生物相似性藥品之審查考量

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本次演講內容僅代表查驗中心之觀點，凡涉及政策方向及法規解釋與適用，應依衛生主管機關之指示為準。

Biosimilar Drugs 定義

- 生物相似性藥品指

  以生物技術衍生之生物藥品，

  於**品質、安全及療效**上，

  與獲得我國核准之原開發廠生物藥品(參考品，reference drug)**相似**

- 範圍: 重組胜肽、重組蛋白質
- 不包括疫苗，致敏原，血液或血漿衍生製劑及其重組替代物，以及如基因或細胞治療產品等。

仿製藥

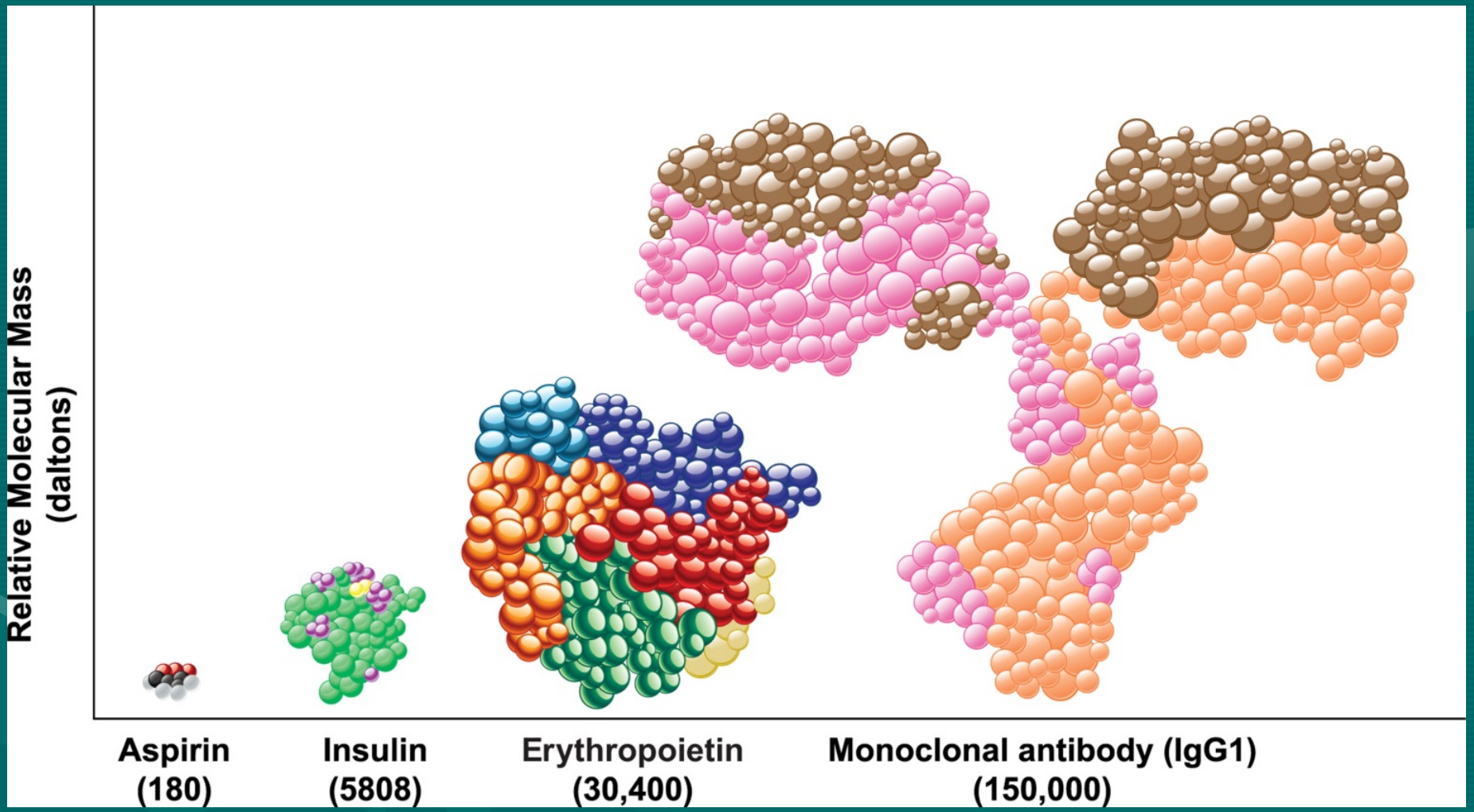
- 小分子藥 → 學名藥 (generic drug)
  Regulatory requirement: **Quality + BE**

- 大分子蛋白質藥 →生物相似性藥品(biosimilar)
  Regulatory requirement: more complex
  → need detail Guidelines (comparative exercises)

Protein Drugs vs. Chemical Drugs

Protein Drugs	Chemical Drugs
Large size M.W. > 10,000 Daltons mostly	Small molecule M.W. < 1,000 Daltons
Complex Structure 1) three dimension (1，2，3，4 級結構) 2) acido-basic variants 3) post-translational modification (glycosylation profile)	Simple straight forward structure
Produced by biosynthetic processes, cannot be easily reproduced	Identical structure reproducible
Administered by injection immunologic response	Several routes

Protein Drugs vs. Chemical Drugs



Mellstedt H. *EJC Supplements* 2013;11:1-11.

Therefore, while developing new drugs imitating marketed products, protein drugs are….

- More difficult to characterize the detail whole structure → nearly not possible to demonstrate EQUIVALENCE
- Subtly different from reference drugs.
- Not applicable for traditional generic bioequivalence approach.

Different Terms

- EU (EMA): Biosimilars
- USFDA: Biosimilars
- Canada: Subsequent Entry Biologics

- 現在大都用 Biosimilar

Basic Terminology

- **NDA**: New Drug Application (US and others)
- **MAA**: Marketing Authorisation Application (EU)
- 新藥查驗登記 (我國)

- Originator (原開發廠藥品): Reference drug (R)
  Biosimilar: Test drug (T)

Disciplines of NDA Review Team

- CMC (quality): Chemistry, Manufacturing & Control
- Pharmacology & Toxicology (Pharm/Tox):
- Pharmacokinetics & Pharmacodynamics (PK/PD)
- Clinical section (efficacy & safety)
- Statistical section

- Clinical reviewers make final decision.

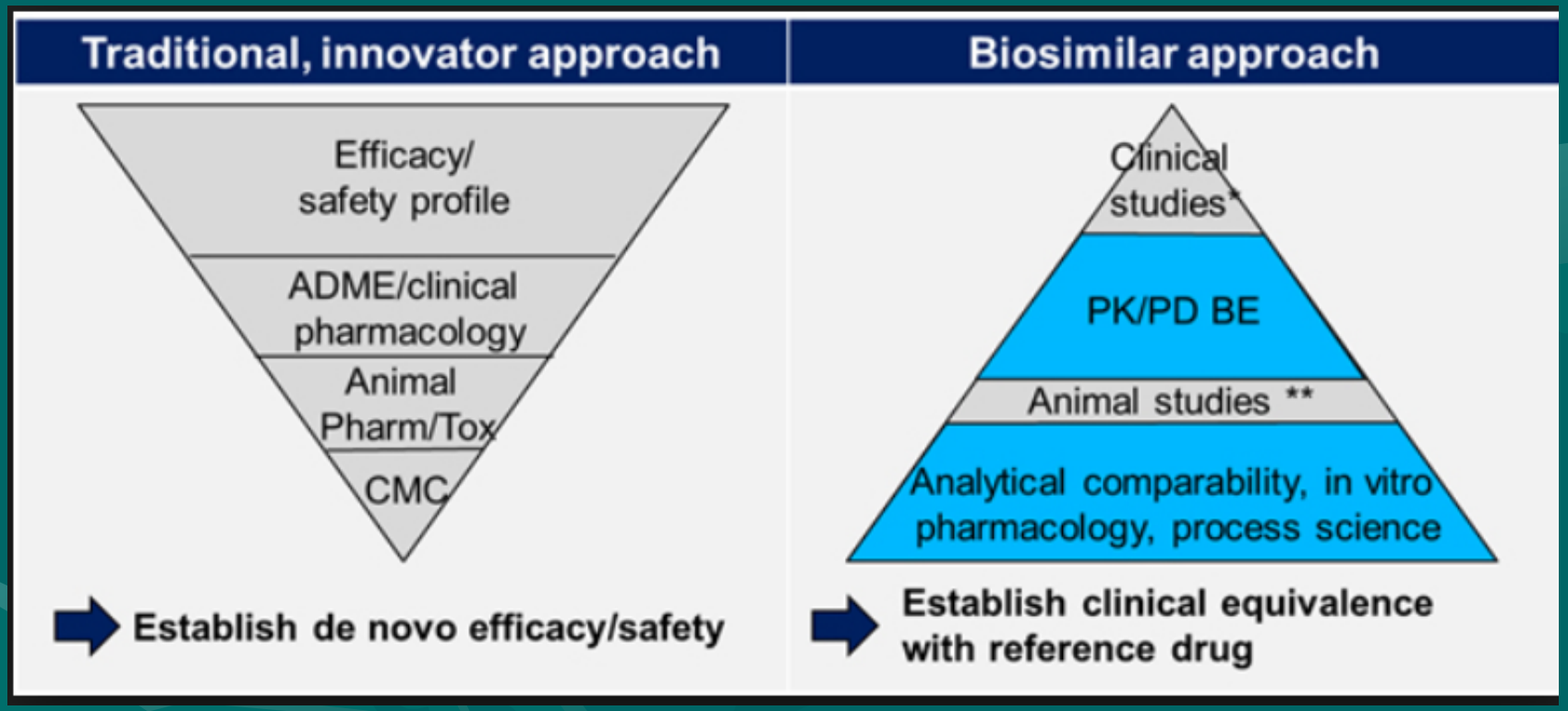
Biosimilar Approach

- Comparative Exercises
  1) 遵循學名藥BE的精神
  2) Stepwise approach
  3) Totality-of-the-evidence

Test Drug		Reference Drug
Quality data	vs.	Quality data
Pharm/Tox data	vs.	Pharm/Tox data
PK/PD data	vs.	PK/PD data
Clinical data	vs.	Clinical data

- Statistician involves the clinical efficacy comparison

Different Developing Strategy



Regulatory Guidelines for Industry & Regulator

- EMA, as early as 2006
- Heath Canada
- USFDA
- Japan
- Korea
- Singapore
- Taiwan

生物相似性藥品查驗登記基準
2015年6月12日

- 總則
- 品質議題 (CMC)
- 非臨床及臨床議題 (Pharm/Tox, PK/PD, Clinical)
- 特定生物相似性藥品之產品準則
  - 重組人類生長激素 (Somatropin)
  - 重組人類胰島素及類胰島素(Human insulin)
  - 重組人類顆粒細胞群落刺激因子 (GCSF)
  - 重組人類紅血球生成素 (EPO)
  - 重組人類α干擾素 (alpha interferon)

生物相似性單株抗體藥品查驗登記基準

2015年12月4日

- 總則
- 品質議題
- 非臨床試驗
- 臨床試驗 (包括PK/PD)
- 藥品安全監視

Important Concepts

- Process is product (製程決定產品)
- CMC comparison is the most important part !
- Sensitive model to tell the difference
- To demonstrate similarity, rather than to confirm efficacy
- State-of-art methods
- Guidelines and review standard liable to be changed according to new information !
- Impact to clinician/pharmacist: Biosimilar/stand-alone biologics

Comparative Exercises - CMC

- Primary structures
  including c-terminal Lysine variability & Proline amidation
- Higher order structures (including aggregation)
- Posttranslational modifications
  - glycosylation
  - phosphorylation
  - oxidation
  - deamidation
  -truncation
- Disulfide bridge
- Impurity and purity
- Stability

Comparative Exercises - Functional Assays (*in vitro*)

- Higher order structures may not be confirmed due to complexity
- Functional assays act to complement physicochemical analyses
- Ligand or receptor binding assays
- Enzymatic assays
- Cell-based assays

Comparative Exercises - Non-Clinical (*in vivo*)

- The scale depends on the similarity of CMC and functional comparability.
- Relevant animal model
- Animal toxicity studies
- Animal PK/PD studies
- Animal immunogenicity

Comparative Exercises - Clinical PK/PD

- Not always feasible in healthy volunteers
- Cross-over (short half-life) or parallel (longer half-life) design
- Select dose(s) on the steep part of the dose-response curve to tell the difference
- PD parameters
  1) Clinically relevant
  2) measurable for a sufficient period of time
  3) Sensitive to detect clinically meaningful difference
- As surrogate endpoint for clinical comparability

Clinical Efficacy Trials

- 延續 PK/PD comparative studies
- Statistical hypothesis:
  Equivalence or Non-inferiority
- Active-control comparative clinical trial
  - margin 之設定
  - assay sensitivity
- Some deviation of design from originator might be acceptable.
- Use sensitive endpoint (e.g. euglycaemic hyperinsulinaemic clamp for insulin)

多個適應症

- 每個適應症都做臨床比較試驗嗎 !?

  For example:

  Reference drug 在我國核准之適應症: **A, B, C, D** and **E**

  Biosimilar drug 欲申請之適應症: **A, B, C, D** and **E**

  Biosimilar drug 之臨床比較試驗只做適應症 **A**

- 則廠商須論述從適應症**A** 外推其療效安全性(or 生物相似性)至其他適應症**B, C, D** and **E** 之科學上之正當性(justification for extrapolation of indications)

Justification for Extrapolation of Indications, Points to Consider

- 臨床經驗
- 現有文獻資料
- 作用機轉(mode of action)
  1) target, receptor
  2) binding, dose/concentration response, signal transduction
  3) relationship between structure and target/receptor
- PK and distribution in different population
- Immunogenicity in different population
- Difference in expected toxicities in each indication
- Totality of the evidence demonstrating biosimilarity
- More challenging for monoclonal antibody

安全性議題

- 療效比較之結果 ≠ 安全性之結果
- Safety population and comparison:
  - 比較 safety profile of test drug vs. reference drug
  - 不良反應之類型、嚴重性及頻率
- 上市前之臨床試驗資料常無法分辨test drug 與 reference drug 間安全性之差異
- 兩大特殊要求：
  - 藥物安全監視計畫、風險管理計畫
  - 免疫原性 (immunogenicity) 之偵測

免疫原性(Immunogenicity)

- 免疫反應之後果可影響療效及安全性
- 影響免疫原性之因素：
  - drug substance, drug product, impurities, excipients, stability, route of administration, regimen and target patients
- 通常無法從動物研究中預知
- 不同適應症，不同風險

Labeling

- USFDA (Mar. 2016)
  Draft Guidance: Labeling for Biosimilar Products
- EMA (May 2012)
  QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product → 沒寫什麼
- TFDA
  1) 有在仿單中標明“生物相性藥品”
  2) 仿單比照Reference Drug
  3) Biosimilar Drug 有某些特有資料也列入仿單

Remsima 仿單

▼ 本藥品必須接受進一步監測。如此一來，將能夠快速發現新的安全性資訊。專業醫護人員必須通報任何可疑的不良反應。

類希瑪® 限由醫師使用

Remsima®

Infliximab

100 mg

HEALTHCARE
CELLTRION™

1. 藥品名稱

輸注溶液用Remsima 100 mg濃縮粉劑

2. 定性與定量組成

每小瓶含100 mg的infliximab*。調配後每mL含10 mg的infliximab。
*Infliximab是透過重組DNA技術，從小鼠融合瘤細胞中製造的嵌合人類 - 小鼠IgG1單株抗體。
詳細賦型劑內容，請見第6.1節。

5. 藥理特性

5.1 藥效學特性

藥物分類：免疫抑制劑、腫瘤壞死因子α (TNFα) 抑制劑、ATC編碼：L04AB02。
Remsima是具有生物相似性的藥品。

Interchangeability

- Interchangeability
  (1) Pharmacist level
  (2) Prescriber's level
- Only USFDA has regulatory document for interchangeability
  Draft Guidance: (Jan. 2017)
  Considerations in Demonstrating Interchangeability with a Reference Product

INN

- 比照EMA。
  配合風險管理畫及藥物安全監視
- USFDA對主成份名有規定
- WHO Document:
  Biological Qualifier An INN Proposal (Oct. 2015)
  與USFFDA類似

Complexity of Biosimilar

- High variations among protein drugs, from CMC, pharmacological mechanism to clinical indications.
- No clear definition of "similarity" (except PK and clinical equivalent trial)
- Current Guidelines are not comprehensive

Thanks for Your Attention