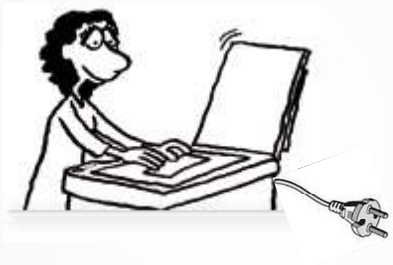
Clinical Strategies for Global Biosimilar Development

- A EU perspective with focus on monoclonal antibodies -

Dr. Diane Seimetz, Biopharma Excellence

Joint Conference of European Human Pharmacological Societies, 21 – 22 May 2015, Brussels

About a copying exercise



Making "copies" isn't a challenging task …

It depends on what kind of copies you are making.

Various r-hEPO products for example

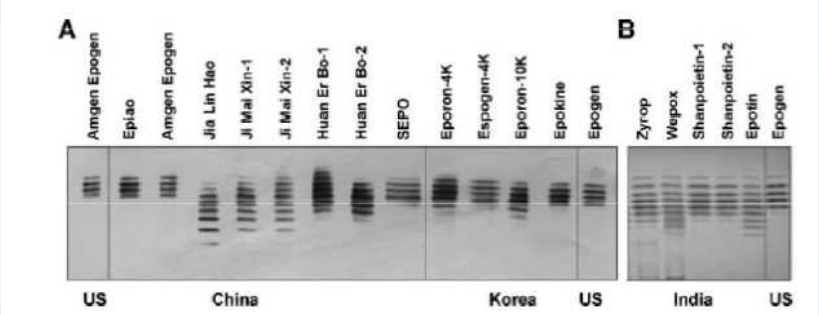


Figure 1. Iso-electro-focus (IEF) Gel with Western blots for isoform detection: (A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).

Park et al., J Pharm Sci Sep 2008. http://dx.doi.org/10.1002/jps.21546

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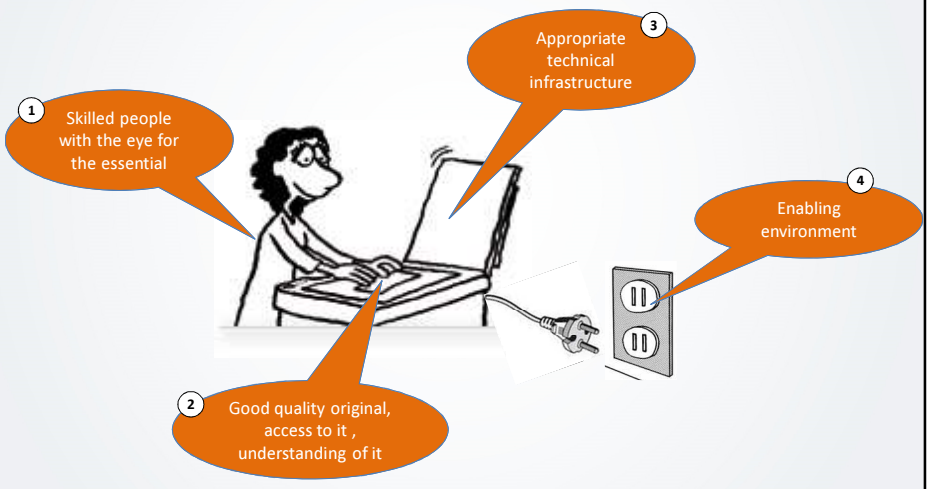
Essentials for successful making of biosimilars



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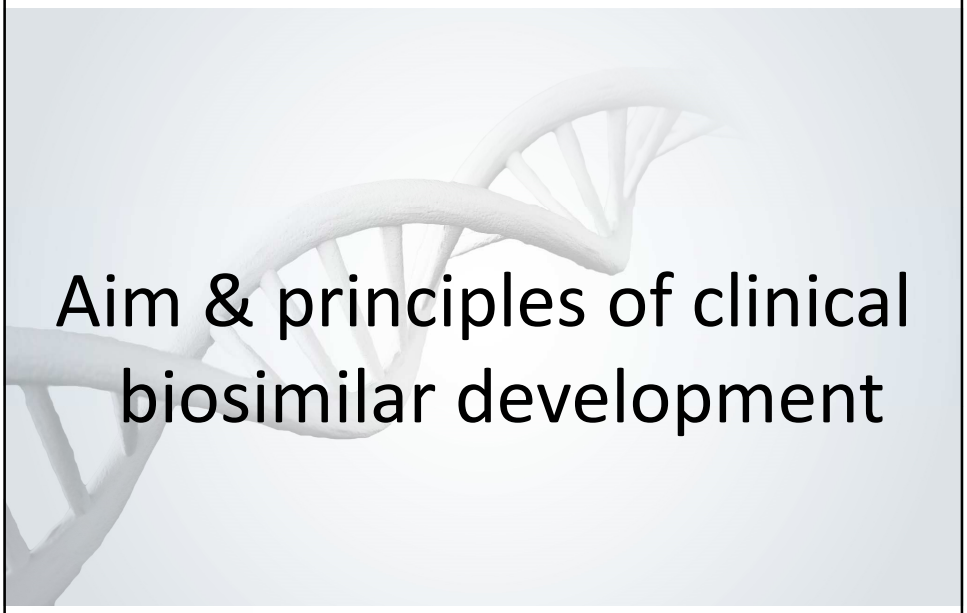
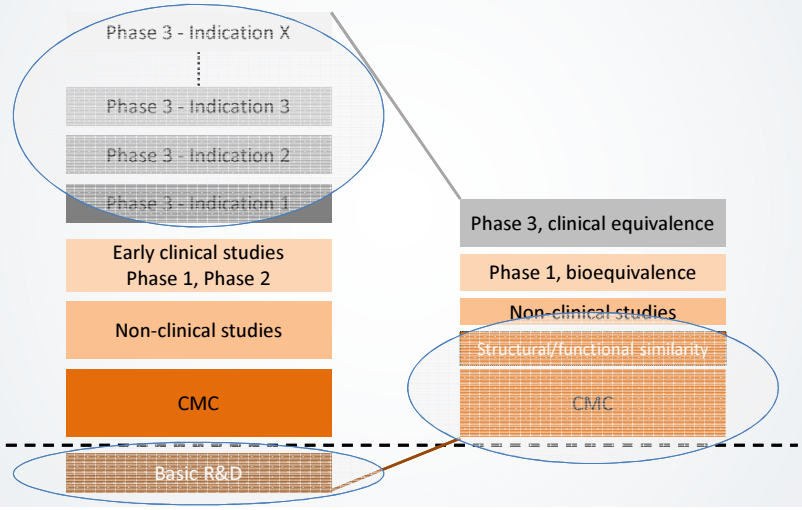
Agenda

- Aim & principles of clinical biosimilar development
- Precedent case Remsima
- Current paradigm & expectations for clinical studies
- Key success factors & challenges
- Future trends
- Why is Europe the place to be?



Aim & principles of clinical biosimilar development

Innovator vs. biosimilar development



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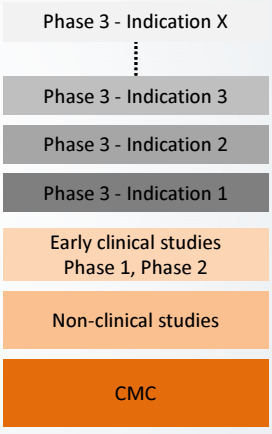
Benefit-Risk principle - innovator

Key for success: an integrated program to demonstrate a positive benefit-risk ratio



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"Benefit-Risk principle" - biosimilar

Similarity ⊕

Differences ⊖

- Phase 3, clinical equivalence
- Phase 1, bioequivalence
- Non-clinical studies
- Structural/functional similarity
- CMC

Key for success: an integrated program to demonstrate high similarity to the originator's product

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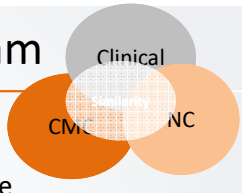
Aim of a biosimilar clinical program



Aim

- Important element of the stepwise similarity exercise
- Addresses slight differences shown at previous steps to confirm comparable clinical performance
- Complements structural, functional and non-clinical similarity data
- Investigates immunogenicity
- Supports the use of RMP sourced from one region for phase III
- Supports extrapolation

The aim is NOT

- to primarily establish efficacy and safety
- to justify substantial differences / dissimilarities in product quality

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Precedent case Remsima

The precedent biosimilar mAb – Remsima

Is setting expectations and paves the way for future biosimilar monoclonal antibodies

- Biosimilar mAb to Remicade, infliximab
- Important benchmark
- **EU approved** for all indications of the innovator (2013)
- **US submission pending**, Arthritis advisory committee meeting postponed (planned for March, 2015)
- Exchange between regulators FDA-EMA-Health-Canada-PMDA Biosimilar cluster, started in 2011

Remsima: clinical basis for approval

Clinical basis for EU approval:

- Phase 1 in AS: comparative PK (~125 pts/group)
- Phase 3 in RA: comparative efficacy + safety, MTX + mAb (~300 pts/group)
- Phase I pilot in RA (~19 pts)
- Small cohort of IBD pts

→ Comprehensive basis for a "generic type of product"

Remsima/Inflectra – Key results PK

- Phase 1 comparative PK study (~125 pts/group)
  - Repeated dose in ankylosing spondylitis patients!
  - Primary PK parameter: AUC_T and Cmax,ss
  - 90% CI for both, AUC_T and Cmax,ss, were within the predefined reference range of 80% to 125%
  - Secondary PK parameter after dose 5 incl. half-life, clearance and volume of distribution were within the 80% to 125% limit
  - a power equal to 90%
  - highly similar immunogenicity profile

Remsima/Inflectra – Key results phase 3

- Phase 3 in RA: comparative efficacy + safety, MTX + mAb (~300 pts/group)
  - Randomised, double-blind study, Remsima met its primary endpoint of therapeutic equivalence to the reference product
  - ACR20 at week 30
  - 73.4% of patients receiving Remsima achieved > 20% improvement in RA symptoms compared with 69.7% treated with Remicade
  - Highly similar immunogenicity profile

Remsima: handling of differences

Observed differences (selection)	Assessment
• Lower level of afucosylated glycans • Lower binding to FcγRIIIa • Lower ADCC?	Additional experiments e.g. patient samples, isolated cells (neutrophils) Clinical results within the predefined margin
• Less intact IgG	Difference small, no difference in binding of TNFα, potency
• Higher level of C-terminal lysine	Rapid cleavage in blood, not relevant
• Higher level of aggregates	No marked differences in immunogenicity up to 54 weeks
• Higher protein content in Remsima	Further RMP batches analysed, within range, intrinsic assay variability
• Imbalance in pts with serious infections (16 vs. 10, incl. active tuberculosis)	Chance finding

- ➢ Risk minimisation measures: educational program and increase of awareness for infections and tuberculosis
- ➢ Substantial number of clinical investigations in pharmacovigilance plan: Studies: 7, one in active CD; Registries: 5, one for CD and UC

Source: Inflectra Assessment Report, 27 June 2013

CHMP conclusion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The EU view

- The differences were not considered clinically meaningful as it did not affect the activity in experimental models relevant to the pathophysiological conditions in patients
- Supported by clinical similarity (PK, efficacy and safety)
- Approval and extrapolation to all approved indications justified

Source: Inflectra Assessment Report, 27 June 2013

Health Canada – approval for selected indications

Health Canada Santé Canada

Different agencies, different opinions

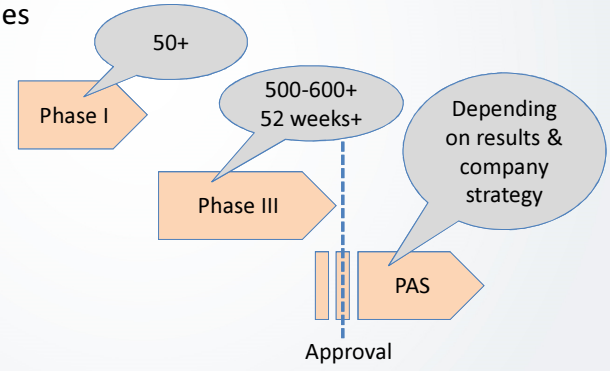
- "Scientific rationales were found to be adequate to support extrapolation to psoriatic arthritis & plaque psoriasis;
- however, extrapolation to indications pertaining to Crohn's disease and ulcerative colitis could not be recommended
- due to differences between Remsima and RMP, that could have an impact on the clinical safety and efficacy."

Source: Remsima, Summary Basis of Decision, Health Canada, April 2014

Current paradigm & expectations for clinical studies

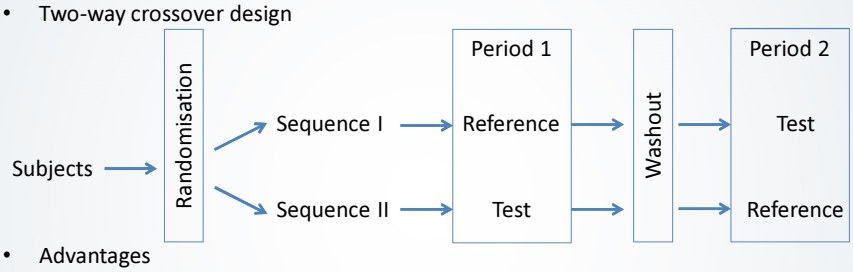
Current expectations on clinical program

- 1 phase 1 comparative PK, where possible in healthy subjects
- 1 phase 3 comparative efficacy + safety in one indication
- Post approval studies



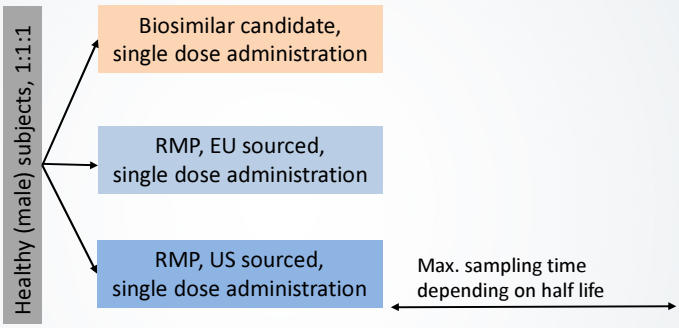
Phase 1 considerations: cross-over design

- Two-way crossover design



- Advantages
  - Powerful design (within-subject treatment comparison), smaller sample size
  - Gold standard classical bioequivalence protocol
- Disadvantages
  - Not optimal for unstable subjects (unequal period effects)
  - Not suitable for drugs with long half-life (washout)
    → mAbs typically have a long half-life

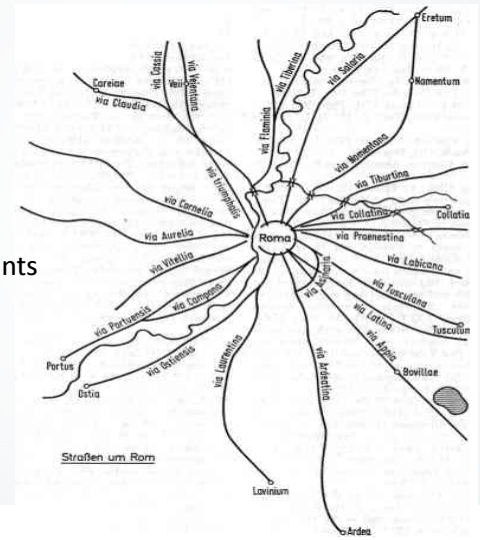
Phase 1 considerations: parallel design



- Appropriate for mAbs with long half life
- Primary endpoints:
  AUCinf + Cmax as co-primary endpoint in case of extravascular (i.e. subcutaneous) administration
- Equivalence range: 80 to 125%

Phase 3 design: several potential paths to Rome …

for selecting
indications & endpoints



A path that needs very careful consideration

the use of non-licensed conditions

Comparability should be demonstrated in scientifically appropriately sensitive clinical models and study conditions (whether licensed or not), and the applicant should justify that the model is relevant as regards efficacy and safety, and sensitive to demonstrate comparability in the indication(s) applied for.

Source: Guideline on similar biological medicinal products containing monoclonal antibodies - nonclinical and clinical issues, May 2012

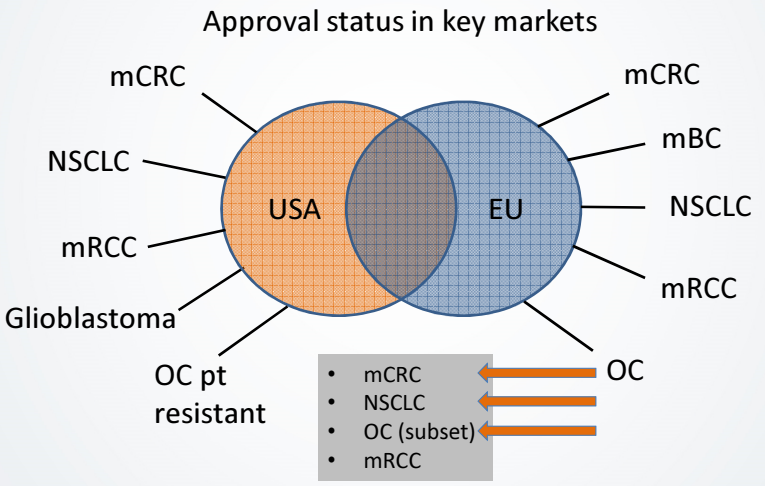
Essential considerations for phase 3 design

Study population
- sensitive to detect potential differences
- sufficiently homogeneous
- e.g. different lines of prior therapy may lead to differences that are difficult to interpret
- representative of approved therapeutic indication(s)

Endpoints
- sensitive to detect potential differences
- may deviate from typical approval endpoints
- Oncology: ORR preferred (PFS/DFS or OS are influenced by multiple factors)
- early signal for similarity

For assumptions: sufficient and reliable information needs to be available

The example Avastin (bevacizumab)



mCRC as potential development option

Avastin pivotal phase III study (AVF 2107g)

Maintaining 50% of treatment effect as approximation

ORR	Treatment effect	50% treatment effect	Approximation equivalence margin
CT backbone* + Placebo 34,8%	10%	5%	+/- 5%
CT backbone + Avastin 44,8%			

* IFL: irinotecan, fluorouracil, and leucovorin

Estimated sample size for phase III equivalence of efficacy: > 1300
Not feasible without further considerations

Source: Hurwitz et al, NEJM, June 3, 2004; Scientific Assessment Report Avastin

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Pt resistant OC as potential development option

Avastin pivotal phase III study (AUREALIA)

Maintaining 50% of treatment effect as approximation

ORR	Treatment effect	50% treatment effect	Approximation equivalence margin
CT backbone* + Placebo 13%	15%	7.5%	+/- 7.5%
CT backbone + Avastin 28%			

* paclitaxel, topotecan or pegylated liposomal doxorubicin

Cave: open label, heterogeneity of population and different chemotherapy regimen in combination with sample size

Source: Genentech press release Aurelia results and FDA approval, 14 November 2014

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NSCLC as potential development option

Avastin pivotal phase III study

Maintaining 50% of treatment effect as approximation

ORR	Treatment effect	50% treatment effect	Approximation equivalence margin
CT backbone* + Placebo 15%	20%	10%	+/- 10%
CT backbone + Avastin 35%			

* paclitaxel, carboplatin

Estimated sample size for phase III equivalence of efficacy: < 850

Source: Sandler et al, NEJM, December 14, 2006

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Ph 3 studies with biosimilar candidates to Avastin

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Efficacy and Safety Study of ABP 215 Compared With Bevacizumab in Subjects With Advanced Non-Small Cell Lung Cancer

Sponsor: Amgen

Phase III Trial BI 695502 Plus Chemotherapy vs. Avastin® Plus Chemotherapy in Patients With Lung Cancer

Sponsor: Boehringer Ingelheim

A Comparative Study Of PF-06439535 Plus Paclitaxel-Carboplatin And Bevacizumab Plus Paclitaxel-Carboplatin Patients With Advanced Non-Squamous NSCLC

Sponsor: Pfizer

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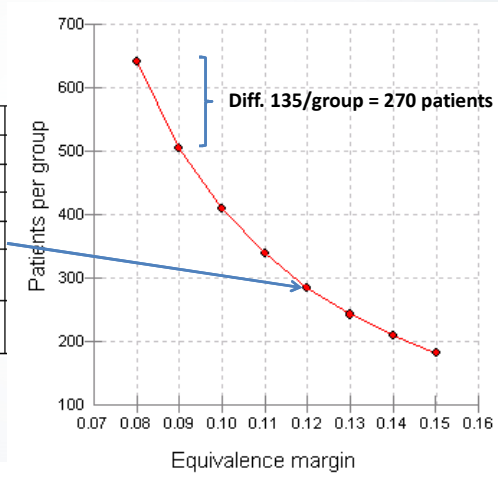
Correlation equivalence margin – sample size

Example

Scenario	A1
Sign.level α, two-sided	0.05
Power	80%
Expected ORR in both arms	60%
Equivalence limit	12%
Number of patients per group without drop-outs	284
Total Number of patients without drop-outs	**568**



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Key success factors and challenges

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Success factors - our experience

- Importance of the concept "biosimilarity by design" from the very early start!
  - Thorough understanding of the RMP*
  - Define the QTPP** and CQA***
  - Adjustment and fine tuning of process
- Proper understanding the impact of differences
- Knowing when to go back to the process to make the biosimilar candidate "highly similar"
- Proper understanding of structure-functional-clinical relationship

*RMP: Reference Medicinal Product; **QTPP: Quality Target Product Profile, ***CQA: Critical Quality Attributes

Some challenges - our experience

- Unsufficient understanding of what a biosimilar is
- The concept "biosimilarity post-hoc" has a high chance for failure
- Insufficient understanding of the impact of differences or a combination of differences, or ignoring them
- Leaving differences to be answered by clinical studies
- Being too fast, e.g. rushing into clinical studies with insufficient similar material
- Underestimation of: formulation development, development DP, devices
- RMP sourcing
- Standard approach in setting equivalence margins
- Operational issues in bioequivalence studies
- …

Future trends

Upcoming trends on the horizon

- Stronger focus on CMC similarity “similarity by design“
- Less (useless) animal studies?
- Simplified (EU) / targeted (US) development approaches
- Use of RMP/RP sourced from other regions (with similar standards) to simplify global biosimilar developments
- Use of unapproved indications for demonstrating clinical similarity?

Less useless animal studies in the EU

Reading highly recommended: mAbs 6:5, 1155-1162, Sep/Oct 14

Biosimilars entering the clinic without animal studies

A paradigm shift in the European Union

Leon AGJM van Aerts[1,2,3,*], Karen De Smet[4,5,6], Gabriele Reichmann[3,5,7], Jan Willem van der Laan[1,8], and Christian K Schneider[9,10]

[1]Medicines Evaluation Board (CBG-MEB); Utrecht, Netherlands; [2]Member of the Safety Working Party (SWP); EMA; London, UK; [3]Expert of the Working Party on Similar Biological Medicinal Products (BMWP) of the Committee for Medicinal Products for Human Use (CHMP); EMA; London, UK; [4]Federal Agency for Medicines and Health Products (FAMHP); Brussels, Belgium; [5]Expert of the SWP of the CHMP; EMA; London, UK; [6]Member of the BMWP; EMA; London, UK; [7]Paul Ehrlich Institute (PEI); Langen, Germany; [8]Chair of the SWP; EMA; London, UK; [9]Danish Health and Medicines Authority (DHMA); Copenhagen, Denmark, and Twincore Centre for Experimental and Clinical Infection Research; Hanover, Germany; [10]Chair of the BMWP; EMA; London, UK

Cave US: in practice currently different expectations

EU forerunner for simplified approaches

Overarching biosimilar guidance, CHMP/437/04 Rev 1

use early!

Adoption by CHMP	23 October 2014
Date for coming into effect	30 April 2015*

* After adoption by CHMP applicants may apply some or all provisions of this guideline in advance of this date.

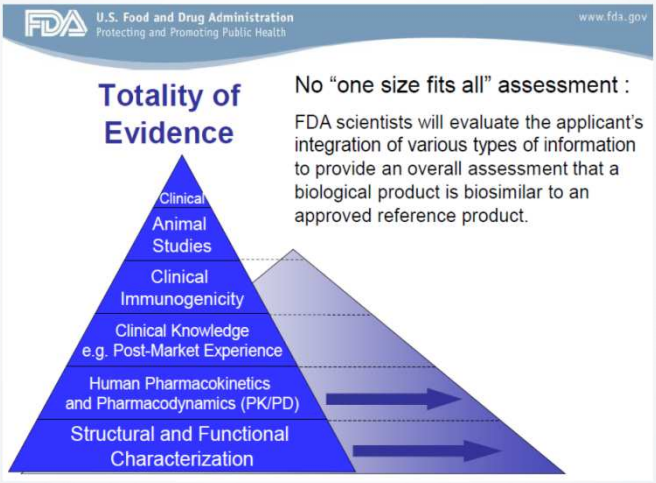
In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In It is recommended to discuss such simplified approaches with Regulatory Authorities.

simplify your program

When efficacy and safety can clearly be deduced

- Physicochemical characteristics and biological activity, and
- PK and/or PD profile of the biosimilar and the RMP

The FDA's view on the future paradigm



S. Kozlowski @ EUCRAF Annual Meeting 2015

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"Different label, similar concept"

Targeted programs, the future for biosimilars

FDA GfI: Scientific considerations biosimilarity, April 2015

CMC foundation

additional studies may be needed. For example, rigorous structural and functional comparisons that show minimal or no difference between the proposed product and the reference product will strengthen the scientific justification for a selective and targeted approach to animal and/or clinical testing to support a demonstration of biosimilarity. It may be useful to further quantify

RMP characteristics

more selective and targeted approach to animal and/or clinical testing. A sufficient understanding of the mechanism of action (MOA) of the drug substance and clinical relevance of any observed structural differences, clinical knowledge of the reference product and its class that indicates low overall safety risks, and the availability of a relevant PD measure(s) may provide further scientific justification for a selective and targeted approach to animal and/or clinical studies.

targeting

In cases where there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary. For example, similar dose-response curves of the proposed product and the

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FDA‘s expectations for clinical data

- FDA‘s minimum expectations for comparative assessment are:
  - PK
  - PD (if a relevant measure is available)
  - and immunogenicity
- Uncertainties after study conduct?
  - additional studies needed

As a scientific matter, FDA expects a sponsor to conduct comparative human PK and PD studies (if there is a relevant PD measure(s))[27] and a clinical immunogenicity assessment. In certain cases, the results of these studies may provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between the proposed biosimilar product and the reference product. However, if residual uncertainty about biosimilarity remains after conducting these studies, an additional comparative clinical study or studies would be needed to further evaluate whether there are clinically meaningful differences between the two products.

FDA GfI: Scientific considerations biosimilarity, April 2015

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Why is Europe the place to be?

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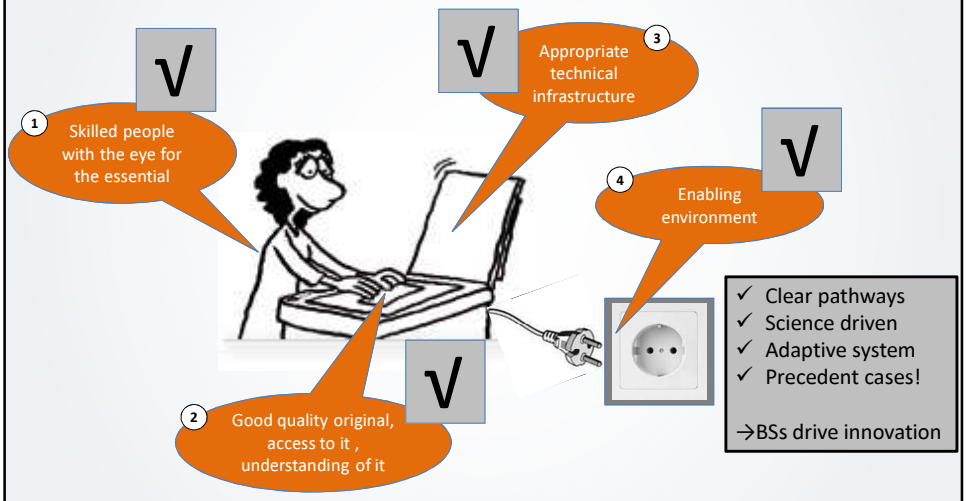
Europe is a good place to be, because



- ✓ Clear pathways
- ✓ Science driven
- ✓ Adaptive system
- ✓ Precedent cases!

→BSs drive innovation

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