Biosimilar Global Development after >10a – Are We Closer?

Perspectives & considerations

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Disclaimer

The views and opinions expressed in the following presentation are those of the individual presenter and should not be attributed to, or considered as reflecting the position of Fresenius-Kabi or its management.

Biosimilar development early 2000

2006 approved: Omnitrope- a recombinant Somatotropin

Key development activities

Nonclinical:

- 14-Day s. c. Toxicity Test in the Rat
- Rat gain weight Bioassays
- Rat tibial width Assay
- Local tolerance in Rabbits

Clinical:

3 PK studies in NHV

- EU: 12 NHV, US: 24 NHV
- Comparison powder to liquid :24 NHV

Pivotal study with sub-studies (powder and liquid): 51 girls and boys prepubertal

Source:EPAR

FDAs position 2006

Omnitrope has a simple protein and is not complex (FDA)

FDA response letter to Pfizer petition 2006

- ***The "Sufficient Similarity" Standard***

According to FDA, the Omnitrope NDA contains data sufficient to demonstrate that Omnitrope is "sufficiently similar" to Genotropin, thus justifying reliance on FDA's previous finding of safety and effectiveness for the pioneer. Critically, the Decision Letter asserts that this "sufficient similarity" standard presents a lower bar than the "sameness" standard required for an ANDA under section 505(j). Indeed, the agency anticipates that 505(b)(2) applications will represent changes to the already approved drug product.

Biosimilar Development 2018

- Monoclonal AB

Almost no in vivo non clinical
Large PK/PD studies – 200-300 NHV
Quite large pivotal studies

- Demand for being **"Highly Similar"**

Reflection of the challenges for Global Developments

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Washington Post: Jan 9, 2019 (Christopher Rowland)

- EMA has approved 40 'Biologic Copy Drugs',
- First US version was approved 2015 (Filgrastim)
- 2019 only 16 approved by FDA
- First oncology Biosimilar approved by FDA 2017: Bevacizumab

40 versus 16
– What are the reasons?

SCRIPT Regulatory Affaires 2012

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A huge step forward' towards global Biosimilar development (EGA Biosimilar conference London 2012)

- Current interpretations of Directive 2001/83/EC as amended is that reference product should be sourced (or batch released, to US terminology) in the EU and data generated with the reference product sourced out site EU can only be consider 'supportive'…
- Recent draft US guidance (Ref 5&6 Script 2012) foresees-subject to scientific bridging between reference products – the possibility to use RP sourced out site US to avoid repetition of clinical trials…

"We would try very hard to make the bridge' Rachel Sherman director of medical policy FDA said, acknowledging that EU is a number of years ahead of US"…

2018: large majority of development programs conducted with EU RMP including a bridging component – only recently Cyltezo (Adalimumab) and Herzuma (Trastuzumab) used US RP in the pivotal study

EPAR Cyltezo: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004319/WC500238609.pdf;
EPAR Herzuma

Where are we now accepting Foreign Reference Biologic?

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Table 1 Summarized requirements of major global jurisdictions for bridging data between local and foreign reference biologic products in the development of biosimilars

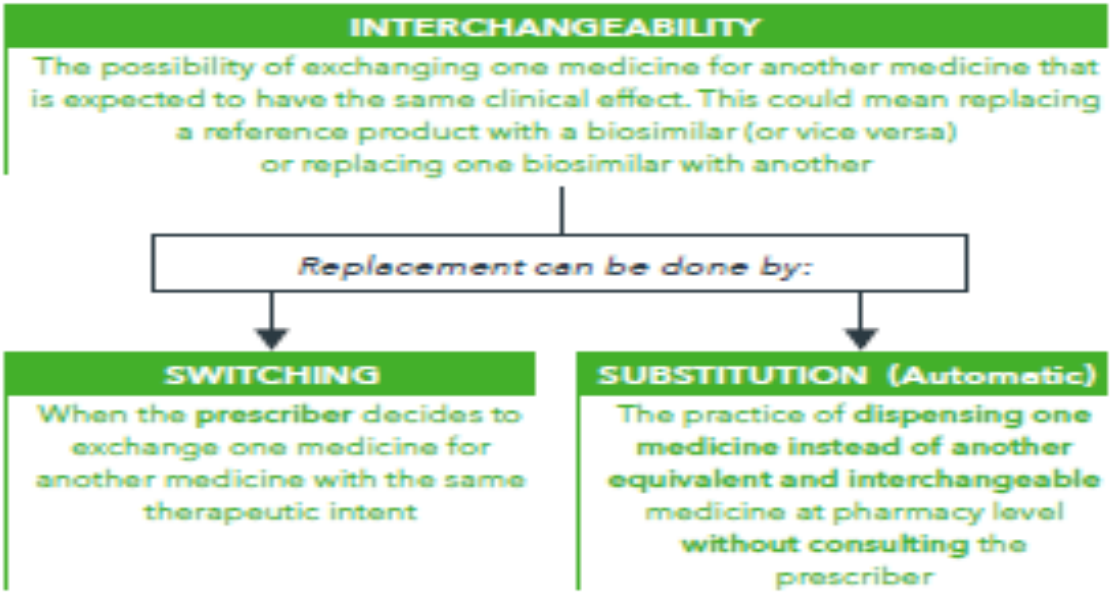
Jurisdiction	Key regulatory texts	Regulatory provisions
Australia	Regulation of biosimilar medicines (guidance) https://www.tga.gov.au/sites/default/files/evaluation-biosimilars-151217_0.pdf	For an FAC, a bridging study must be provided. This study may be abridged or omitted if evidence is provided that the drug is manufactured in a single site for global sales
Canada	Draft—revised guidance document: information and submission requirements for subsequent entry biologics (SEBs) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/biolog/submission-seb-exigences-pbu-eng.pdf	Bridging studies are often not required, but are required when two different references are used in clinical studies. Each reference should be shown to be analytically similar to the biosimilar, or the sponsor should demonstrate analytical similarity between the different references and perform appropriate clinical bridging studies (i.e. PK/PD studies)
European Union	CHMP/437/04 Rev 1 Guideline on similar biological medicinal products http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf	Bridging studies required—most commonly only analytical data
Switzerland	AW—Administrative ordinance—Authorization of similar biological medicinal products (Biosimilars) https://www.swissmedic.ch/ZL101_00_002e_VV	Bridging data required
United States	Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Guidance for Industry http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf	Bridging studies required—usually analytical and human PK data
WHO	Guidelines on evaluation of similar biotherapeutic products (2009)[a] http://www.who.int/biologicals/areas/biological_therapeutics/biotherapeutics_for_web_22april2010.pdf?ua=1	Bridging studies between RBP/FACs of different origins not explicitly required

FAC foreign approved comparators, *PK/PD* pharmacokinetics/pharmacodynamics, *RBP* reference biologic products, *WHO* World Health Organization

[a] WHO is not a regulatory authority, but its guidances are highly influential on many regulators, especially in the emerging markets

Interchangeability-Switch-Substitution

Exhibit 2: The EMA's Definitions of Interchangeability, Switch and Substitution



Source: European Medicines Agency. Biosimilars in the EU – Information guide for healthcare professionals. 2017[7].

Interchangeability – Real or Vision?

Draft Guidance US: January 2017 – revised one expected 5/19/19
Challenges:

- Multiple switches require use of US RP - no evidence that bridge to EU RMP would be accepted
- Hardly any Biosimilar developing company uses US RP for the pivotal study- COSTS!
- Unclarity what it means related to settlements and exclusivity..and..and…

Other Key Challenges for a real Global Development

- Different Equivalence margins often mandated by EMA and FDA
- Different Standard deviations: FDA 90%- EMA 95%
- POP PK- EMA-strongly recommended, FDA no real need
- Switch : FDA –mostly YES, EU not required
- Different endpoint and patient population expectations are not the exception
- FDA: unclarity in statistical approaches to Evaluate Analytical Similarity-Guidance withdrawn June 2018

It Depends…..

BE FOR HIGHLY VARIABLE DRUGS: 3 REGULATORY AUTHORITIES

EMA	FDA	HEALTH CANADA
ABEL	RSABE	ABEL
C_{max} only	C_{max} & AUC	AUC only
$\sigma_{W0} = 0.294$	0.25	0.294

PARALLEL BUT SEPARATE CONSIDERATIONS

DIFFERING REGULATORY RULES!

HARMONIZATION WOULD BE DESIRABLE

László Endrényi and László Tóthfalusi
University of Toronto, Canada and Semmelweis University, Hungary

3rd Biosimilars Forum
October 25-27, 2018
Budapest, Hungary

Have We Made Progress..

- Was this due to the lack of experience with biosimilars? Are more recent biosimilar development programes more consistent?

- Case study: biosimilars with the reference product Herceptin (trastuzumab)
  - Ontruzant (Samsung Bioepis, approved 15.11.2017)
  - Herzuma (Celltrion, approved 09.02.2018)
  - Kanjinti (Amgen, approved 16.05.2018)
  - Trazimera (Pfizer, approved 26.07.2018)

Ref. Johanna Mielke (Biosimilars Forum 2018)

PK Studies

	Ontruzant	Herzuma	Kanjinti	Trazimera
Number of studies	1	2	1	1
Total number of subjects	108	140 (70/70)	157	105
Study design of largest study	Parallel group	Parallel group	Parallel group	Parallel group
Dose	Single dose, IV, 6mg/kg	Single dose, IV, 6mg/kg	Single dose, IV, 6mg/kg	Single dose, IV, 6mg/kg
Study population	Healthy males	Healthy males	Healthy males	Healthy males
Primary PK endpoints	AUC(inf)	AUC(inf) AUC(last) Cmax	AUC(inf) Cmax	AUC(inf) AUC(last) Cmax

➔ Fairly consistent

Therapeutic equivalence

	Ontruzant	Herzuma	Kanjinti	Trazimera
Number of studies	1	1	1	2
Total number of subjects	875	549	725	933 (707*)
Power	80%	80%	?	85%*
Study population	HER2-positive early breast cancer or locally advanced breast cancer	HER2-positive early breast cancer	HER2-positive early breast cancer	HER2-positive early breast cancer*
Primary endpoint	Difference in complete response rate	Difference in complete response rate	Difference in complete response rate	Risk ratio of overall response rate*
Equivalence margin	(-13,13)	(-15,15)	(-13, 13)	(0.8, 1.25)*
Result (95% CI)	(4.13, 17.26) Not equivalent	(-12.38, 5,16) Equivalent	(0.0, 14.6) Not equivalent	(0.842, 1.049) Equivalent*

*: pivotal study

➔ Higher heterogeneity than for PK studies

➔ No standardisation of biosimilar development

Certain Elements Have Improved- Still A Long Way to Go

- Biosimilar approval in EU ahead of US
- Lack of Homogeneity between biosimilar applications
- First approvals despite failed efficacy studies
- Some more complex statistical approaches
- Acceptance of one Reference Product if not RP US ?

The Next 2 Days

…..I Trust You All

To Prove Me Wrong

Thank You
Merci
Danke

