Biosimilar Products Regulation in Taiwan

Chi-Hsun Chen, M.D. (陳紀勳 醫師)
Senior Clinical Section Chief
Division of New Drugs
Oct. 07, 2024

Disclaimer

This presentation was not officially cleared, and the views offered here do not necessarily represent the official positions at MOHW, including TFDA.

Definition of Biosimilar Products

- A biologic product which is highly similar to the reference product approved in this country, highly similar means that there is no clinical meaningful differences in terms of quality, efficacy and safety
- Scope:
  Polypeptide and protein manufactured by recombinant DNA technique (i.e. solid-phase synthesis is excluded)
- Vaccines, allergens, blood products or derivatives are not included

Regulations in Taiwan

- **Regulations for Registration of Biosimilar Product**
  (Announced in April 2024, first edition 2008)
  「生物相似性藥品查驗登記基準」
- Including specific products in Appendix
  (1) Human Growth Hormone
  (2) Human Insulin
  (3) Human G-CSF
  (4) Human Erythropoietin (EPO)
  (5) Human Interferon-Alpha
  (6) Monoclonal Antibodies

Reference Products

- Reference products (R) should be approved in this country
- Biosimilar products (B) cannot not be Reference products
- Originator's product of from other manufacturing sites (not approved in this country) can be used as reference product (R'). But comparative exercises should be done among B, R and R'.

- Consideration of IV and SC Routes of the same active ingredient
  (1) Same product, with both IV and SC routes
  → one Reference product, one NDA
  (2) Different product (different formulation)
  → Separate Reference product, separate NDA

Basic Principles to Recognize as Biosimilar Products Upon NDA Submission

- Reference product (R) should be approved in this country:
  licensed number should be provided
- The claimed indications should be approved in reference product
- The posology and rout of administration should be the same as reference product
- Other considerations:
  (1) Presentations: vial, pre-filled syringe (PFS), injection pen……..etc.
  (2) Concentration
  (3) Strength (e.g. xx mg/vial)
  It is expected that the presentation, concentration and strength should be the same.
  If there is any deviation to reference product, the sponsor should ensure that such deviation would not contradict the posology or cause miss use. (e.g. recommended dose: 25 mg/kg for a PFS)
- Any deviation to reference product to enhance efficacy would be regarded as new drug.

Check-List for Refuse-to-File (RTF)

一、行政資料

員填寫，廠商請勿自行填寫。

確認項目 (major issue)	業者審視情形 是	否	不適用 (請列原因)	TFDA 審核結果 (廠商請勿填寫)
1. 檢附「新藥及生物藥品(含生物相似性藥)查驗登記退件機制(Refuse to File; RTF)查檢表」?	☐	☐		☐是 ☐否
2. 檢附「藥品查驗登記申請書正、副本」?	☐	☐		☐是 ☐否
3. 依據西藥及醫療器材查驗登記審查費收費標準繳納審查規費?	☐	☐		☐是 ☐否
4. 檢附「中文仿單擬稿」?	☐	☐		☐是 ☐否
5. 檢附「資料專屬期及國內外臨床試驗資料表」	☐	☐		☐是 ☐否
6. 申請新藥類別 ☐屬新療效、新複方、新使用途徑新藥及生物相似性藥，是否檢附西藥專利連結施行辦法附件二「藥品專利狀態之聲明表」? 註：1. 送件時未檢附聲明表，即退件，不接受自行補件。 2. 屬藥事法第 48 條之 9 第 4 款，送件後 42 天發文通知資料齊備(續審)/退件(RTF)。 ☐非屬新療效複方、新使用途徑新藥及生物相似性藥，是否敘明新藥類別?	☐	☐		☐是 ☐否
7. 係屬輸入藥品者，執行國內臨床試驗或檢送製售證明、採用證明(請勾選下列其中一項，文件可於領證前補齊)				
(1) 依查驗登記審查準則第 38 條之 1 執行國內臨床試驗，毋須檢送採用證明。	☐			☐
(2) 依查驗登記審查準則第 38 條之 2 執行國內臨床試驗，併檢送 1 張採用證明。	☐			☐
(3) 無執行國內臨床試驗，依查驗登記審查準則第 38 條之 4 檢送 2 張採用證明。	☐			☐
(4) 非屬新成分新藥，檢送出產國製售證明。	☐			☐
8. 若為生物相似性藥品，是否明述參考藥品品名及參考藥品於我國之許可證字號? 參考藥品許可證字號:_____	☐			☐是 ☐否
(1) 其給藥途徑及建議之用法用量是否與我國核准上市之參考藥品相同? 若不相同，應提供提供合理說明。	☐			☐是 ☐否
(2) 其產品包裝型態(例如 vial、pre-filled syringe、injection pen 等)是否與我國核准上市之參考藥品相同? 若不相同，應提供提供合理說明。	☐			☐是 ☐否
(3) 其產品濃度是否與我國核准上市之參考藥品相同? 若不相同，應提供提供合理說明。	☐			☐是 ☐否
退件判定				
審核結果第 1 至 6 任一項為「否」者，予以退件。輸入藥品若未勾選第 7 項之其中一項者，予以退件。生物相似性藥品第 1 至 6 及第 8 項任一項為「否」者，予以退件。				☐續審 ☐退件
說明欄				

Strategy of Drug Development: Comparative Studies

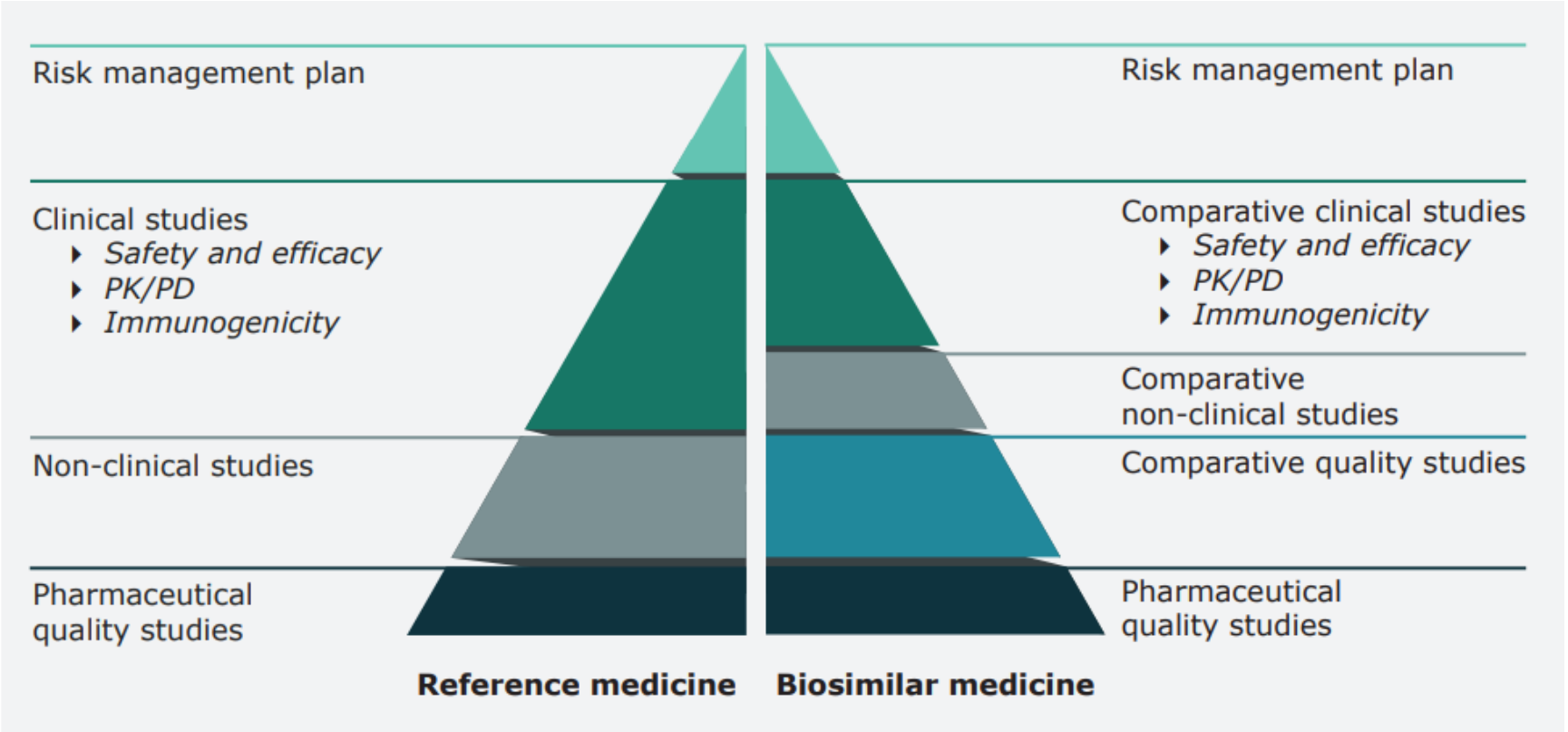
- Comparative Exercises in following disciplines
  (1) Structure (CMC)
  (2) Non-clinical
  (3) PK, PD, immunogenicity
  (4) Clinical efficacy and safety (including immunogenicity)
- Stepwise approach
- Totality-of-the-evidence to demonstrate similarity

- Biosimilars vs. Generics

PK: pharmacokinetics; PD: pharmacodynamics

Innovators vs. Biosimilars

- Extensive comparative exercises in structure and *in vitro* studies



from EMA: Biosimilars in the EU, Information guide for healthcare professionals

Important Concepts

- Process is product
- Using most sensitive model/design and state-of-art methods to tell the difference
- **The purpose of comparative studies is to demonstrate similarity rather than to confirm efficacy!**
- The design of clinical trial may be deviated from the pivotal study done by the originator (e.g. ORR instead of OS in cancer trial)
- Guidelines and review standard might be kept up with time
- For healthcare providers:
  Same outcomes as reference drug will be expected when using biosimilars(same concept of generic)

Ethnic Difference

- Bridging study evaluation submission is not required for biosimilar products.
- Ethnic difference was evaluated in reference product.

Approval Bases

- Acceptable quality (no deficiency precluding approval)
- Totality of evidence of similarity:

1. Structure (most important) :

(1) 1°, 2° and higher order (*in vitro* functional assays)

(2) Amino acid sequence be the same

2. Non-clinical studies

3. PK/PD studies

(1) Traditional PK study (BE criteria)

(2) Clinically relevant PD biomarker, steep part of dose-response curve

(3) May be adequate to demonstrate comparable efficacy (e.g. insulin)

(4) Immunogenicity

4. **Clinical efficacy**

(1) Equivalence results are preferred, non-inferiority in exceptional case

(2) Comparable safety profile

(3) Comparable impact of immunogenicity to efficacy and safety,

(4) At least 1 year F/U of immunogenicity for long term use settings

Multiple Indications

- Clinical comparative studies are not required for each claimed indications; the sponsor may conduct one or more clinical comparative studies (choose the appropriate indication population as study models case-by-case).
- **The similarity of clinical outcomes** of indications not studied would be justified by extrapolated of indications.
- For example:
  Approved indications of Reference drug: **A, B, C, D** and **E**
  Claimed indications of Biosimilar product: **A, B, C, D** and **E**
  Comparative clinical studies of biosimilar drug: **A and B**
- The sponsor should provide article/report to justify the extrapolation of indications A and B to C, D and E
- Simple placebo-control trial of C, D and E cannot justify similarity。

Justification for Extrapolation of Indications, Points to Consider

- Clinical experience and relevant journal articles
- Mode of actions (MOAs)
  1) target, receptor
  2) binding, dose/concentration response, signal transduction
  3) relationship between structure and target/receptor
- PK in different population
- Immunogenicity in different population
- Expected toxicities in each indication
- Totality of the evidence demonstrating similarity
- More challenging for monoclonal antibody

Post-Marketing Activities

- Post-marketing safety surveillance is required (pharmacovigilance plan)
- Additional risk minimization measures (風險管理計畫) other than labeling should provided in the following conditions:
  (1) When reference product was required
  (2) When there is additional risks not in reference drugs

Interchangeability

- Interchangeability
  (1) Pharmacist level (substitution)
  (2) Prescriber's level (switch)
- Substitution is not allowed
- Switch:
  Neither endorsed nor prohibited

INN

- Follow EMA's principle，same INN as reference product

Label

- Follow the reference product with some modification。The indications and posology should be WITHIN the scope of reference product
- Highlight the attribute as biosimilar product at the top of first page:
  「XXXXXXX」(tradename of biosimilar) is the biosimilar product to「YYYYYYY」(tradename of reference product)
- The results of comparative studies will not be shown in labels of biosimilar products

Management in Pharmacy

- Prescribe in trade name is encouraged to avoid confusion
- Batch number recording in Pharmacy is encouraged to facilitate pharmacovigilance

Patent Infringement

- Patent linkage is applied to biosimilar products in this country
- Data exclusivity for new indication of reference products

Information of Biosimilars in TFDA Website

https://www.fda.gov.tw/TC/siteContent.aspx?sid=11262

Reevaluation of the Need for Comparative Clinical Efficacy Studies

- Conclusion of IPRP Workshop Report (6 May 2024) :
  To continue efforts toward regulatory convergence on a framework for streamlining biosimilar development
- EMA: the importance of dedicated clinical efficacy and safety data should be re-evaluated.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 24 November 2023
2 EMA/CHMP/BMWP/35061/2024
3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper for the development of a Reflection Paper
5 on a tailored clinical approach in Biosimilar development
6

Agreed by Biosimilar Medicines Working Party	29 November 2023
Adopted by CHMP for release for consultation	25 January 2024
Start of public consultation	01 February 2024
End of consultation (deadline for comments)	30 April 2024

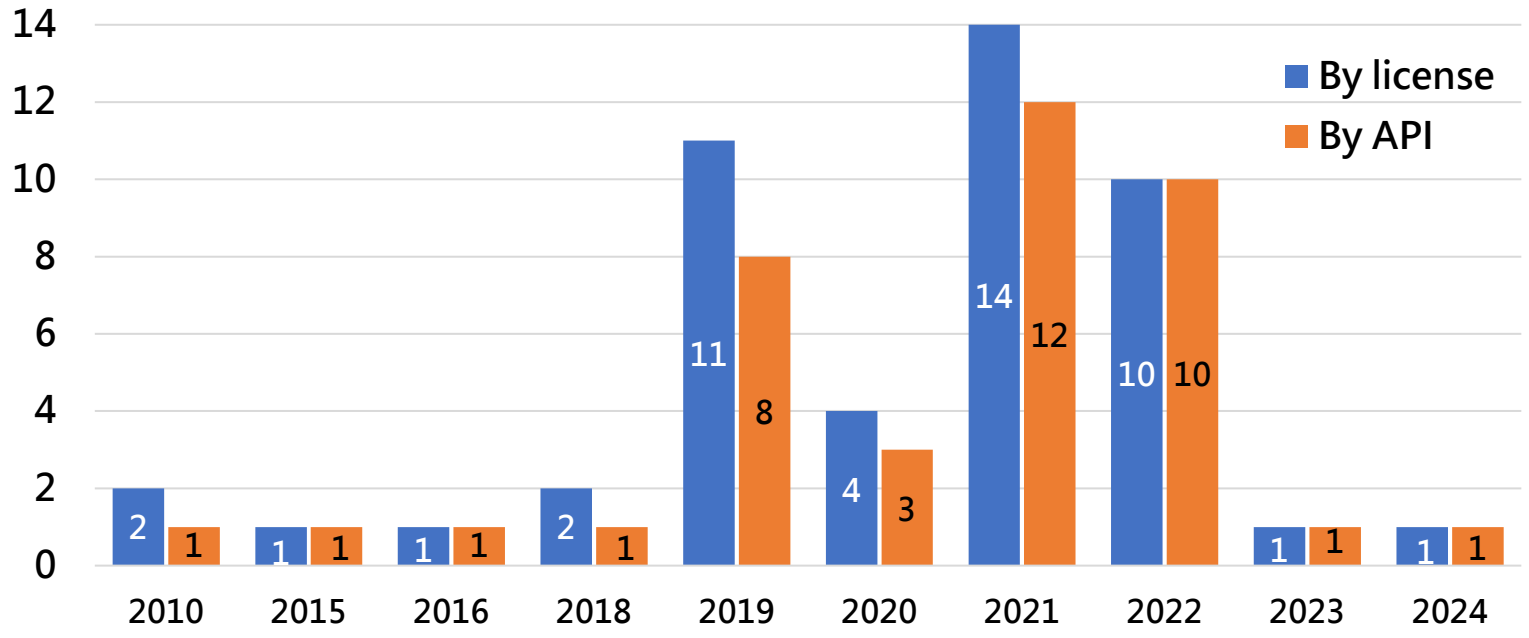
7

Approved Biosimilar Products (by API)
up to May 2024

API	No. of Approved products
Adalimumab	7
Bevacizumab	6
Etanercept	3
Filgrastim	1
Infliximab	3
Insulin glargine	3
Pegfilgrastim	2
Ranibizumab	1
Rituximab	4
Somatotropin	1
Teriparatide	2
Trastuzumab	6

API: active pharmaceutical ingredient

Approved Biosimilar Products (by year)
up to May 2024



Pilot Plan of Encouraging Use of Biosimilar Products

- Announced by National Health Insurance Administration (NHIA) on June 14, 2024
  「全民健康保險推動使用生物相似藥之鼓勵試辦計畫」
- Objectives:
  To achieve the target rate of 30% of prescriptions within 3 years
- Scope:
  Biosimilars products with difference of price > 20% as compared to reference products
- Incentives:
  (1) Additional funding from NHIA
  (2) Reward to prescribers and hospitals
- https://www.nhi.gov.tw/ch/cp-15234-3f6cd-2523-1.html

THANKS FOR YOUR ATTENTION

ご清聴ありがとうございました

財團法人醫藥品查驗中心
Center For Drug Evaluation

Backup Slides

Consultation

- Consultation to TFDA/CDE is encouraged
  (1) to know regulators' current thinking
  (2) to know the unexpected deficiencies in advance
  (3) to resolve discrepancies and gap
  (4) to reduce risk of failure
  (5) to reduce the inquiries during NDA review
- As early as possible!