An opportunity or a mirage: Single global development for generic products

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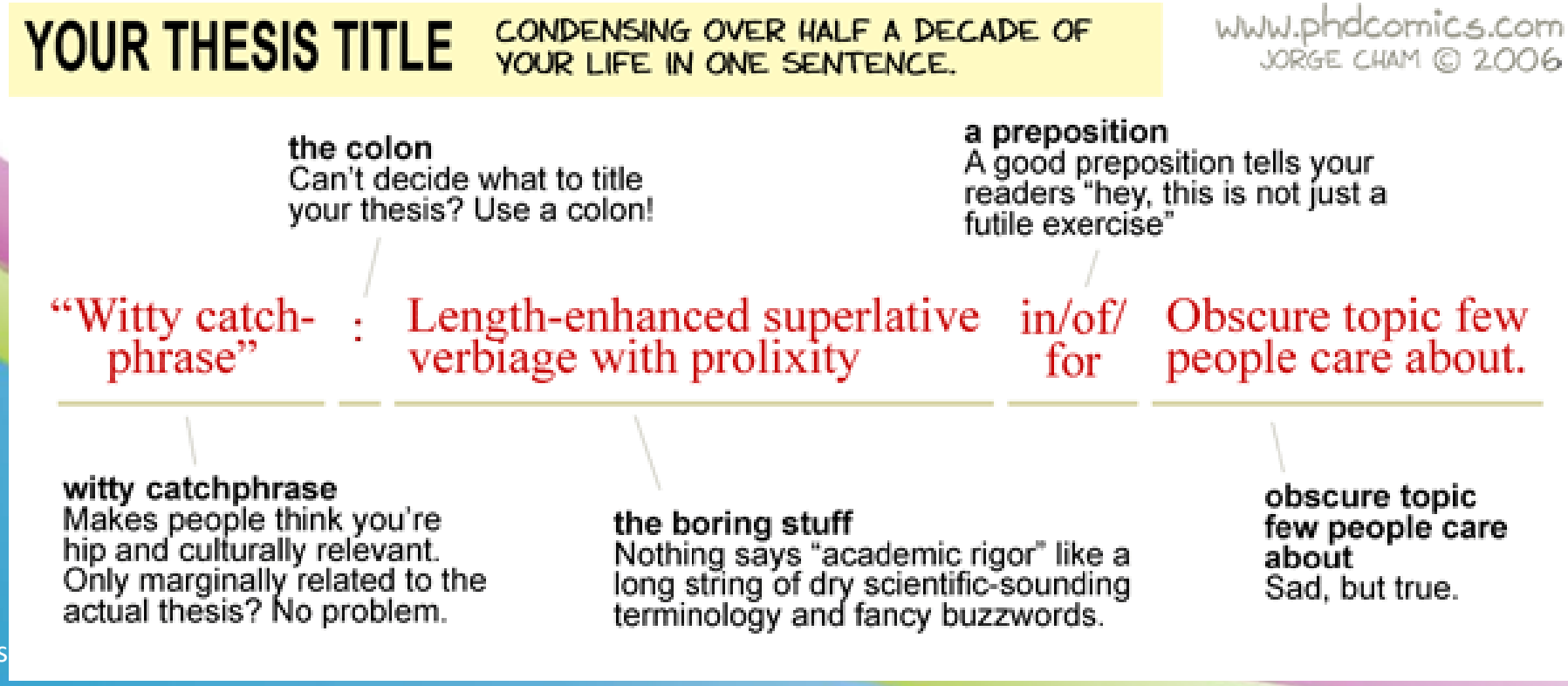
An opportunity or a mirage: Single global development for generic products



Current situation

- General convergence on the assessment of BE
- Still some differences persist – harmonization?
- Requirement to use local comparator product in many regions

Current Industry Approach

BE Studies for US against US comparator

- usually fed and fasting
- usually on the highest strength

BE Studies for EU against EU comparator

- one food condition often sufficient for Immediate Release Products
- usually additional steady state studies for Modified Release Products
- sometimes additional studies on different strengths due to stricter proportionality requirements
- higher sample sizes for highly variable drug products

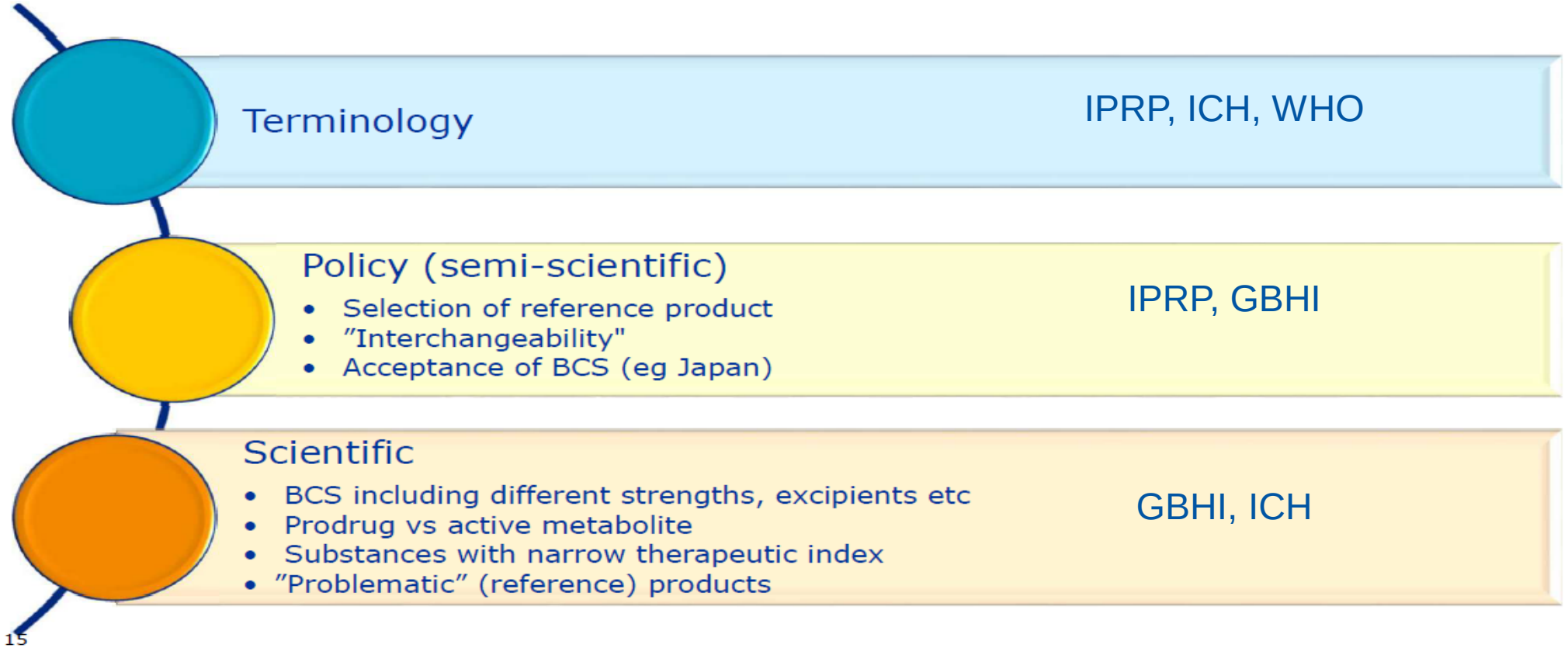
BE Studies for other regions

- sometimes due to requirement to perform studies against local comparator
- sometimes due to requirement to perform studies in the local population

G. Beuerle. Bioequivalence studies in the context of global development: Challenges and current initiatives. Medicines for Europe Annual Regulatory and Scientific Affairs Conference. 31-Jan 01-Feb 2019, London, UK.

Areas that would benefit from further work

EUROPEAN MEDICINES AGENCY

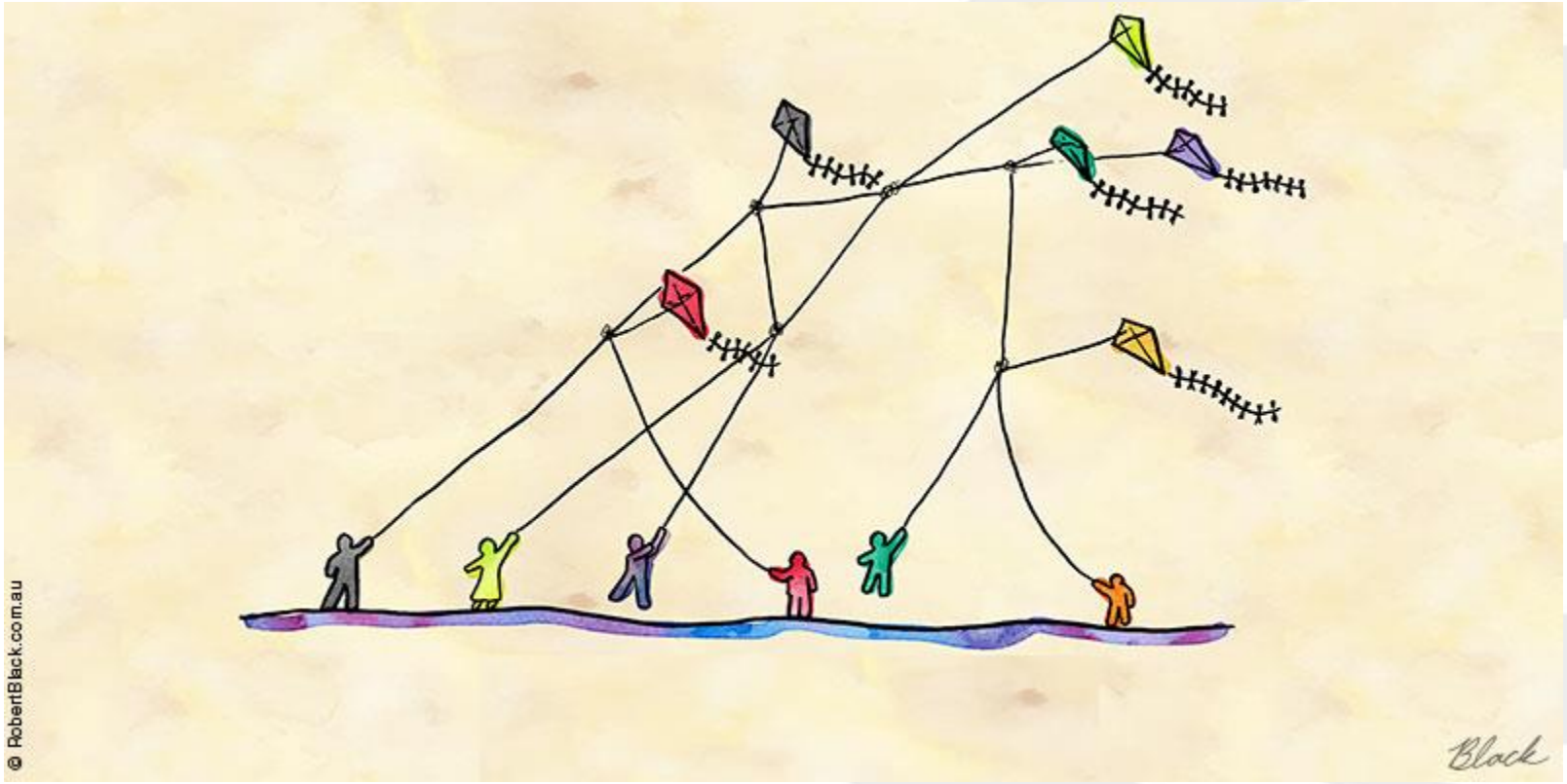


T. Salmonson.

A perspective from EMA on international harmoniz/sation…

3rd Global Bioequivalence Harmonisation Initiative, Amsterdam, April 2018.

Current situation: multiple standards (a tangled mess)



Harmonization and convergence

Current high profile international initiatives

- International Council for Harmonization (ICH)
- International Pharmaceutical Regulators Programme (IPRP)
- Global Bioequivalence Harmonization Initiative (GBHI)
- Regional regulatory bodies
- …

medicines for europe
better access. better health.

IPRP
International Pharmaceutical Regulators Programme

The International Pharmaceutical Regulators Programme (IPRP) was created in 2018 to promote convergence of regulatory approaches for pharmaceutical medicinal products for human use.

patients • quality • value • sustainability • partnership

IPRP: BE Working Group

1. Key Milestones and Deliverables

i. Deliverable 1: BCS-based biowaivers

Concerning biowaiver applications where in vitro *data based on the Biopharmaceutics Classification System (BCS) may replace* in vivo *bioequivalence study data*

ii. Deliverable 2: Additional strength biowaivers

Concerning biowaiver applications where in vivo *bioequivalence studies conducted in certain strengths of the generic product can be extended to the remaining 'additional strengths'*

iii. Deliverable 3: Biowaivers by dosage form

Concerning biowaiver applications where certain dosage forms may be accepted without in vivo *bioequivalence study data*

iv. Deliverable 4: Acceptability of foreign comparator products in bioequivalence studies

Concerning situations where an in vivo bioequivalence study involves a foreign-sourced comparator product as the reference instead of the locally-sourced comparator product

v. Deliverable 5: Alternative comparator product policies

Concerning the identification of the appropriate comparator product when the innovator product is no longer registered or marketed locally

vi. Deliverable 6: Type and number of bioequivalence studies

Concerning the policies and approaches for the selection of type and number of BE studies

ICH

- Did you know?

  ICH EWGs include representatives from regulatory agencies and industry?

- M9 & M10 guidelines are being finalized
- Informal Generic Drug Discussion Group (IGDG): technical discussion group for issues relevant to harmonisation of scientific and technical standards for generic drugs (30 Jan 2019)

  According to the workplan:
  - Continued Review and Consideration of Topic Proposal on "BE for IR Solid Oral Dosage Forms" (first priority)
  - Continued information sharing, as needed, with a goal to identify additional BE topics for harmonization or BE guideline series (second priority)
  - Review of existing ICH Guidelines (third priority)
- Informal Quality Drug Discussion Group (IQDG): technical discussion forum for issues relevant to the ICH Quality Vision to "develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science"

WORKSHOP

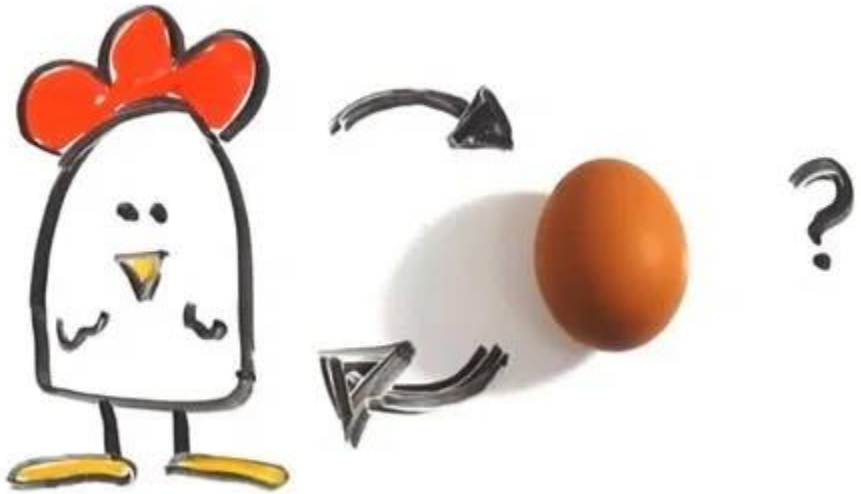
Fourth International Workshop on Global Bioequivalence Harmonization Initiative (GBHI) FDA/AAPS/EUFEPS CO-SPONSORSHIP AGREEMENT

DECEMBER 12-13, 2019

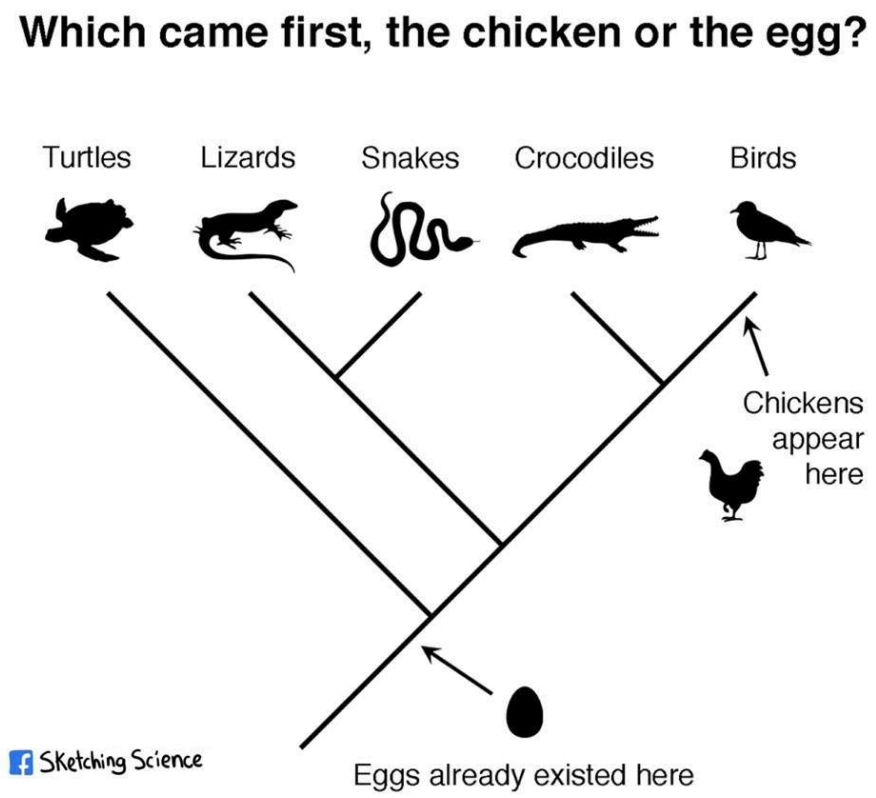
- Liposomal formulations
- Long acting injectables and implants
- Orally inhaled products
- Fasted/fed studies
- Comparator product
- …

Single global development

- Harmonization of bioequivalence?
- Foreign reference?



By the way



Source: https://www.science.org.au/curious/everything-else/which-came-first-chicken-or-egg

Problem statement

- If Reference products are approved based on the same pivotal clinical trials…

… how can they be different?

- How do we know this?

…public assessment reports

Only for generics?

- New drugs: product for comparator active control is not sourced from local markets

Comparator products

Are they different?

Context in Europe

- Rationale to use local comparator: switchability

But…

- Within the EU: acceptability of foreign comparator from another EU country is mandatory without further proof of similarity

Mutual Recognition and use of foreign reference within EU has been followed for many years

Garcia et al. Survey of the Regulatory Requirements for the Acceptance of Foreign Comparator Products by Participating Regulators and Organizations of the International Generic Drug Regulators Programme. Pharm Pharm Sci (www.cspsCanada.org) 22, 28 - 36, 2019

However, the use of non-European comparators is not accepted

Acceptance of foreign comparators

Table 1. Comparison of General Aspects of Foreign Comparator Product Acceptance (Y: Yes; N: No)

General aspects	Australia	Brazil	Canada	Colombia	European Union	Japan	Mexico	New Zealand	Singapore	South Africa	South Korea	Switzerland	Taiwan	US	WHO
Accept BE studies using foreign comparator products (under certain conditions)	Y	N	Y	N	N	N	N	Y	Y	Y	N	Y	Y	N	Y

Origin of foreign comparator products	Australia	Canada	New Zealand	Singapore	South Africa	Switzerland	Taiwan	WHO
Restricted to countries/regions with a comparable regulatory system	Y	Y	Y	N	Y	Y	N	(NA)
Has a positive list of countries/regions	N	N	N	N	Y	Y	N	(NA)
From same corporate entity as local comparator product	Y	Y	Y	Y	Y	Y	Y	(NA)

[a] Brazil, Colombia, the EU, Japan, Mexico, South Korea and US are not mentioned in this table as they do not currently accept foreign comparator products.

Garcia Arieta A, Simon C, Lima Santos GM, Calderón Lojero IO, Rodríguez Martínez Z, Rodrigues C, Park SA, Kim JM, Kuribayashi R, Okada Y, Nolting A, Pfäffli C, Hung WY, Crane C, Braddy AC, Van Oudtshoorn J, Gutierrez Triana D, Clarke M. A Survey of the Regulatory Requirements for the Acceptance of Foreign Comparator Products by Participating Regulators and Organizations of the International Generic Drug Regulators Programme. J Pharm Pharm Sci. 2019;22(1):28-36.

How to select which countries could be accepted?

- Stringent Regulatory Authority → "WHO-Listed Authority" (WLA)
- Currently identified "SRAs" will be regarded as WHO-Listed
- Designation of additional authorities be based on WHO Global Benchmarking Tool (GBT) + completion of 'confidence-building process'
- Procedure for listing be developed through usual public consultation process

Ward M. WHO-listed Authorities (WLA): promoting timely access and reliance. Copenhagen, Denmark 24 – 27 September 2018

Interesting example

- Paliperidone long acting injectable
- Same innovator company
- (looks like different strength but it is the same strength – one is referring to the salt the other to the free drug)
- Batch number appears to be the same in the US and EU market

Use of foreign comparators

Eur J Drug Metab Pharmacokinet
DOI 10.1007/s13318-017-0409-y

ORIGINAL RESEARCH ARTICLE

Evaluating the Feasibility of Use of a Foreign Reference Product for Generic Drug Applications: A Retrospective Pilot Study

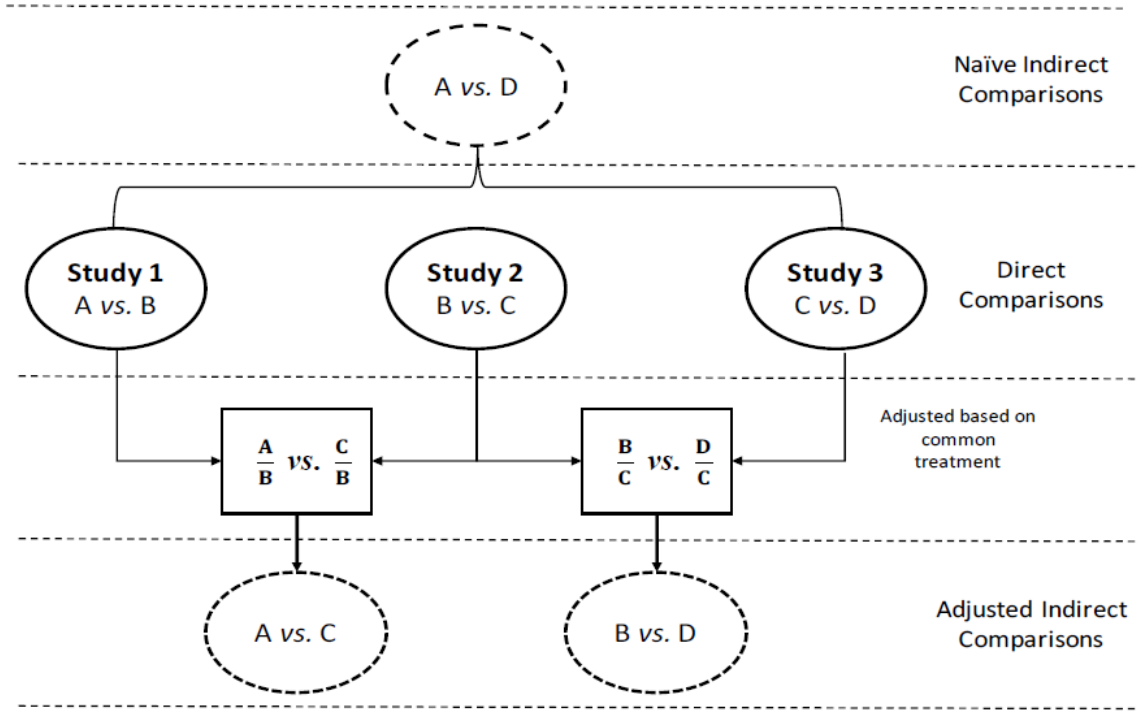
Yi-lin Wang[1] · Li-feng Hsu[1]

- Analysis of drug applications submitted in Taiwan with more than one comparator product (retrospective): 10 drugs
- Indirect comparisons of comparator products
- The results suggest that using a foreign comparator could be a valid alternative option for generic drug applications
- Duplicated bioequivalence studies comparing respective domestic reference products may not always be required

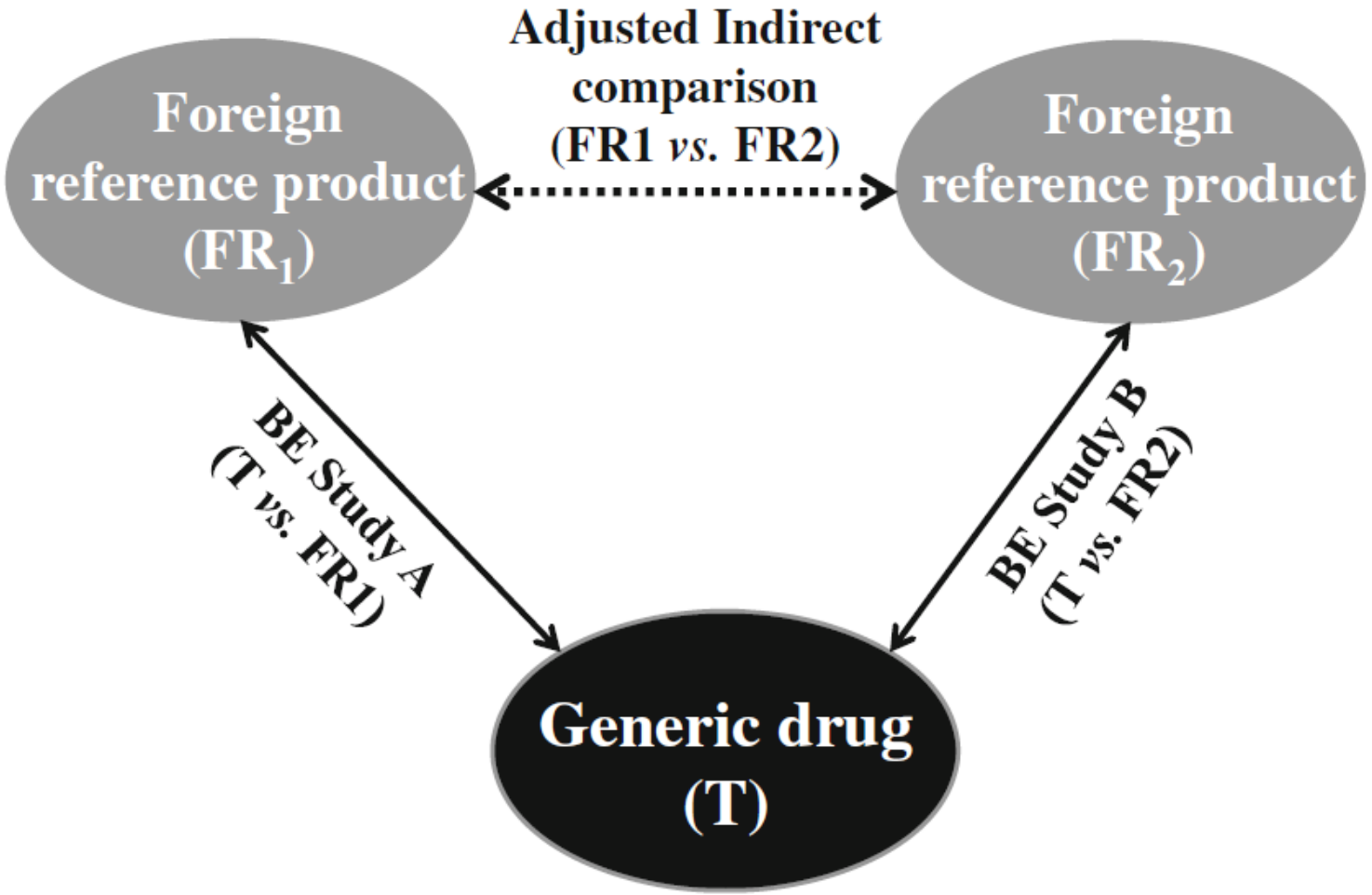
Wang YL, Hsu LF. Evaluating the Feasibility of Use of a Foreign Reference Product for Generic Drug Applications: A Retrospective Pilot Study. Eur J Drug Metab Pharmacokinet. 2017 Dec;42(6):935-942

Indirect comparisons

- Evaluation of different health interventions using information from independent studies



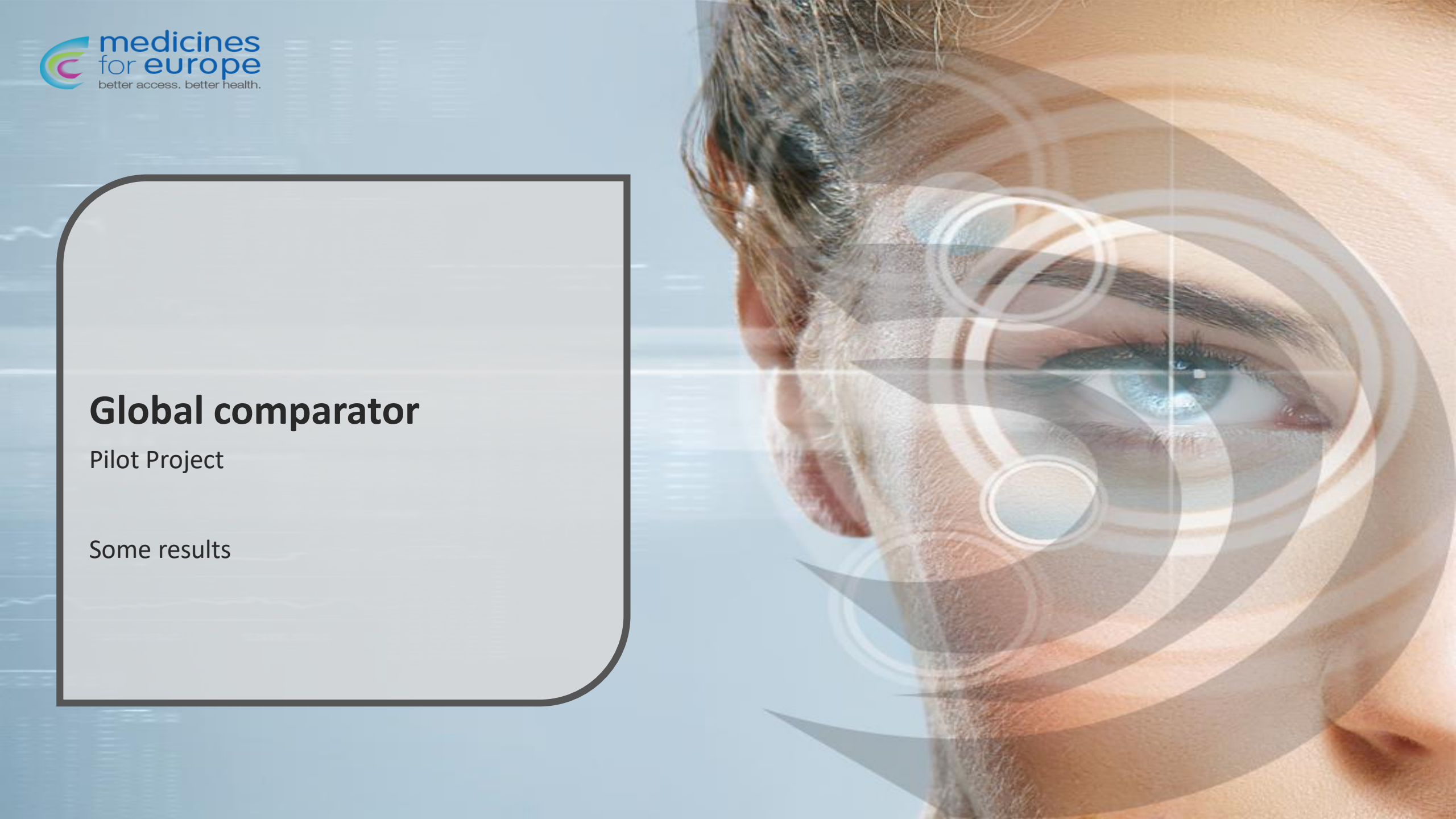
Gwaza L. Adjusted indirect treatment comparisons of bioequivalence studies. Thesis Utrecht University – with ref. – with summary in Dutch, 2016.



Wang YL, Hsu LF. Evaluating the Feasibility of Use of a Foreign Reference Product for Generic Drug Applications: A Retrospective Pilot Study. Eur J Drug Metab Pharmacokinet. 2017 Dec;42(6):935-942

Examples from literature

- Gwaza L, Gordon J, Welink J, Potthast H, Hansson H, Stahl M, García-Arieta A. Statistical approaches to indirectly compare bioequivalence between generics: a comparison of methodologies employing artemether/lumefantrine 20/120 mg tablets as prequalified by WHO. *EurJ ClinPharmacol*. 2012; 68(12):1611-8.
- Herranz M, Morales-Alcelay S, Corredera-Hernández MT, de la Torre-Alvarado JM, Blázquez-Pérez A, Suárez-Gea ML, Alvarez C, García-ArietaA. Bioequivalence between generic tacrolimus products marketed in Spain by adjusted indirect comparison. *EurJ ClinPharmacol*. 2013; 69(5):1157-62.
- Gwaza L, Gordon J, Welink J, Potthast H, Leufkens H, Stahl M, García-Arieta A. Adjusted indirect treatment comparison of the bioavailability of WHO-prequalified first-line generic antituberculosismedicines. *ClinPharmacolTher*. 2014; 96(5):580-8.
- Gwaza L, Gordon J, Potthast H, Welink J, Leufkens H, Stahl M, García-Arieta A. Influence of point estimates and study power of bioequivalence studies on establishing bioequivalence between generics by adjusted indirect comparisons. *EurJ ClinPharmacol*. 2015; 71(9):1083-9
- Yu Y, Teerenstra S, Neef C, Burger D, Maliepaard M. Investigation into the interchangeability of generic formulations using immunosuppressants and a broad selection of medicines. *EurJ ClinPharmacol*. 2015; 71(8):979-90.
- Gwaza L, Gordon J, WelinkJ, Potthast H, Leufkens H, Stahl M, García-Arieta A. Interchangeability between first-line generic antiretroviral products prequalified by WHO using adjusted indirect comparisons. *AntivirTher*. 2017; 22(2):135-144
- Pejčić Z, Vučićević K, García-Arieta A, Miljković B. Adjusted indirect comparisons to assess bioequivalence between generic clopidogrel products in Serbia. Br J Clin Pharmacol. 2019 Sep;85(9):2059-2065.



Global comparator

Pilot Project

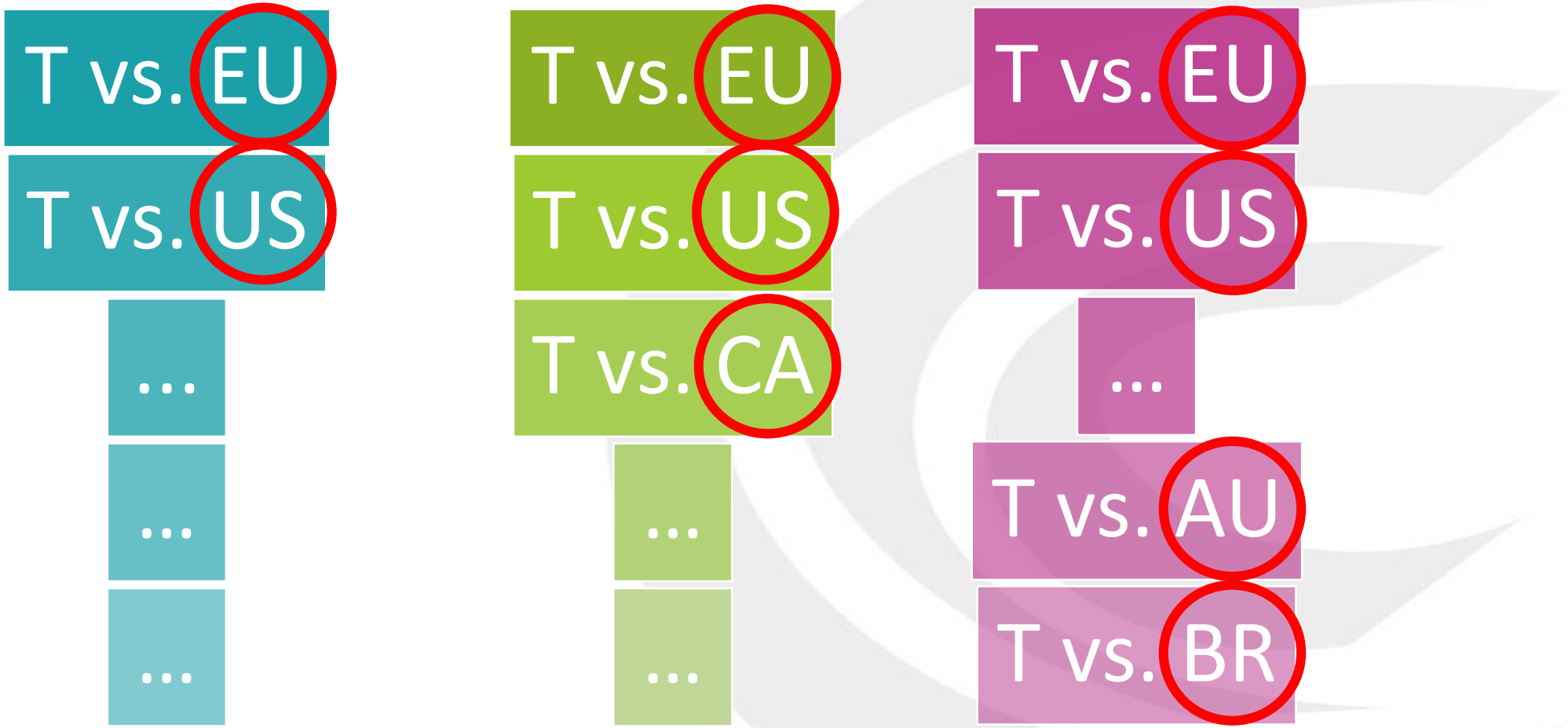
Some results

What is the GCPP?

- Subgroup of Medicines for Europe members who have previously developed generics or conducted studies for multiple jurisdictions using local comparator products
- 6 members: 4 generic companies + 2 CROs
- Same general design for more than one territory
- Same test formulation (not always same batch)
- Major focus on products submitted in Europe via Centralised Procedure

INDIRECT COMPARISON OF COMPARATOR PRODUCTS FROM DIFFERENT JURISDICTIONS

Datasets from Members



Interpretation

As with the traditional BE methodology:

- Inability to show bioequivalence by means of indirect comparisons does not mean that the products are not equivalent - simply there may not be sufficient statistical power.
- When equivalence is shown, we can consider not only that the products are bioequivalent but also quite similar

Gwaza L. Adjusted indirect treatment comparisons of bioequivalence studies. Thesis Utrecht University – with ref. – with summary in Dutch, 2016.

Acceptance limits for indirect comparisons

70-143%

“In contrast with the ±20% acceptance range used for adjusted indirect comparisons, a ±30% acceptance range is proposed for adjusted indirect comparisons due to the limited precision of indirect comparisons”

Gwaza L. Adjusted indirect treatment comparisons of bioequivalence studies. Thesis Utrecht University – with ref. – with summary in Dutch, 2016.

Entecavir

- Comparator product

Region	EMA	FDA	Australia
Name of the reference product (with strength and pharmaceutical form)	Baraclude 0.5 mg film-coated tablets Baraclude 1 mg film-coated tablets	Baraclude 0.5 mg film-coated tablets Baraclude 1 mg film-coated tablets	BARACLUDE® entecavir BARACLUDE film coated tablets contain 0.5 mg and 1.0 mg of entecavir
Innovator company/MAH	MAH BRISTOL-MYERS SQUIBB PHARMA EEIG Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH United Kingdom	Bristol-Myers Squibb Company Princeton, NJ 08543 USA	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court, Mulgrave, Victoria 3170, Australia.

Composition

Region	EMA	FDA	Australia
Qualitative composition	**0.5 mg film-coated tablet** Crospovidone Lactose monohydrate Magnesium stearate Cellulose, Microcrystalline Povidone Tablet coating: Titanium dioxide Hypromellose Macrogol 400 (ie PEG 400) Polysorbate 80 (E433) **1.0 mg film-coated tablet** Crospovidone Lactose monohydrate Magnesium stearate Cellulose, Microcrystalline Povidone Tablet coating: Titanium dioxide Hypromellose Macrogol 400 Iron oxide red	**0.5 mg film-coated tablet** lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, polysorbate 80 **1.0 mg film-coated tablet** lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, magnesium stearate The tablet coating contains titanium dioxide, hypromellose, polyethylene glycol 400, iron oxide red (1 mg tablet only).	**0.5 mg film-coated tablet** Lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate, titanium dioxide, hypromellose, Macrogol 400, polysorbate 80. **1.0 mg film-coated tablet** Lactose monohydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate, titanium dioxide, hypromellose, Macrogol 400 and iron oxide red CI177491.

Clinical studies on the basis of registration

Pivotal studies cited by EMA, FDA and TGA:

- Nucleoside-naïve HBeAg positive subjects (study A1463-022)
- Nucleoside-naïve HBeAg negative subjects (study A1463-027)
- LVD-refractory HBeAg positive subjects (studies A1463-026 and A1463-014).

Baraclude

- Same tradename
- Same Marketing Authorisation Holder
- Same qualitative composition
- Same pivotal clinical studies in approval package

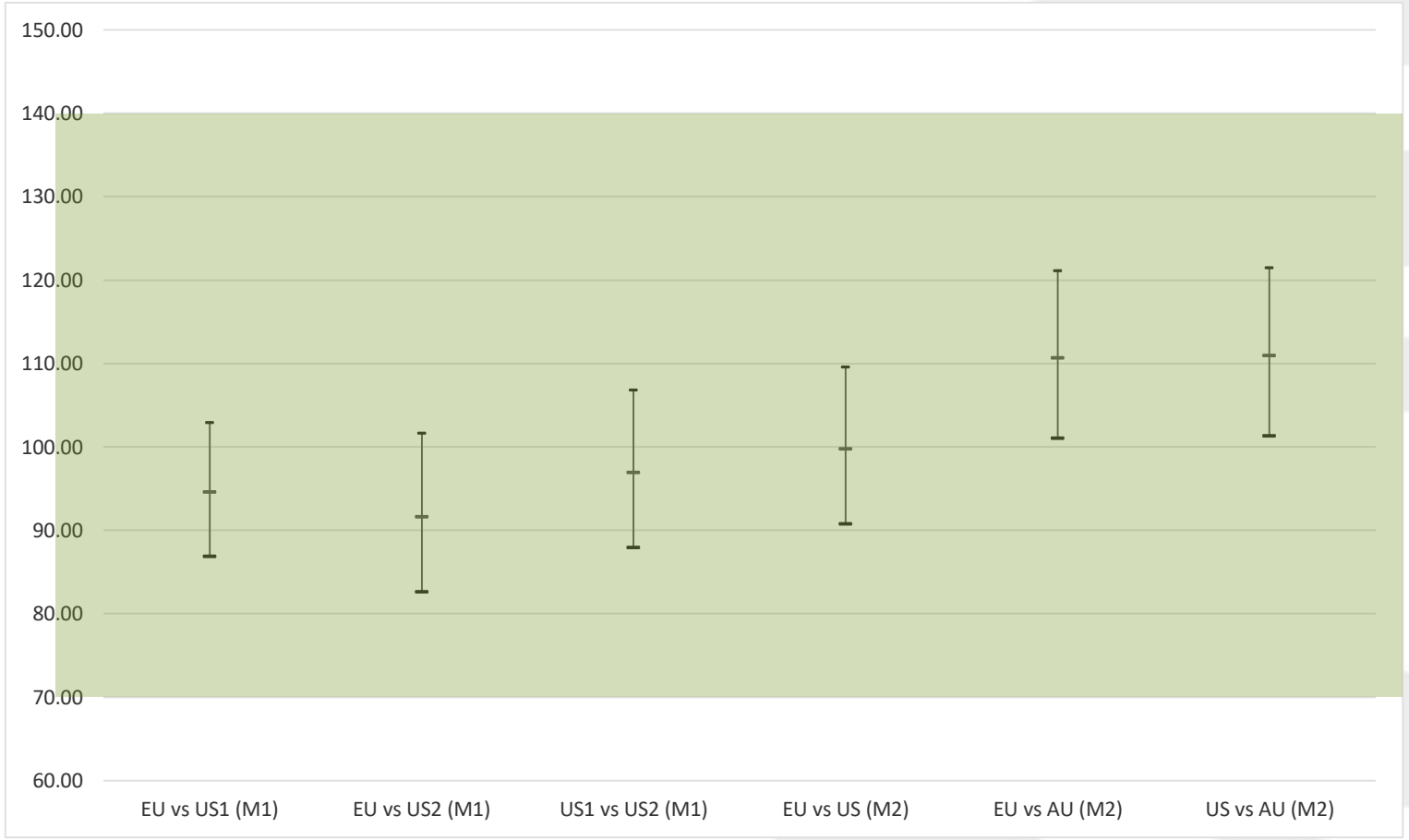
Assumption

- If products are approved based on the same clinical pivotal package, then they must be clinically equivalent
- Entecavir reference: likely the same product

Indirect comparison of entecavir references

				PE	LL	UL
	M1	Cmax	EU vs US1 (M1)	94.52	86.81	102.92
	M1	Cmax	EU vs US2 (M1)	91.59	82.56	101.61
	M1	Cmax	US1 vs US2 (M1)	96.90	87.91	106.81
	M2	Cmax	EU vs US (M2)	99.71	90.75	109.55
	M2	Cmax	EU vs AU (M2)	110.59	101.00	121.09
	M2	Cmax	US vs AU (M2)	110.91	101.28	121.47
	M1	AUCt	EU vs US1 (M1)	100.28	97.12	103.54
	M1	AUCt	EU vs US2 (M1)	99.37	96.38	102.45
	M1	AUCt	US1 vs US2 (M1)	99.09	96.37	101.90
	M2	AUCt	EU vs US (M2)	97.21	89.08	106.08
	M2	AUCt	EU vs AU (M2)	112.18	104.52	120.40
	M2	AUCt	US vs AU (M2)	115.41	107.22	124.22

Cmax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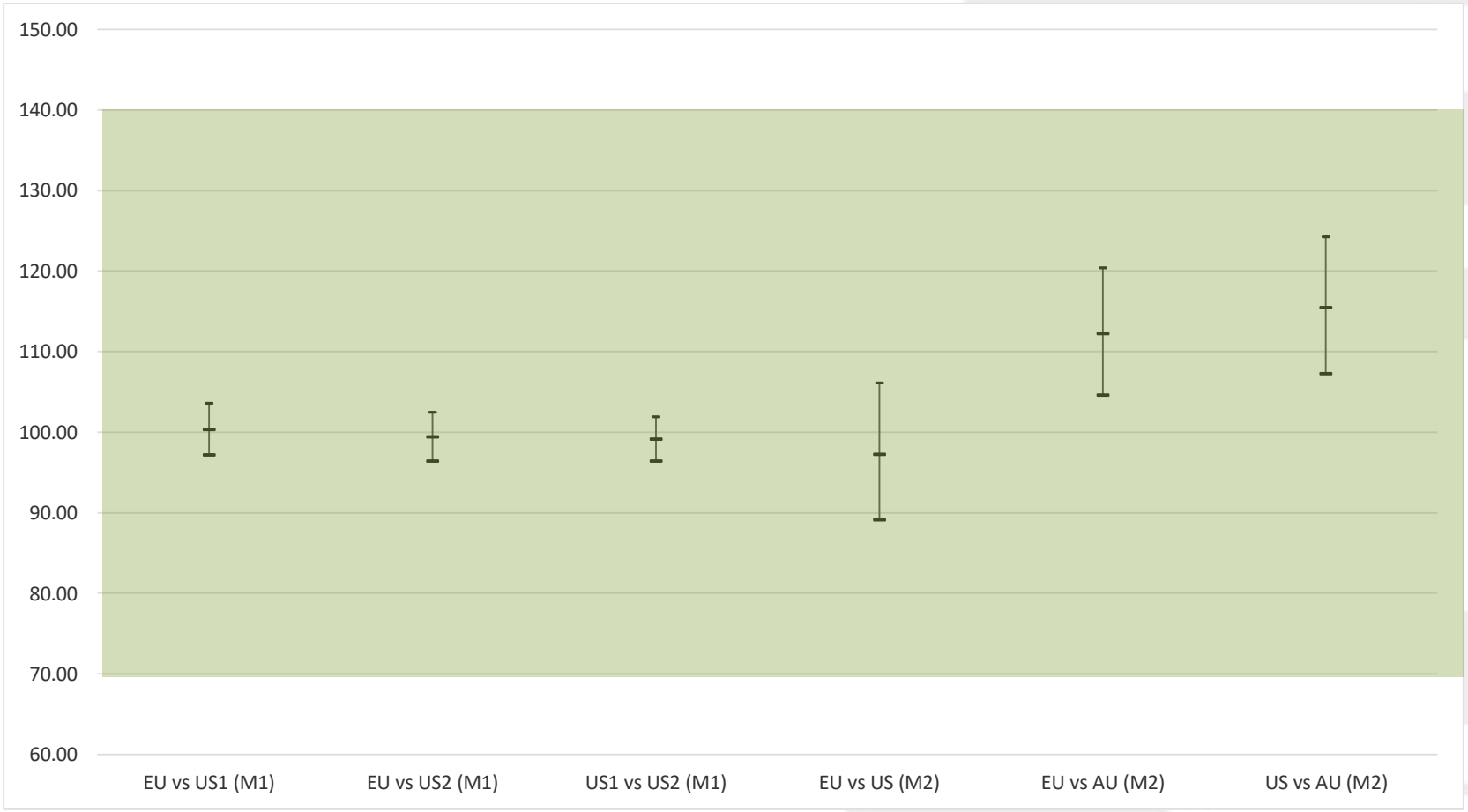
AUClast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US vs AU (M2)

Next steps GCPP

- Analysis for replicate designs
- Impact of the power of the original Bioequivalence studies
- Study with more than one reference product: obtain results for direct comparison

Next steps
Macro

- Future prospective approach: how
- Building on the experience of EU mutual recognition of reference product and other territories accepting foreign references

- More results expected to be presented at GBHI in December

Take home message

- Discussion on the harmonization of bioequivalence is at a key moment
- Several relevant initiatives at different levels on the scientific principles and policy aspects
- An ICH standard on bioequivalence would provide a unified approach on the demonstration of bioequivalence
- Ongoing projects seek to determine whether reference products could be similar in different regions: this could help identify a scientific basis to discuss a global comparator product