SCIENTIFIC FACTORS IN BIOSIMILAR PRODUCT DEVELOPMENT

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BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT

FDA Guidances

April, 2015

- **Scientific considerations**
- **Quality consideration**
- **Questions and answers**

Scientific considerations

To deal with judgment based on several features

Demonstrate biosimilarity by stepwise approach

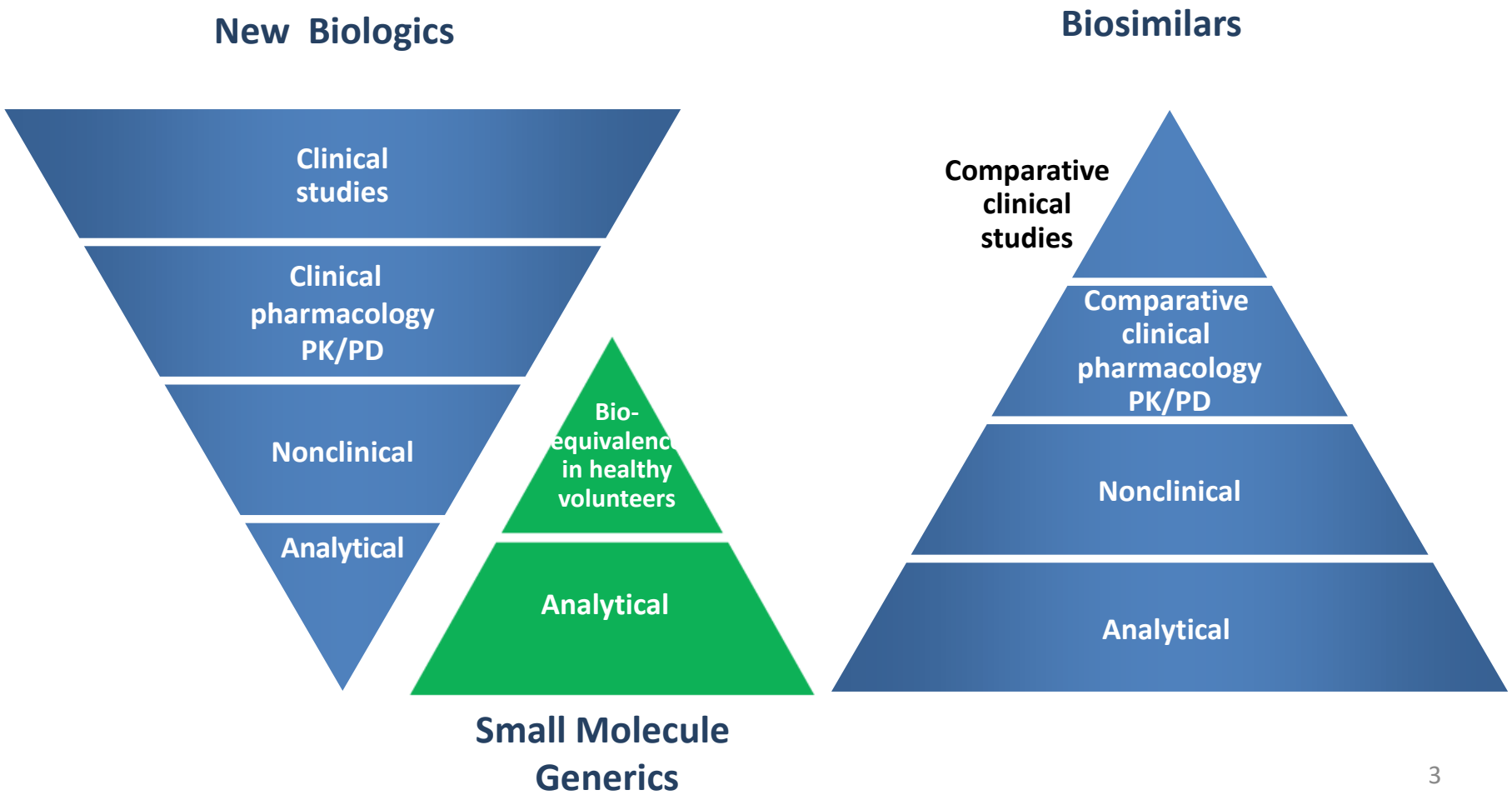
Assess biosimilarity based on the totality of the evidence

STAGEDPRIORITIES OF DRUG DEVELOPMENT

Totality of evidence

Demonstrate: No clinically meaningful differences

Question: Residual uncertainty?



STEPWISE APPROACH TO DEMONSTRATE BIOSIMILARITY

Structural and functional characterization and comparison of biosimilar and reference products

A comprehensive exercise

Animal data: Toxicity, additional evidence of biosimilarity

Comparative human PK & PD studies

Comparative clinical immunogenicity

Additional clinical data

Confirmatory

BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT
EXTENSIVE ANALYTICAL ASSESSMENT

-

- **Structural analysis**

  Physicochemical properties

  Analytical methodology:

  With sensitivity, specificity

  (Primary, higher-order structure)

  (Enzymatic post-translational modifications: e.g. phosphorylation, glycosylation)

  (Other potential variants, e.g. deamydation, glycosylation)

- **Functional assays**

  (In vitro and/or in vivo)

  (Bioassays, binding assays, enzyme kinetics)

COMPARATIVE ANALYTICAL CHARACTERIZATION:

Levels of assessment

To provide a level of confidence for similarity between biosimilar and reference products: Level of residual uncertainty?

Highly similar with fingerprint similarity

Meets the statutory standard for analytical similarity based on integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.

Highly similar

Meets the statutory standard for analytical similarity

Similar

Additional information needed to determine high similarity between biosimilar and reference products

Not similar

Differences in the results of analytical characterization

BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT
ANIMAL STUDIES

Animal toxicity studies

If and to the extent needed (based on reference information)

Animal PK and PD measures

Similarity may support totality of evidence

Animal immunogenicity assessments

To interpret animal study results

Do not support human immunogenicity

BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT
COMPARATIVE HUMAN PK & PD STUDIES

Human PK & PD endpoints are generally more sensitive than clinical responses

Comparative human PK& PD studies are usually expected

PK study

When exposure correlates with clinical safety and effectiveness

PD study

When PD measure correlates with safety and effectiveness

On the steep part of the dose-response curve

Crossover study with short half-life (up to 5 days)

Parallel design with longer half-life (more than 5 days)

BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT
CLINICAL IMMUNOLOGY ASSESSMENT

Comparative immunogenicity between biosimilar and reference product

At least one such study

Preferable: Collect immunogenicity data in all clinical studies

Comparative parallel design in treatment-naïve patients

In a subset of patients: single crossover from reference to biosimilar

Safety risks should be evaluated also during post-marketing

BIOSIMILARITY:
DEMONSTRATION AND ASSESSMENT
COMPARATIVE CLINICAL STUDIES

Supportive, but usually required

Comparative safety and effectivenes studies

Endpoints, study population, study design:

Should enable to discriminate between clinically meaningful differences

Margins:

Symmetric, equivalence design

Asymmetric, noninferiority

QUALITY DATA PACKAGE
- MANUFACTURING PROCESS

Quality attributes and molecular characteristics of biosimilar and the reference product should be comparable

Manufacturing process of the biosimilar itself should have acceptable performance and consistence

Batches of the commercial manufacturing process should generate data for quality, safety and efficacy

Biosimilars have a lifecycle

- **Changes arise during development and after approval**
- **Comparability should be assessed**

ASSESSMENT OF QUALITY ATTRIBUTES

Quality attributes

Comparative analytical similarity data

- **Structural analysis**
- **Functional assays**
- **Physicochemical attributes**

Manufacturing process

FDA classification of quality attributes

- **Depending on impact on clinical outcomes**

Tier 1: **Critical quality attributes**
Tier 2: **Less critical quality attributes**
Tier 3: **Least critical quality attributes**

ASSESSMENT OF QUALITY ATTRIBUTES

Statistical assessment

Tier 1: Equivalence test

Not fixed BE limits (margins):

Proportional to variation of mean response in reference lots

Margin = 1.5* s_R

1.5: FDA regulatory constant

(to ensure similarity in practice)

With 10 lots per product, power = 85%

Margin is narrower with larger sample size

ASSESSMENT OF QUALITY ATTRIBUTES

Tier 2: Quality Range Approach

Range: [Mean – k*s, Mean + k*s]

k to be chosen by user, with justification

E.g., k = 1.96: 95% of reference lots lies within range

A large proportion of test values should lie within range

Tier 3:

Side-by-side comparisons

Raw data and graphical comparisons

POSSIBLE CRITERIA FOR ASSESSING SIMILARITY

- **Average versus variability**

  Comparing means, variances or CVs

  Sensitive to small change/variation; Highly variable

- **Moment-based versus probability-based**

  Can take variability into account

- **Aggregated versus disaggregated**

- Can address degree of similaritys

- **Scaled versus unscaled**

  Adjust for intra-subject variability

- **Weighted versus unweighted**

  Different weights for variance components

- **Fixed versus flexible**

  Adjust for intra-subject variability and/or therapeutic index of the reference product

ASSESSMENT OF EQUIVALENCE / SIMILARITY - PRESCRIBABILITY, SWITCHABILITY

Prescribability

A subject is naïve to the drug, i.e. has not taken it in any form. The drug may be prescribed and its licensed products may be administered. But an ingested product may not be substituted with another.

Total variation (between + within subjects) is important.

Switchability

A subject has already taken a product of the drug (e.g. brand-name, reference) and is to be switched to another formulation (e.g. generic, test).

Within-subject variation is important.

R → T

HOW SIMILAR IS "SIMILAR"?
- BIOSIMILARITY INDEX, FOR A GIVEN RESPONSE

Step 1: Assess **average biosimilarity** for a given response

E.g., for pharmacokinetic response: 90% confidence limits between 80% and 125%.

Step 2: Calculate the **reproducibility (p_{RR})**, in a second study, based on the same observed contrast (difference or ratio), i.e., estimate its **variability**.

Step 3: Claim biosimilarity if the 95% confidence lower bound of the reproducibility is larger than a **pre-specified number (p_0)**

S.-C. Chow. *J.Bioeq.Bioavail.* 2011;Suppl.1--002:1-8.

S.-C. Chow, et al. *Biosimilars*, 2011;1:13-26.

T.-C. Hsieh, et al. *Stat. Med.* 2013; 32: 406-414.

HOW SIMILAR IS "SIMILAR"?
- BIOSIMILARITY INDEX, FOR A GIVEN RESPONSE

- p_0 can be obtained based on the comparison of a "reference product" to the "reference product". That is, we can calculate the reproducibility (p_{RR}), i.e. a measure of variability.

- p_0 can be chosen e.g. as 80% of p_{RR}. For example if p_{RR} = 90%, then we may choose p_0 = 80% X 90% = 72%.

- p_0 can reflect the degree of similarity that the sponsor would like to achieve; i.e. 'how similar is "similar"?'

HOW SIMILAR IS "SIMILAR"?
- BIOSIMILARITY INDEX, FOR ALL RESPONSES

Step 1: Obtain p_{iRR}, the reproducibility probability for the *i*-th response,

Step 2: Define the **Global or Total biosimilarity index**

$$pT = \sum_{i=1}^{K} w_i \, p_{RRi}$$

where w_i is the weight for the *i*-th response

Step 3: Claim **global biosimilarity** if the 95% lower confidencebound of p_T is higher than a pre-specified value (p_{0T})

INTERCHANGEABILITY OF BIOLOGICALS
(BPCI ACT)

Interchangeable or **interchangeability** means that:

- The biological product is **biosimilar** to the reference product; furthermore:

- It can be **expected** to produce the **same clinical result** as the reference product **in any given patient**;

- For a product administered more than once, the **risks of alternating or switching**, in terms of safety and reduced reduced efficacy, **are not greater than with use of the reference product without alternating or switching**.

(R vs. T) risk, and also, say, (T1 vs. T3) risk, compared with (R vs. R) risk!

INTERCHANGEABILITY

US Federal BPCI Act

"The term 'interchangeable' or 'interchangeability', means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

Many states have passed enabling legislations

- **BPCI Act condition:**

  "Same clinical outcome in any given patient"

  Could perhaps be interpreted:

  "Same clinical outcome in any given patient

  with some stated (statistical) assurance"

INTERCHANGEABILITY: US vs. STATES

Interchangeability –
Responsibility of state legislations

Several states consider the issue and 18 have already passed enabling legislation (January, 2016)

- **In many: pharmaceutical substitution is allowed but the physician should be notified**

- **Substitution = prescribability or switchability?**

Direct conflict with BPCI Act
A lawyers' delight!

INTERCHANGEABILITY

EMA Q&A (September 27, 2012)

The Agency's evaluations do not include recommendations on whether on a biosimilar should be used interchangeably with its reference medicine. For questions related to switching From one biological medicine to another, patients should speak to their doctor or pharmacist."

Health Canada

"Health Canada does not support the automatic substitution of a subsequent-entry biologic for its reference biologic drug. Health Canada therefore recommends that physicians make only well-informed decisions regarding therapeutic interchange."

…It is up to the 28 member states, and 11 provinces and territories!

INTERCHANGEABILITY:
EMA vs. MEMBER STATES

Consequence – very diverse expectations:

Member states:

*** Require prescription by brand name (Austria)**

*** Prohibit automatic substitution (most states)**

*** Require active prohibition by the physician (Czech Rep., Slovenia)**

*** Official list states substitutable products (e.g. Denmark, Finland)**

*** Permit substitution (Croatia, Poland)**

INTERCHANGEABILITY: EMA vs. MEMBER STATES

Differing expectations!

P.K. Thimmaraju, et al. GaBI Online (2015).

INTERCHANGEABILITY OF NBCD AND BIOSIMILARS

Interchangeability and substitution of NBCD and biosimilars

Schellekens, H., et al., *AAPS J*. 2014; 16(1): 15-21.

A clear statement:

(1) Substitution without the involvement of a healthcare professional should be discouraged to ensure traceability of the treatment of individual patients.

(2) Keep an individual patient on a specific treatment if the patient is doing well and only switch if unavoidable.

(3) Monitor the safety and efficacy of the new product if switching occurs.

STUDY DESIGN FOR INTERCHANGEABILITY

Crossover studies in healthy volunteers are often problematic due to:

Frequently long half-life
Emergence of auto-antibodies
(period effects)

Crossover study would be ineffective & unethical

Therefore, need to undertake study with parallel groups

Can not estimate within-subject variation (since there is no R vs. R)

There is no basis for
switchability
interchangeability

STUDY DESIGN FOR INTERCHANGEABILITY

- **Bridging crossover studies**

Switching

R→T, T→R, R→R', T→T'

Balaam's crossover design

4x2: (RT, TR, RR', TT')

Alternating

R→T→R', T→R→T'

2x3 dual design:

(RTR', TRT')

Switching and alternating

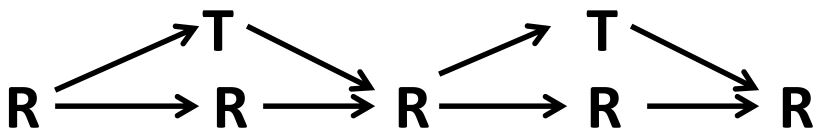
Modified Balaam's design:

(TT', RR', TRT', RTR')

STUDY DESIGN FOR INTERCHANGEABILITY

FDA Draft Guidance, 2017

Dedicated switching design



Switching and non-switching arms
Primary analysis: equivalence of PK endpoints, PD endpoints
Secondary analysis: safety, efficacy, immunogenicity

Integrated study design

Two studies, same subjects, re-randomization

First biosimilarity, then switching

CONDITIONS FOR INTERCHANGEABILITY STUDIES

Population

Strongly recommended: patients

Route of administration

Immunogenic route (e.g. s.c. rather than i.v.)

To assess impact of immune response on clinical performance

Extrapolation of data

Scientific justifications for interchangeability under each condition

SWITCHING INDEX

Switching

R→T, T→R, R→R', T→T'

(4x2 Balaam's design)

Switching index

Step 1. Obtain pT_i, $I = 1,\ldots,4$

Step 2. Switching Index:

$SI = max\{pT_i\}$

The largest Total Biosimilarity Index

Step 3. Claim biosimilarity if 95% lower bound of *SI* is larger than a prespecified p_{S0}

S.-C. Chow et al., Stat. Med. 2013; 32: 442-448

SWITCHING/ALTERNATING INDEX

Switching/Alternating

T→T', R→R', T→R→T', R→T→R'

(Modified Balaam's design)

Switching/Alternating Index

Step 1. Obtain pT_i, $i = 1,\ldots,4$

Step 2. Switching/Alternating Index:

$$SAI = \max\{pT_i\} - \min\{pT_i\}$$

The range of the Total Biosimilarity Indexes

Step 3. Claim biosimilarity if 95% lower bound of *SAI* is larger than a prespecified p_{SA0}

S.-C. Chow et al., Stat. Med. 2013; 32: 442-448
Y. Lu, et al., Drug Des 2013; 2(3): 1-6

A new proposed SCDI criterion for drug interchangeability

Step 1: Unscaled ABE criterion

For biosimilarity:

$$\frac{1}{BEL} \leq GMR \leq BEL$$

BEL: Bioequivalence/biosimilarity limit (usually 1.25)
GMR: Ratio of geometric means

Or:

$$-log(BEL) \leq log(GMR) \leq \log(BEL)$$

Or:

$$-log(BEL) \leq \mu_T - \mu_R \leq \log(BEL)$$

μ_T, μ_R: logarithmic means

A new proposed SCDI criterion for drug interchangeability

Step 2: Scaled ABE (SABE) criterion

Difference between logarithmic means is adjusted for intra-subject variability:

$$-\boldsymbol{log(BELS)} \leq \frac{\boldsymbol{\mu_T - \mu_R}}{\boldsymbol{\sigma_W}} \leq \boldsymbol{log(BELS)}\,,$$

Or:

$$-\boldsymbol{log(BELS)}\,\boldsymbol{\sigma_W} \leq \boldsymbol{\mu_T - \mu_R} \leq \mathbf{log}(\boldsymbol{BELS})\boldsymbol{\sigma_W}$$

σ_W^2: within-subject variance

In practice, σ_{WR}^2 (the within-subject variance of the reference product) is often considered.

A new proposed SCDI criterion for drug interchangeability

Step 3: Proposed scaled criterion for drug interchangeability (SCDI)

Consider:

$$\frac{(\mu_T-\mu_R)^2+\sigma_D^2}{\sigma_W^2} = \frac{2\delta\sigma_D+(\delta-\sigma_D)^2}{\sigma_W^2}$$

Here $\delta = \mu_T - \mu_R$

σ_D^2: Variance component for Subject-by-product interaction

Note: The expressions contain the first two terms of the model for individual bioequivalence

When δ and σ_D are similar then:

$$\frac{\delta^2+\sigma_D^2}{\sigma_W^2} \approx \frac{2\delta\sigma_D}{\sigma_W^2}.$$

The assumption is reasonable when both δ and σ_D are small

A new proposed SCDI criterion for drug interchangeability

The proposed scaled criterion for drug interchangeability (SCDI) :

$$-log(BELS) \leq \left(\frac{\mu_T - \mu_R}{\sigma_W}\right)\left(\frac{2\sigma_D}{\sigma_W}\right) \leq log(BELS)$$

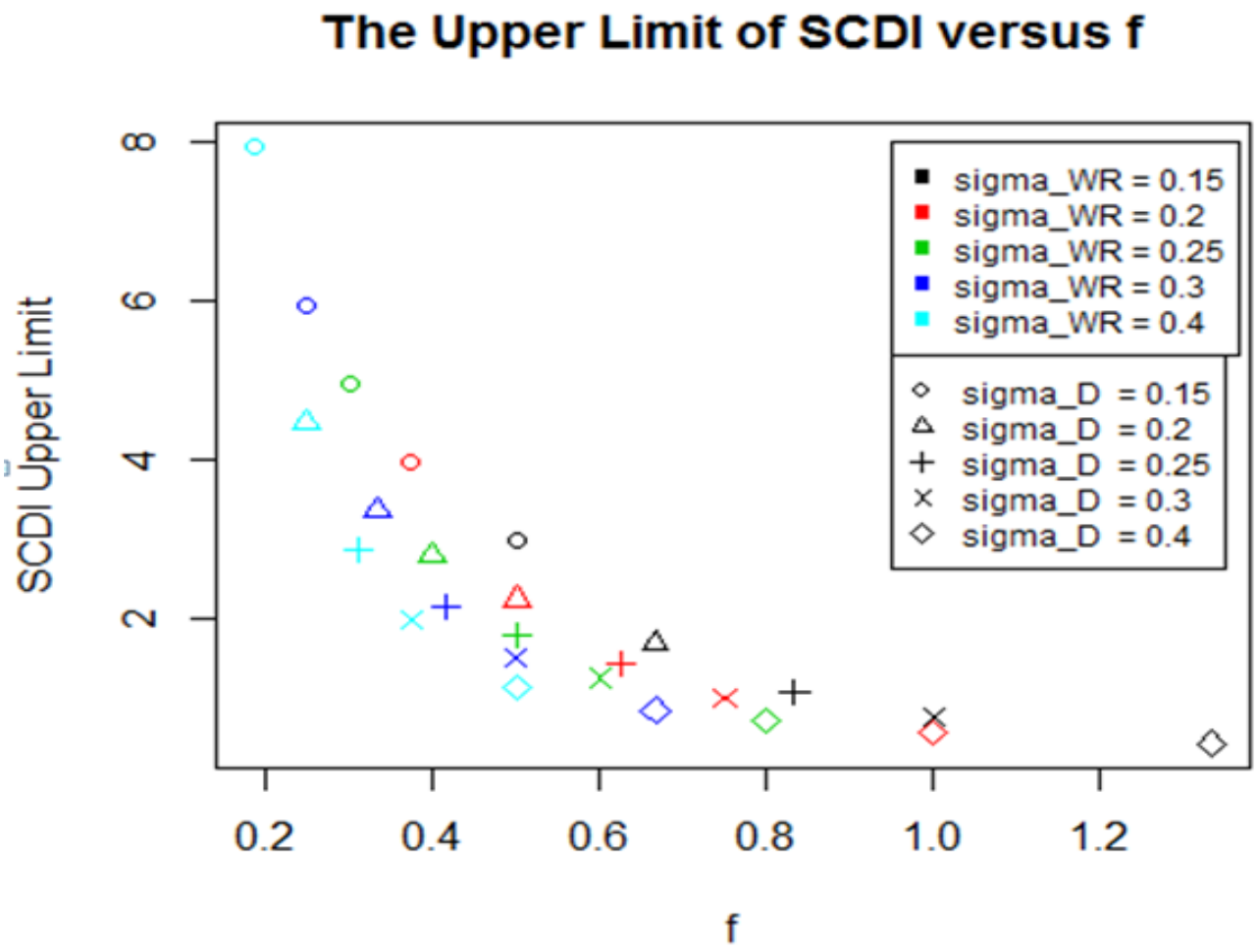
Correction factor for drug interchangeability:

$$f = \sigma_W/(2\sigma_D)$$

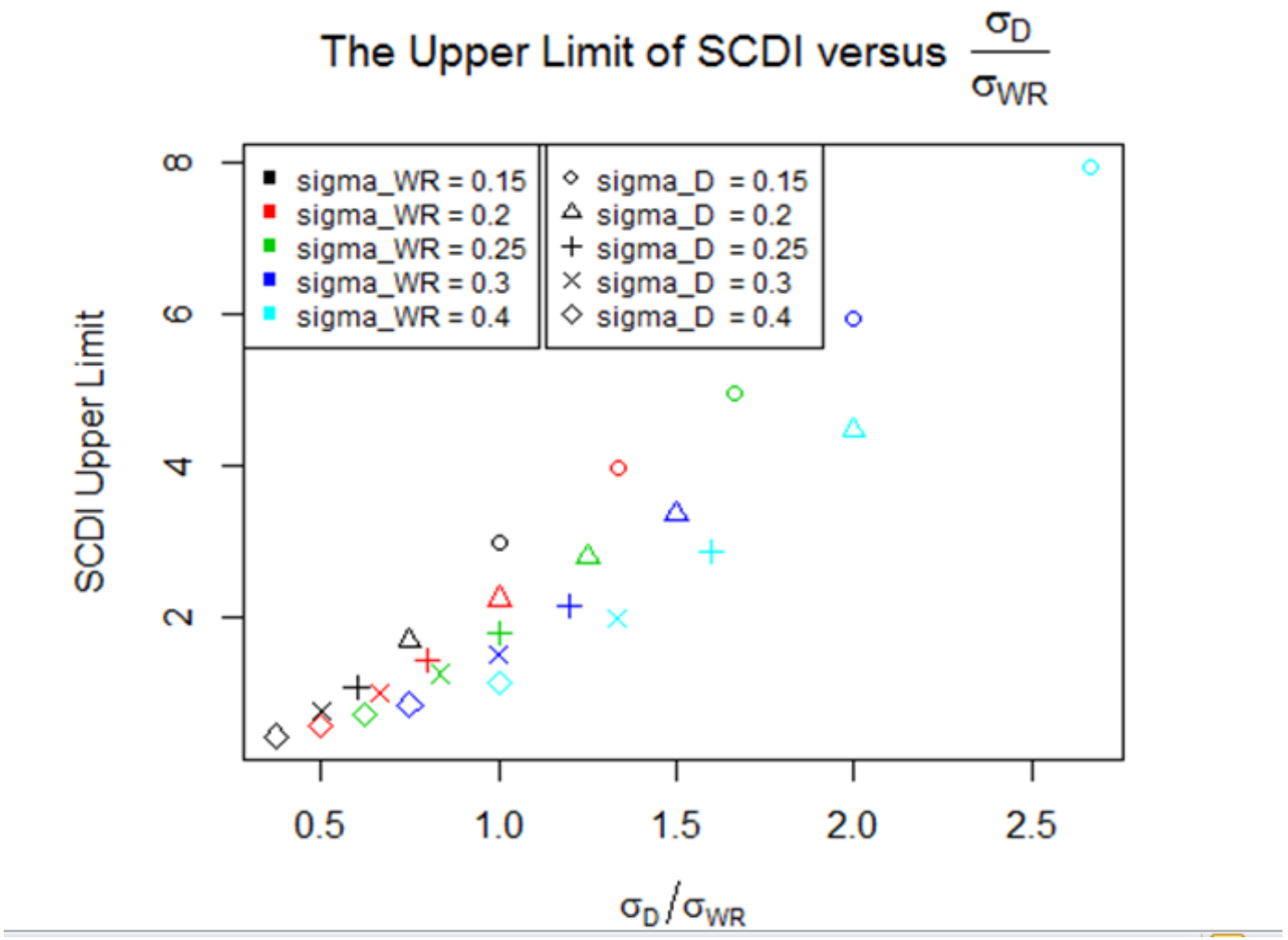
The proposed SCDI criterion is:

$$-log(BELS)\, f\sigma_W \leq \mu_T - \mu_R \leq \log(BELS) f\sigma_W$$

Note that statistical properties and finite sample performance need further research.



SCDI upper limit decreases with rising f



SCDI upper limit increases (proportionately) with rising σ_D/σ_{WR}

CONCLUSIONS

Scientific considerations provide valuable background and guide for the development of biosimilar products.

The assessment of quality attributes depends on their impact on clinical outcomes.

Quantitative approaches assessing and biosimilarity and interchangeability were proposed. Others will be developed.

Interchangeability of biosimilars is controversial. It should be pursued with careful thought and caution.

A NEW BOOK

Development of Biosimilar Drug Products

Editors: Laszlo Endrenyi (Toronto)**, Paul Declerck** (Leuven)**, Shein-Chung Chow** (Durham)

Publisher: CRC / Taylor Francis

THANK YOU!

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