitlana Smiyan,[9] Mie-Jin Lim,[1] Vladimir Kadinov,[10] Carlos Abud-Mendoza,[11] HoUng Kim,[12] Sang Joon Lee,[12] YunJu Bae,[12] SuYeon Kim,[12] Jürgen Braun[13]

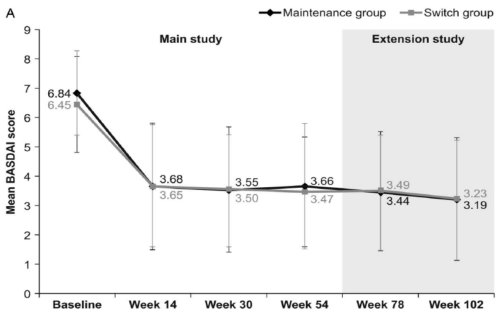
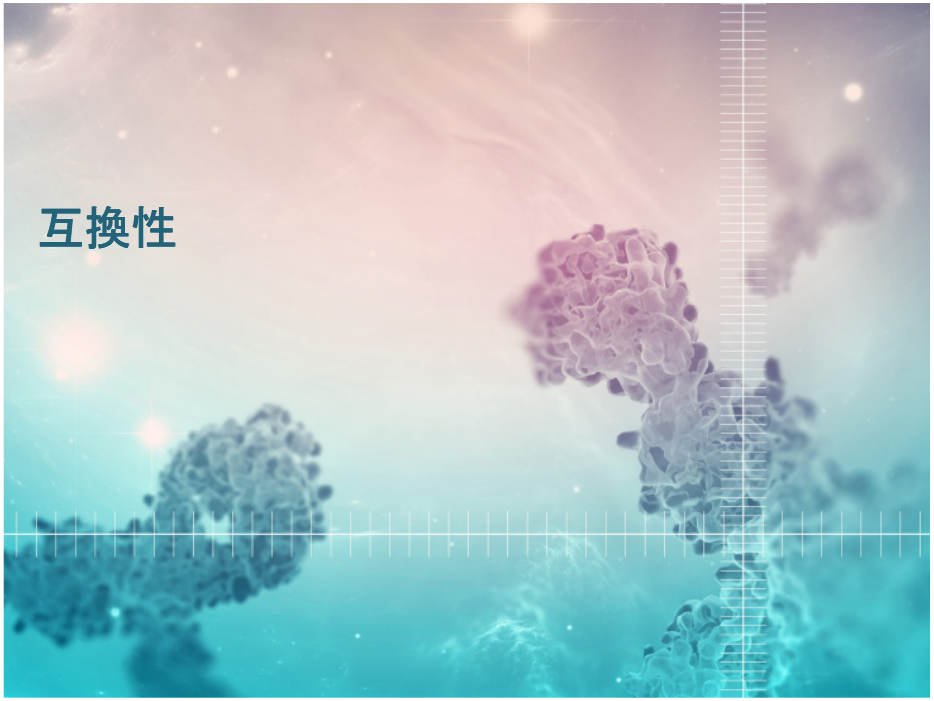


Table 3 Proportion of patients with ankylosing spondylitis (AS) who were positive for antidrug antibodies (ADAs) and neutralising antibodies (NAbs) in PLANETAS: the main 54-week parallel-group study and the extension study (safety population)

	Patients positive for ADAs and NAbs, n (%)		
Time point	Maintenance group* (n=90)	Switch group† (n=84)	p Value
Main study period			
Week 14 ADAs	7 (7.8)	8 (9.5)	0.79
NAbs	6 (85.7)	8 (100.0)	
Week 30 ADAs	18 (20.0)	17 (20.2)	1.00
NAbs	17 (94.4)	16 (94.1)	
Week 54 ADAs	20 (22.2)	22 (26.2)	0.60
NAbs	20 (100.0)	22 (100.0)	
Extension study period			
Week 78 ADAs	21 (23.3)	25 (29.8)	0.39
NAbs	21 (100.0)	25 (100.0)	
Week 102 ADAs	21 (23.3)	23 (27.4)	0.60
NAbs	21 (100.0)	23 (100.0)	
ADA persistency (n/N‡, %)			
Sustained ADAs	24/28 (85.7)	24/27 (88.9)	1.00
Transient ADAs	4/28 (14.3)	3/27 (11.1)	1.00

Park W, *et al. Ann Rheum Dis* 2016;**0**:1–9. doi:10.1136/annrheumdis-2015-208783



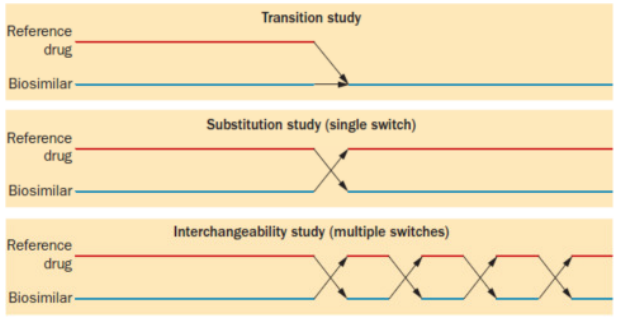


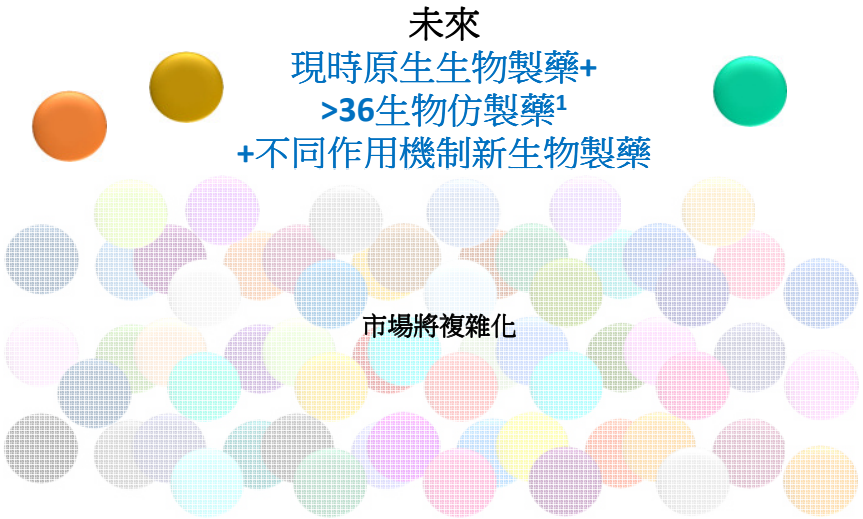
Figure 4 | Study design to compare the efficacy of reference drugs and biosimilars. Switching, as has been carried out in clinical trials of some biosimilars, is compared with substitution involving single or multiple switches, as potential study designs to support the FDA designation of interchangeability. Switch studies are not required for approval by the EMA.

反覆切換的潛在免疫原性風險

- 反覆切換會增加對免疫原性的潛在的負面影響[1]
  - 不同的蛋白結構和表位(epitopes)可能誘發出原先隱藏的mAbs[2]
  - 反覆暴露於不同表位後有機會影響患者自身耐受性，亦有機會對曾耐受的藥物產生免疫原性反應[2]

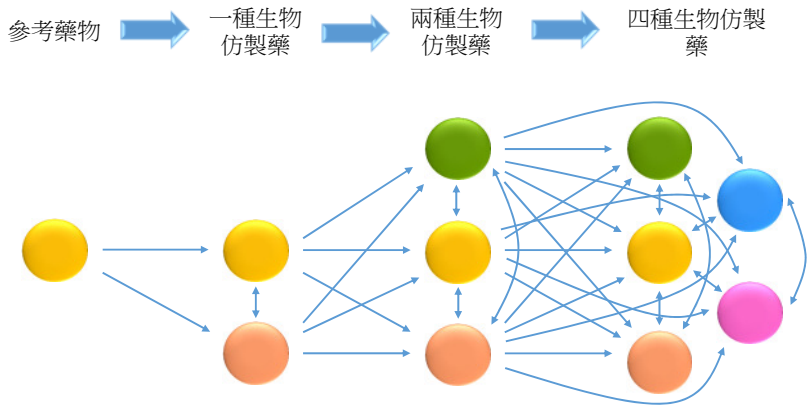
1. Scott et al. J Clin Pharmacol 2015;55:S123–32; 2. Wang et al. BioProcess International 2014;12:32–7

放眼未來：生物的數量在炎性疾病將大幅提升



1. Dörner T and Kay J. Nat Rev Rheumatol. 2015;11:713-24

不斷增新生物仿製藥下多重切換情況



1. Biopharma® Biosimilars/Biobetters Pipeline Database. Available at: http://www.biosimilarspipeline.com/. Accessed September 3, 2015.
2. Dörner & Kay. Nat Rev Rheumatol 2015;11:713–24

互換性

- 生物相似性並不意味互換性[1–6]
- 如果
  1. 預計將會給患者產生與參考藥物相同的臨床結果
  2. 於生物仿製藥和參考藥物之間反複切換沒有增加任何安全性或有效性的風險
  - 指定生物仿製藥為可互換
- 食品藥物管理局對藥物能否達致互換性要求之門檻仍有待界定
- 在歐洲，藥物互換性由國家主管部門決定，並非歐洲醫學機構EMA/ CHMP的職權範圍[8]
- 世界各地的衛生局在處理生物仿製藥的互換性和替代問題上的位置也不同，很多情況下都沒有明確界定

1. Declerck. GaBi J 2012;1:13–6; 2. FDA. Biosimilar Guidance Webinar 'Biosimilar Biological Products' 2012; 3. EMA. Q&A on biosimilar medicines, 2012; 4. MHLW. 'Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics', 2009 by PhRMA; 5. FDLI's Food and Drug Policy Forum. 2012;2:1–20; 6. Health Canada. 'Q&A on Information and Submission Requirements for Subsequent Entry Biologics', 2010; 7. FDA Biologics Price Competition and Innovation Act 2009; 8. EMA CHMP Procedural advice for users of the Centralised Procedure for Similar Biologicsl Medicinal Products applications, Dec 2015.

總結(1)

- 生物仿製藥是不是通用的生物製劑;它們是不相同的[1]
- 在製造過程中，即使是輕微的蛋白質結構變型也可影響藥物的功能[1-5]
- 生物仿製藥的評估必須根據以下原則:[1,3,7]
  - 在成分分析，功能，免疫原性和臨床效用方面皆與其原生產品相似
  - 全面的風險與效益分析

1. WHO Guidelines on evaluation of similar biotherapeutic products. Geneva: WHO, 19–23 Oct, 2009; 2. Schellekens. Nat Rev Drug Discov 2002;1:457–62; 3. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 4. Scott et al. J Clin Pharmacol 2015;55:S123–32; 5. Chamberlain. Biosimilars 2014;4:23–43; 6. ICH 5QE FDA scientific considerations 2012. 7. EMA CHMP Guideline on Similar Biological Medicinal Products Containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Dec 2014

總結(2)

- 生物相似性並不意味著互換性[1–6]
- 要通過足夠的臨床證據支持，才可以進行互換
- 現時需要更多研究去探討非醫療互換及多重互換的安全性及效用[8,9]
- 生物製劑市場將會愈來愈大，藥物數據也愈來愈多。因此生物產品的安全性更為可靠[10]

1. Declerck. GaBi J 2012;1:13–6; 2. FDA. Biosimilar Guidance Webinar 'Biosimilar Biological Products' 2012; 3. EMA. Q&A on biosimilar medicines, 2012; 4. MHLW. 'Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics', 2009 by PhRMA; 5. FDLI's Food and Drug Policy Forum. 2012;2:1–20; 6. Health Canada. 'Q&A on Information and Submission Requirements for Subsequent Entry Biologics', 2010; 7. Christl. FDA Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. Webinar UMC428732. September 2014. 8. CADTH. Rapid Response Report, February 2015, https://www.cadth.ca/; 9. Dörner T and Kay J. Nat Rev Rheumatol. 2015;11:713–24; 10. Vermeer et al. Expert Opin Drug Saf 2015;14:63–72

Abbreviations

Ab	Antibody	IFX	Infliximab
AE	Adverse event	INN	International non-proprietary name
ADA	Anti-drug antibody	mAb	Monoclonal antibody
ADR	Adverse drug reaction	MoA	Mechanism of action
BQ	Biologic qualifier	NMS	Non-medical switch
CADTH	Canadian Agency For Drugs And Technologies In Health	OL	Open label
CD	Crohn's disease	PD	Pharmacodynamics
CHMP	Committee for Medicinal Products for Human Use	PK	Pharmacokinetics
CMC	Chemistry and manufacturing controls	PTM	Post-translational modification
FAERS	FDA Adverse Event Reporting System	QC	Quality control
EMA	European Medicines Agency	RWE	Real world evidence
ER	Endoplasmic reticulum	TNF	Tumor necrosis factor
FDA	US Food and Drug Administration	UC	Ulcerative colitis
G-CSF	Granulocyte-colony stimulating factor	WHO	World Health Organisation
IBD	Inflammatory bowel disease