Harmonis(z)ation of BE and beyond

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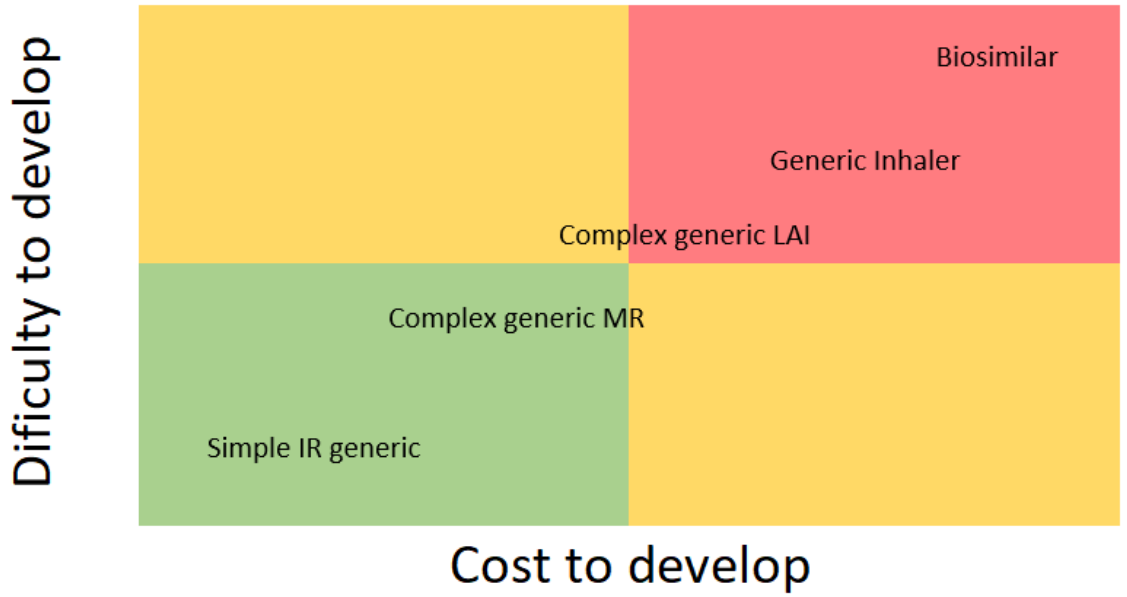
Generic development: an evolving landscape

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

Risk of fewer follow-on products

Less competition, less access

Off-patent products are not all simple to develop



- Not all small molecules follow on products are “easy to develop”
- streamlining development for complex generics is key for patient access

- Failing to recognize the challenges for development of complex generics could compromise patient access!

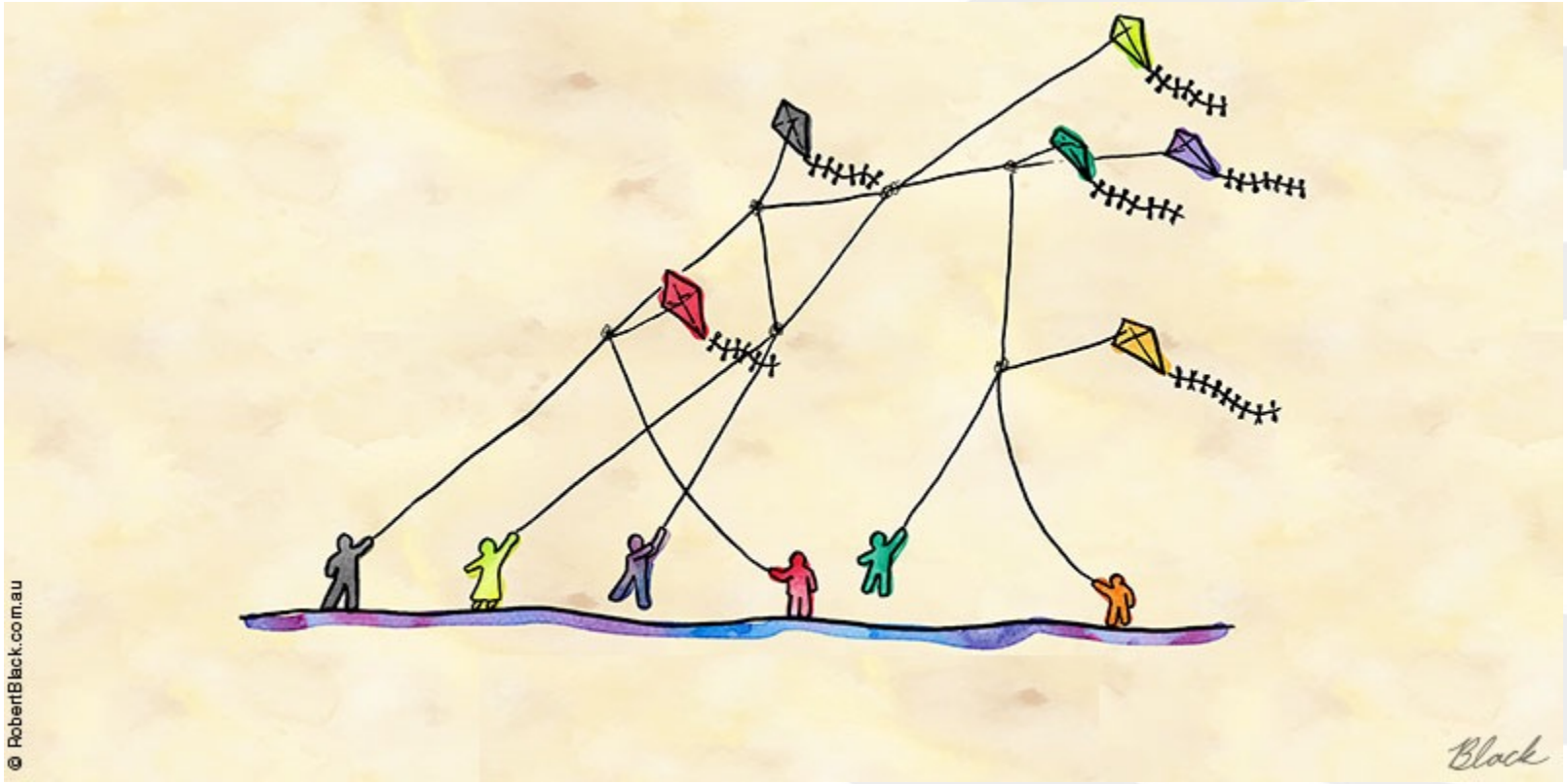
IR – immediate release; LAI – long acting injectable, MR – modified release

1. Harmonization of bioequivalence standards

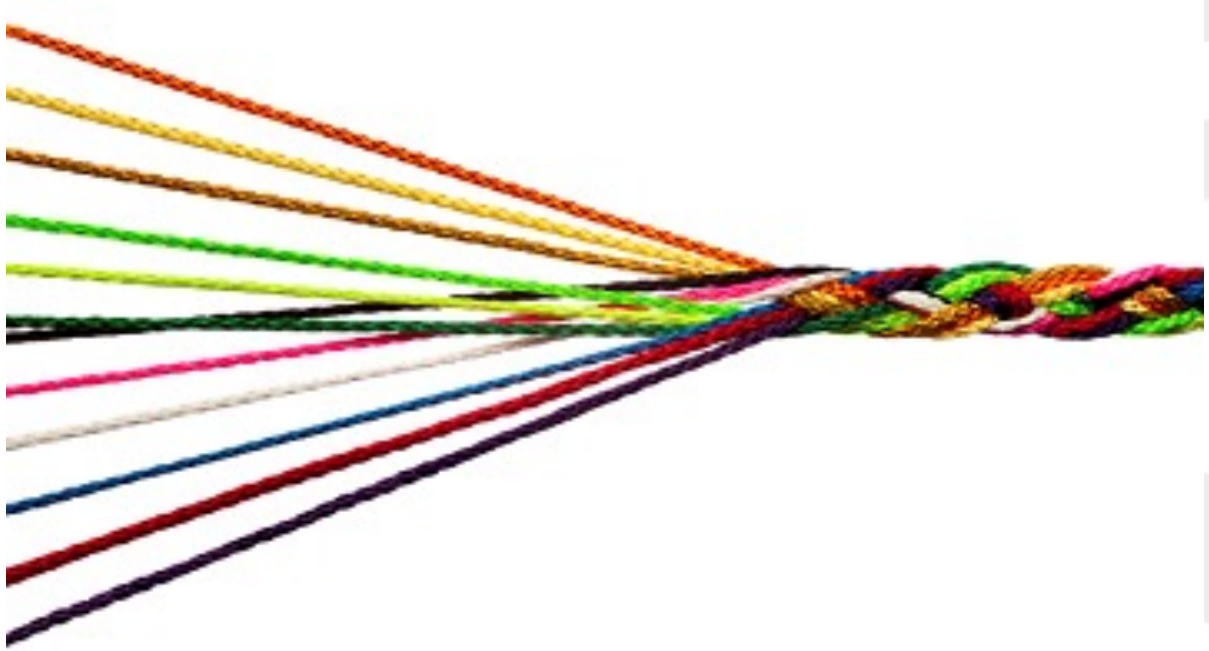
- Ongoing and advancing
- Draft of first international guideline (immediate release) expected to be released for consultation in 2022.

- Who: ICH

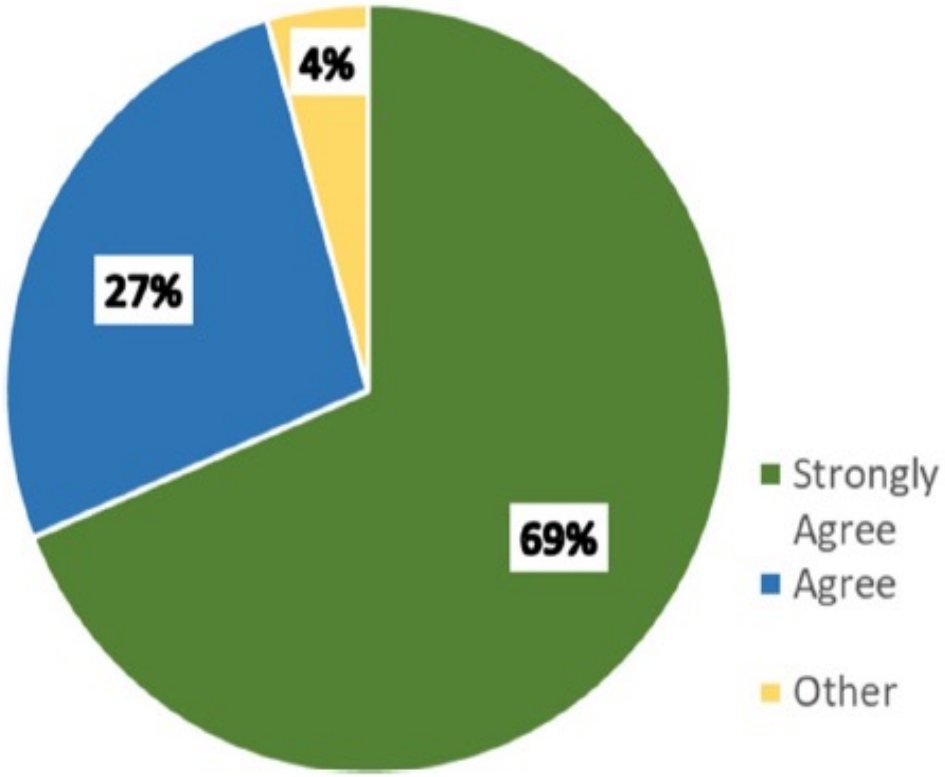
Before M13: multiple standards (a tangled mess)



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.

M13

M13 EWG Bioequivalence for Immediate-Release Solid Oral Dosage Forms

This topic was endorsed by the ICH Assembly in November 2019.

Further to the MC's endorsement of the M13 Concept Paper and Business Plan in July 2020, the M13 EWG was established to work on the development of the M13 Guideline to harmonise bioequivalence study design and standards, which is expected would benefit both innovator and generic product developers as the same scientific approach would be followed in multiple jurisdictions, potentially reducing duplicative work. Patients would also benefit as harmonisation would help regulatory agencies in the timely authorisation and availability of quality, safe and effective drugs based upon harmonised acceptance criteria. Furthermore, harmonisation could improve global access to drugs.

Further information can be found in the M13 Concept Paper and Business Plan.

Rapporteur: Dr. Lei Zhang (FDA, United States)

Regulatory Chair: Dr. Jan Welink (EC, Europe)

Status: *Step 1*

Endorsed Documents

- M13 Concept Paper
- M13 Business Plan
- M13 Work Plan

WG list

M13 guideline series

Immediate release

- General considerations and principles on BE study design
- Data analysis
- Biowaivers for additional strengths
- Advanced BE study design considerations
- Data analysis and BE assessment for HVD and NTI

ICH M13 Concept paper (10 Jul 2020)
ICH M13 Workplan (28 Jan 2022)

medicines for europe
better access. better health.

M13 series

Tier 1

Crossover vs. parallel

Single dose vs. multiple dose

Study population

Sample size

Study conditio

Dose or dose s

Analyte(s) to b

Endogenous s

Multiple comparator (reference) products in one study

Multiple test products in one study

Considerations for data analysis will include but not limited to:

- Statistical methods for BE related to non-replicate study design
- BE criteria
- Handling of outliers
- Long half-life drugs
- Truncated or partial AUC considerations

Tier 2

Biowaiver considerations for additional strengths

Second guideline in the series of the M13 guidelines (e.g., M13B or as an annex to M13).

This topic is important to drug development and should be started as soon as feasible.

The development of the Tier 2 topic will commence once the topics included in Tier 1 complete ICH step 1 (consensus building)

Tier 3

Data analysis and BE assessment for

1) highly variable drugs

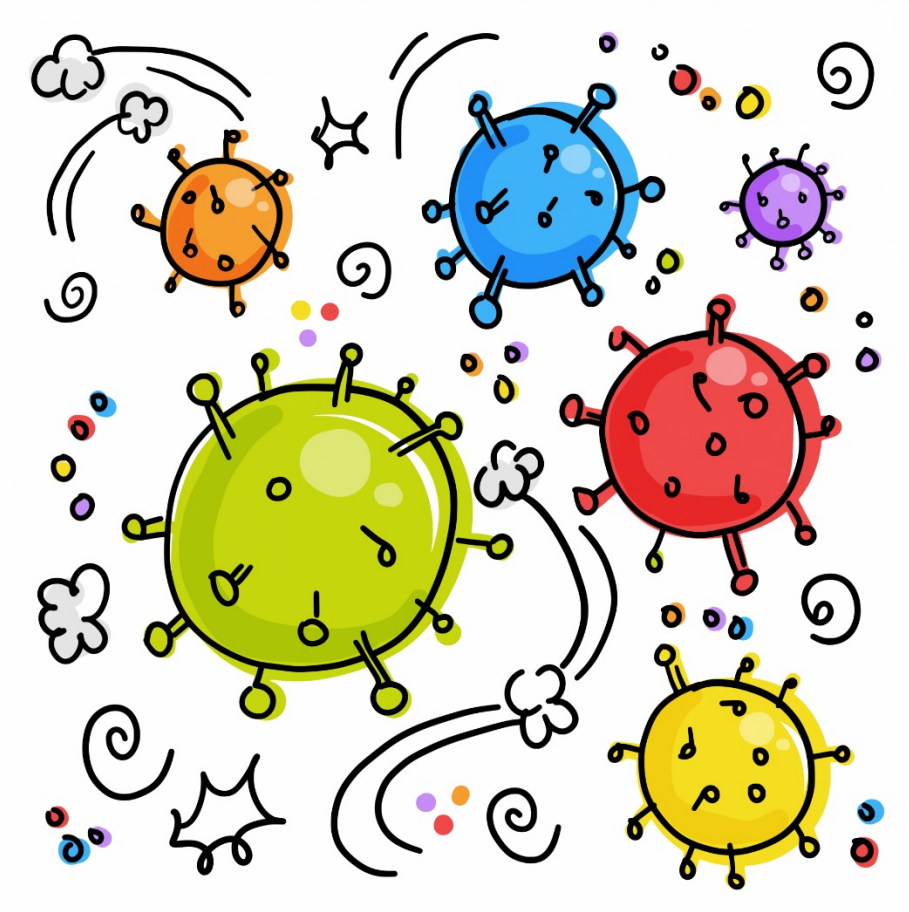
2) drugs with narrow therapeutic index, and

3) advanced BE study design and data analysis considerations.

Concept paper

• Finalisation of the Concept Paper and Business Plan	June 2020
• Approval of Final Concept Paper & Business Plan	July 2020
• Teleconferences of EWG	July 2020 - until the end of the EWG
• First face-to-face meeting of the EWG	November 2020
• Consensus on Technical Document (Step 2a/2b)	June 2022
• Adoption of ICH Harmonised Guideline (Step 4)	November 2023
Estimated starting time for second guideline in the series or annex	July 2022
Estimated starting time for third guideline in the series or annex	July 2024

Pardon the interruption



Most recent version of the workplan

Nov. 2022	**Nov. 2022**	1. *Possible Face-to-Face Meetings*	• *Address comments, resolve differences, and finalise the draft technical document of the first guideline in the series with Tier 1 topics (M13A)* • *Step 1 topic leads sign-off*
Dec. 2022	**Dec. 2022**	1. *Hold multiple EWG teleconferences every month as needed*	• *Step 2a/2b ICH endorsement of the first draft guideline in the series (M13A)* • *Initiate public consultation*

Public consultation on M13A

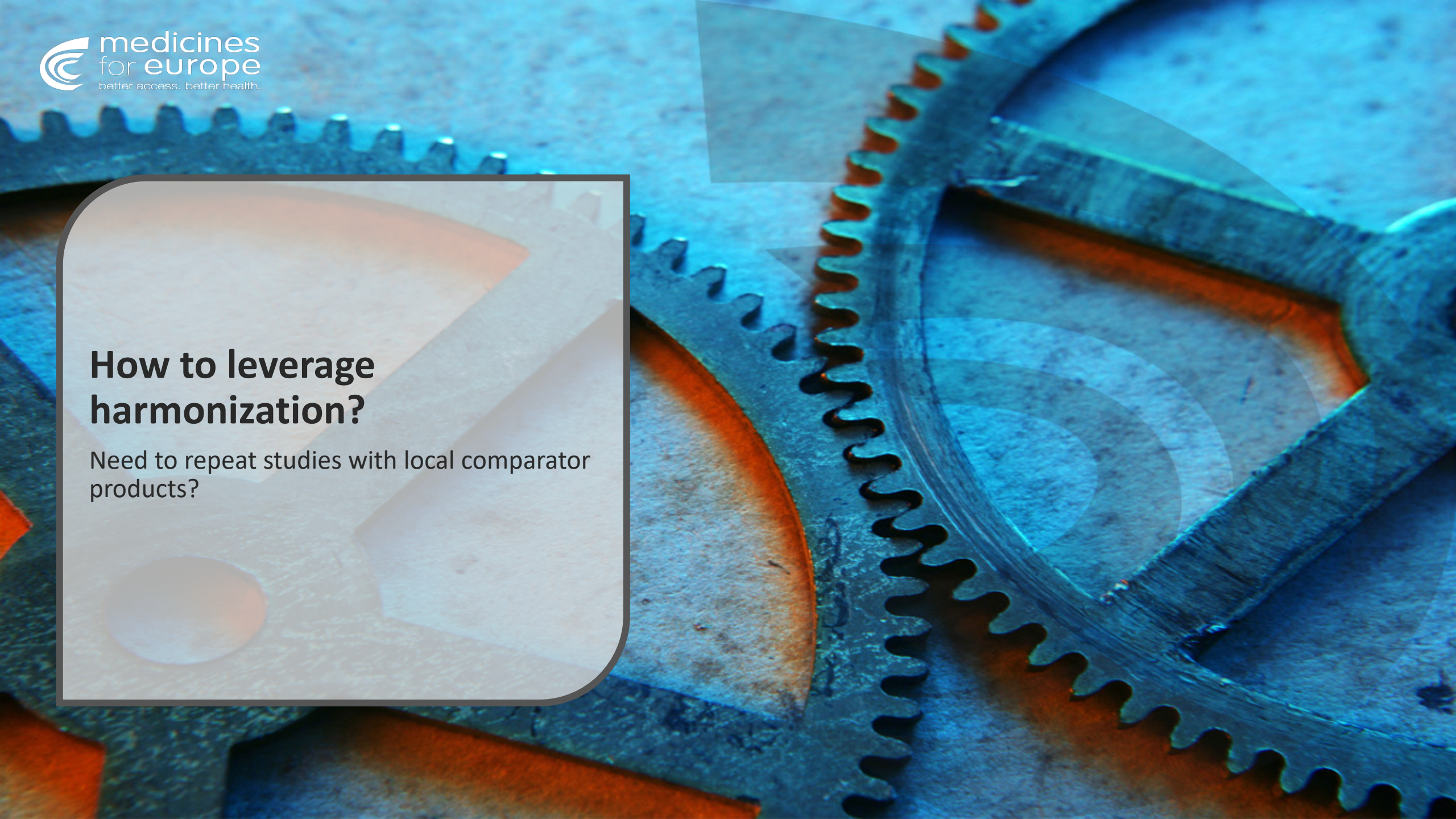
Tier 2 and Tier 3… what's next?

What about afterwards?

- Areas where there is reasonable existing consensus could be candidates for ICH harmonization

- New scientific tools available (for example, model based BE): let's work together to develop them
- GBHI next week

Consensus building



How to leverage harmonization?

Need to repeat studies with local comparator products?

2. Legal framework for acceptance of foreign comparators

- Several jurisdictions already accept the use of foreign comparator products

- Legislation in EU does not currently prevent
- But it is not explicit either

Terminology is important

Two important yet distinct terms

- Reference product – local originator product
- Comparator product – the product used to establish BE (currently missing from the legal text)

Pharma legislation

Let’s not miss the opportunity, EU!

3. Which foreign comparators are acceptable?

- A guideline is needed!
- Scientific criteria and the conditions of acceptability of foreign comparators for bioequivalence

- Competent Authority

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

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, 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.

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 of the jurisdiction

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.

- 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?

Government of Canada / Gouvernement du Canada

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 acce 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 manufacturer should continue to anticipate that the Bureau will treat any explanation for a failure to supply reference products 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.

ANVISA
Agência Nacional de Vigilância Sanitária

VOTO Nº 08/2021/SEI/DIRE2/ANVISA

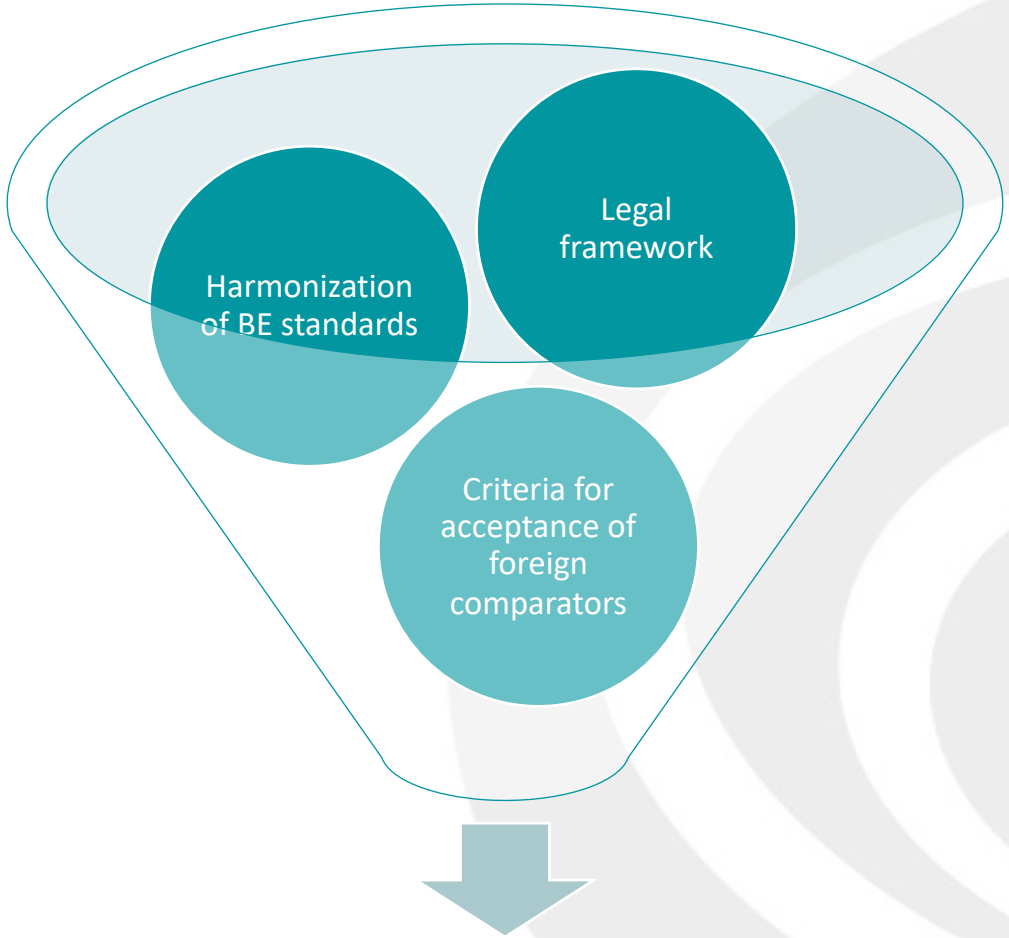
Processo nº 25351.941370/2020-00
Expediente nº 0244343/21-7

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

Single global development

- Standard approach for originator development
- Now commonly acceptable for biosimilar development
- Foreign comparators already accepted for generic development by several highly regulated regions

3 pillars that must advance simultaneously



Single global development of generic medicines

Importance of single global development

- ✓ Avoids redundant (hence unethical) clinical trials
- ✓ Helps increase patient access to generic medicines
  - Especially important in cases like **orphan drugs or complex generics**
- ✓ Contributes to competition, therefore increases access
- ✓ 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!
- 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
- We need to continue to advance harmonization
- The use of foreign comparators is necessary to leverage the benefits of harmonization – criteria should be defined
- The time to act is now

2019


What is necessary?
Single global development
When is it necessary?
As soon as possible

2022


What is necessary?
Single global development
When is it necessary?
NOW