medicines for europe
better access. better health.

2nd BIOEQUIVALENCE WORKSHOP

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#BIOEQ23

Single global development of generic medicines

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Generic development: an evolving landscape

- More complex products
- Increasingly complex clinical development
- Niche therapeutics and orphan products
- Personalized medicine

Risk of fewer follow-on products developed and registered, and reduced surety of supply

Less competition, less patient access, less incentives to efficient development and manufacturing

Generic development: solutions

- Number of patients requiring treatments and the cost of medicines are increasing
- Timely access to affordable therapies is more important than ever!

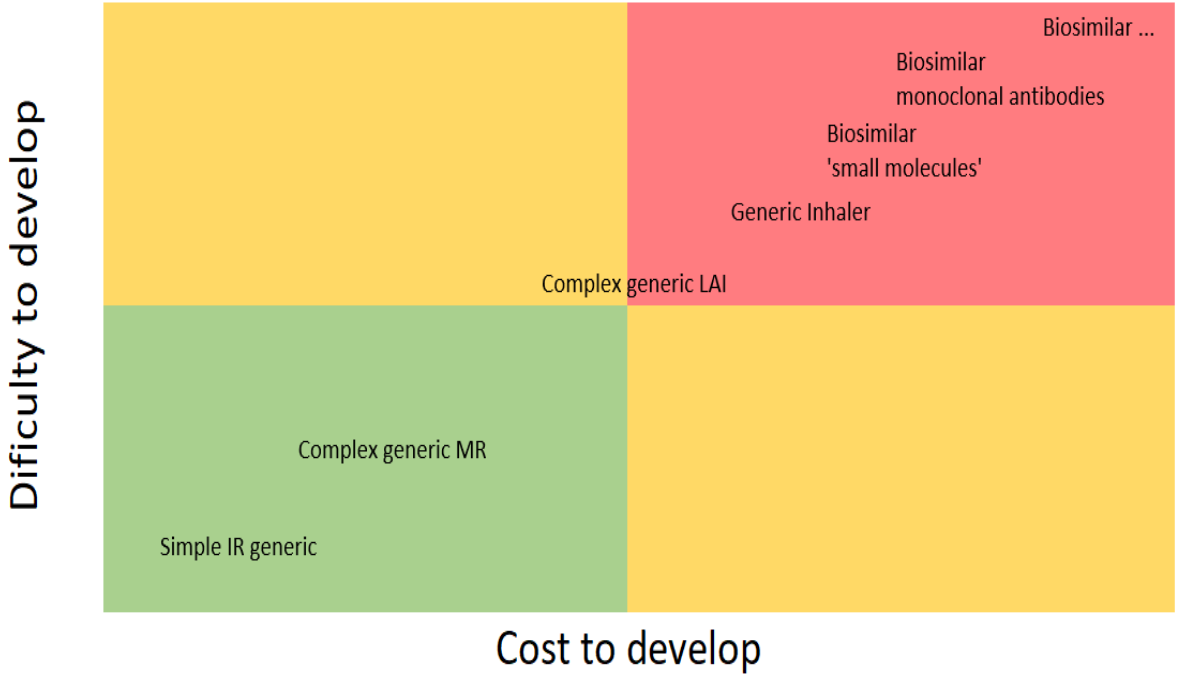
- Global development of generic medicines is a modern necessity of streamlined product development.

Single global development

- Supports consistent high quality worldwide
- Standard approach for originator development
- Now commonly acceptable for biosimilar development – though regulatory discretion is significant
- Foreign comparators already accepted for generic development by several highly regulated regions

(we will come back to this point)

Development of off patent products



IR – immediate release; LAI – long acting injectable, MR – modified release

Development of off patent products

- Not all small molecules follow on products are “easy to develop”
- Streamlining development for complex generics and biosimilars is key for **patient access**
- Failing to recognize the challenges for development of off patent products could compromise patient access to affordable medicines!

Generics are important! Bioequivalence matters

- Recognized at ICH level – Generic Discussion Group + several relevant active topics

- EMA new Methodology Working Party - new guideline development includes[1]:

Clinical Pharmacology, including guidance on pharmacokinetics, modelling and simulation, and supporting bioequivalence to support a thriving generics industry;

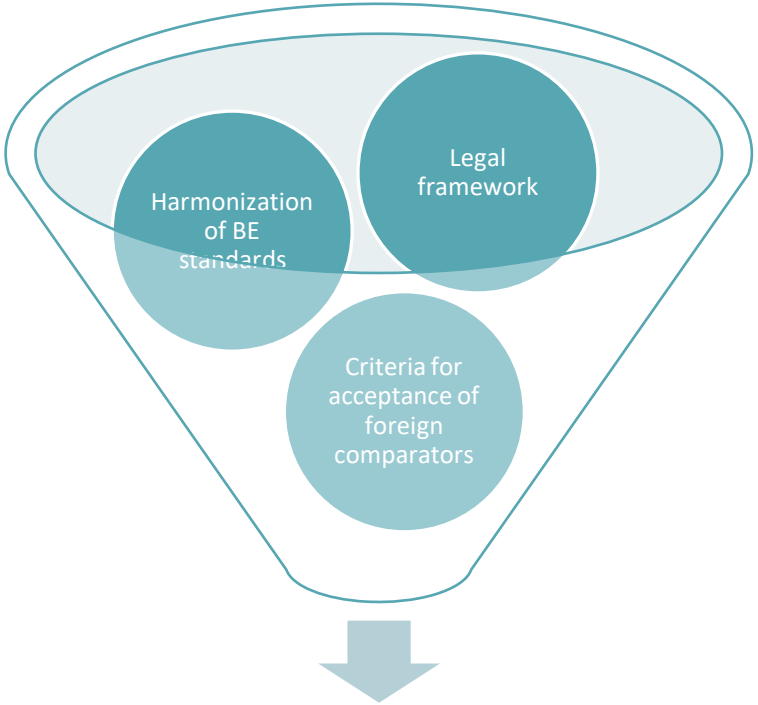
1 – EMA BIG DATA HIGHLIGHTS Issue 5, March 2023.

Several international initiatives

- ICH
- Generic drug cluster
- IPRP BE Working Group
- Bilateral initiatives

Important to identify the scope and rate limiting steps

Generic single global development
3 pillars that must advance simultaneously



Single global development of generic medicines

1. Harmonization of bioequivalence standards

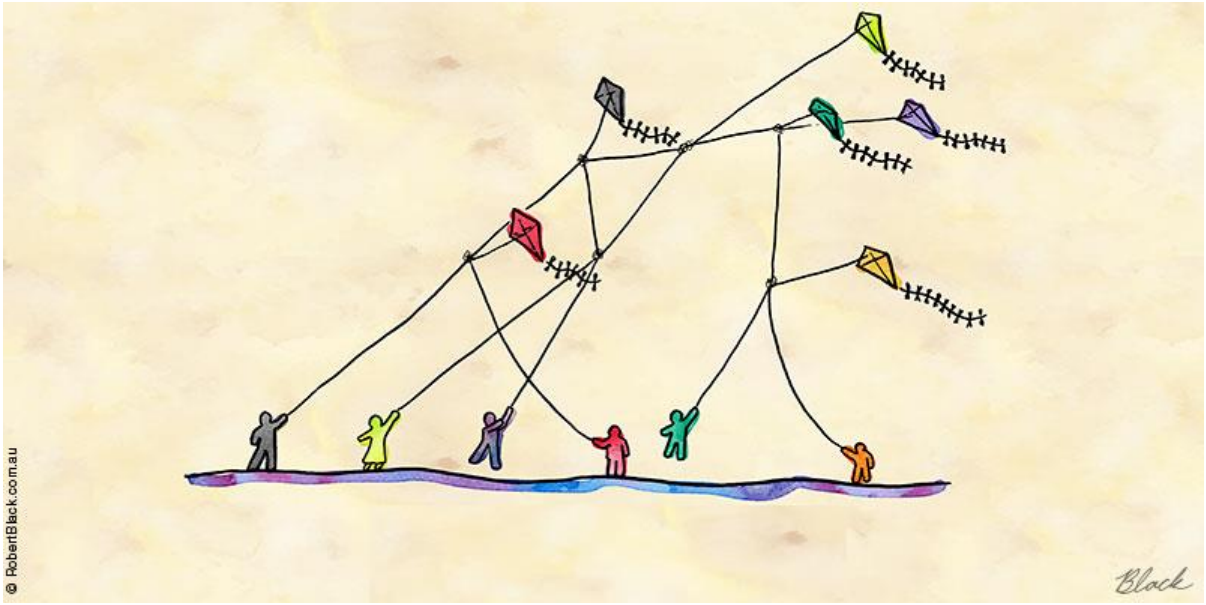
Ongoing and advancing

Draft of first international guideline (immediate release) released by ICH in December 2022

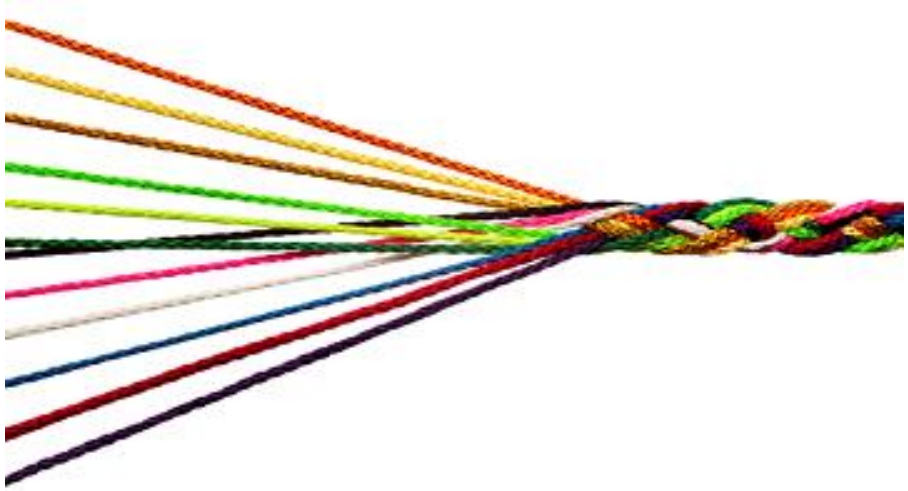
M13A consultation ongoing

Who: ICH

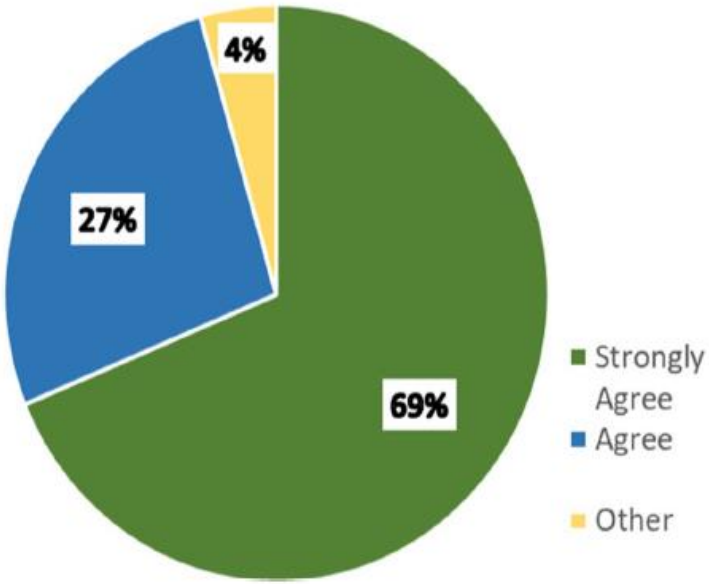
Before M13: multiple standards (a tangled mess)



After M13:
Harmonization and convergence



Harmonization of BE: does it matter?



It matters A LOT!

Recent international survey on complex generics:

96% Agree or Strongly Agree on the importance of a harmonized international approach for complex generics

Stern S, Coghlan J, Krishnan V, Raney SG, Babiskin A, Jiang W, Lionberger R, Xu X, Schwendeman A, Polli JE. Research and Education Needs for Complex Generics. Pharm Res. 2021 Dec;38(12):1991-2001. doi: 10.1007/s11095-021-03149-y. Epub 2021 Dec 24. PMID: 34950975.

2. Legal framework

It is necessary to assess legal frameworks and address any possible barriers

Predictability is important!

Opportunity in Europe to deliver on the access goals in the Pharmaceutical Strategy for Europe.

3. Which foreign comparators are acceptable?

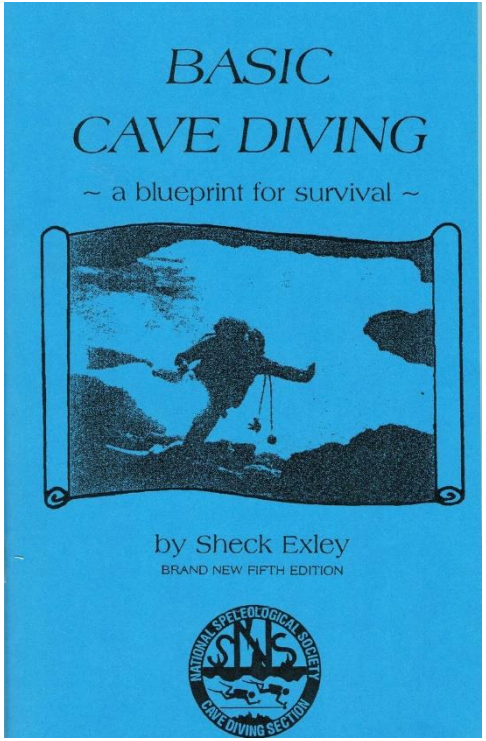
A guideline is needed!

Scientific criteria and the conditions of acceptability of foreign comparators for bioequivalence

Who:

Local competent authorities (or jointly, or together with more regions)

(could the Generic Drug Cluster discuss this?)



Learning from those with experience

This is not a new concept!

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.

UK joined this list

Garcia Arieta A, et al. J Pharm Pharm Sci. 2019;22(1):28-36.

Swiss example

Guidance document

Authorisation of human medicinal product with known active pharmaceutical substance (v4.2, 2022)

Comparability of a foreign comparator product with the Swiss reference product (pharmaceutical bridging)

Swiss example - summary

Comparison between foreign comparator vs. Swiss reference:

- List of countries on the Swissmedic website
- Comparison of several administrative characteristics
- If used in BE study: quali+quanti active substance + quali excipient composition (differences to be explained)
- Similarity assessment for *in vitro* dissolution profiles (EMA guideline) (differences in release rate need to be explained)

Let’s use the knowledge that is already available

Source: https://dev.to/quantumsheep/why-you-should-reinvent-the-wheel-4ha2

Size matters!?

Acceptance of foreign comparators appears to correlate reasonably well with the market size*

Garcia Arieta A, et al. J Pharm Pharm Sci. 2019;22(1):28-36.

Orphan medicines, niche therapeutics, personalized medicine, complex products:

Is any market large enough?

Sourcing of comparator product is a barrier to generic development in some jurisdictions!

Access to Product Samples: The CREATES Act

The law widely known as CREATES, which was enacted in December 2019 as part of the Further Consolidated Appropriations Act of 2020, makes available an important new pathway for developers of potential drug and biological products to obtain samples of brand products[1] that they need to support their applications. The full text of the new law is available here (/media/136039/download). CREATES establishes a private right of action that allows developers to sue brand companies that refuse to sell them product samples needed to support their applications. If the product developer prevails, the court will order the sale of samples, award attorneys' fees and litigation costs to the product developer, and may impose a monetary penalty on the brand company.

The product developer must take a number of specific steps (outlined in the law) before the brand company must sell them product samples under CREATES. One of these steps – if the brand product for which samples are sought is subject to a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) – is that the product developer must first obtain a Covered Product Authorization (CPA) from FDA. CREATES does not require this step for products that are not subject to REMS with ETASU.[2]

Q: How do I obtain a CPA from FDA?

Competition Bureau and Health Canada strengthen collaboration on key issues in the pharmaceutical industry

From: Competition Bureau Canada

News release

January 10, 2022 – GATINEAU, QC – Competition Bureau

- The Bureau and HPFB have collaborated on a variety of issues, such as mergers and acquisitions, deceptive and misleading claims and claims of abuse of dominance. More recently, the ability for generic manufacturers to access samples of reference products has been an area of ongoing collaboration.
- Given the guidance and warnings provided from the Bureau and HPFB on this issue, branded drug manufacturers should continue to anticipate that the Bureau will treat any explanation for a failure to supply reference products, in a timely manner, with an extremely high degree of skepticism.
- Should generic manufacturers face similar issues in the future, they are encouraged to bring any concerns to the Bureau's attention at an early stage.

03/02/2021 SEI/ANVISA - 1317510 - Voto

ANVISA
Agência Nacional de Vigilância Sanitária

VOTO Nº 08/2021/SEI/DIRE2/ANVISA

Processo nº 25351.941370/2020-00
Expediente nº 0244343/21-7

Analisa a solicitação de excepcionalidade para aquisição do produto Revlimid (lenalidomida) para realização de ensaios comparativos para registro de medicamento genérico/similar.

EMA/FDA Parallel scientific advice

Announced in 2021

Initial survey among Medicines for Europe's members indicated 89% considered this initiative Important or Very important for international convergence

However, during subsequent discussions, the following challenges were identified:

- Possibility of increased requirements
- Risk of having to repeat studies due to the necessity of using local comparators – acceptance of foreign comparators would likely increase adherence significantly
- High cost for EMA scientific advice (vs. National Scientific Advice)

Importance of single global development

- Avoids redundant (hence unethical) clinical trials
- Helps increase patient access to generic medicines (**orphan drugs or complex generics)**
- Contributes to competition, therefore increases access (resilience of supply chains)
- Leverages the benefits of harmonizing BE standards
- Helps to overcome challenges on sourcing of the comparator products, in some regions
- Enables regulatory reliance and mutual recognition agreements

Way forward

Internationally:

Advancing harmonization and dialogue

Locally or jointly:

Regions/countries to assess their legal frameworks:

- Move forward if there are no legal barriers!
- Address any potential legal barriers

Define (ideally common) criteria for acceptance of foreign comparators in guidelines

Take home messages

- Single global development is fundamental to support global access & global competitiveness of generic medicines
- M13 Guideline should be a building block for global development to avoid the unnecessary repetition of bioequivalence studies when the comparator product is similar across highly regulated regions.
- Other highly regulated regions have already established criteria for use of foreign comparators.
- The EU should do the same to deliver on its access goals in the Pharmaceutical Strategy for Europe.

- The time to act is now

Thank you for your attention!

"If you wish to make an apple pie from scratch, you must first invent the universe."

Carl Sagan, Cosmos

Acknowledgments:

Medicines for Europe's BE WG

IGBA's Single Global Development task force