Global Comparator Product for Biosimilar Development and Waiving of Bridging Studies

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Suzette Kox, Secretary General IGBA
International Generic and Biosimilar medicines Association

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Outlines

- Vision: equity of access to medicines
- Shared responsibility
- Tool: true global development
- 1. phase: foreign comparator accepted
- Next phase: bridging studies to be waived
- Scientific publication: C. Webster/G. Woollett
- Implementation of concept
  - Criteria and definitions
  - Health Canada
  - WHO
  - International regulators fora

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About IGBA

- The International Generic and Biosimilar medicines Association (IGBA) was founded to strengthen cooperation between associations representing manufacturers of generic and biosimilar medicines from around the world

- The IGBA is at the forefront of preserving sustainable competition within our industry, by stimulating competitiveness and innovation in the pharmaceutical sector; thereby, **ensuring millions of patients around the world have access to high quality, pro-competitive medicines**

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Shared vision: equity of access to medicines

- <u>The 2030 Agenda for Sustainable Development (2015)</u>
  - Urgent call for action by all countries - developed and developing - in a global partnership
  - Sustainable Development Goal 3 is to *"ensure healthy lives and promoting well-being for all at all ages"*

- **All UN Member States have agreed to try to achieve universal health coverage (UHC) by 2030, as part of the Sustainable Development Goals**
  - An equitable access to healthcare, including medicines, contributes to healthier lives

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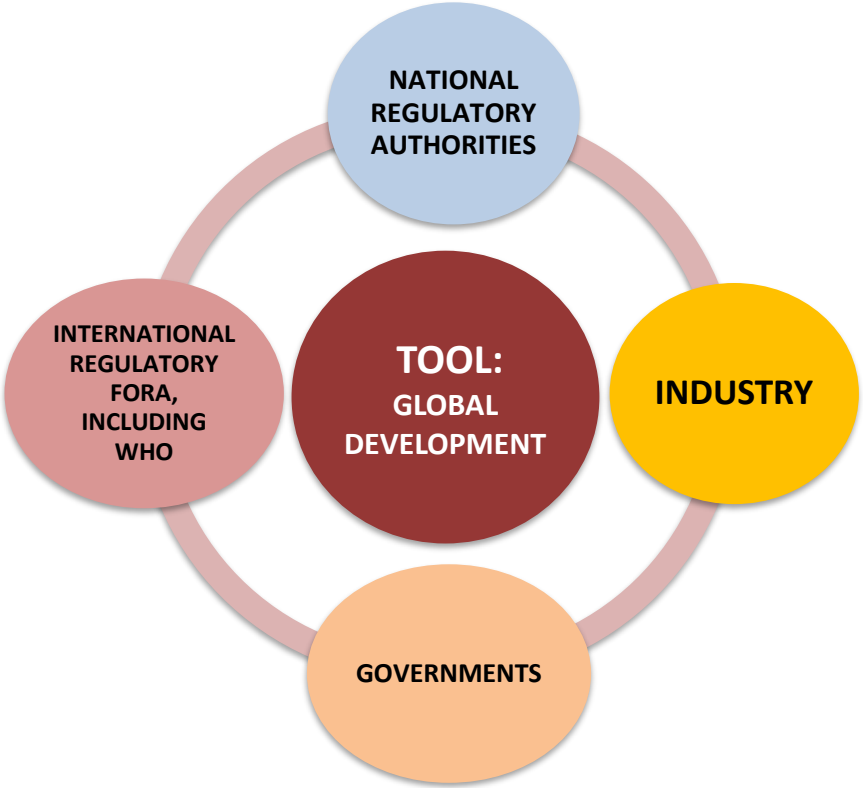
Shared responsibility to support equity of access to medicines
Postponing actions is no longer an option



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Global development supported by ICH for originator products

"Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are ***developed and registered in the most resource-efficient manner****."*

ICH website

ICH
harmonisation for better health

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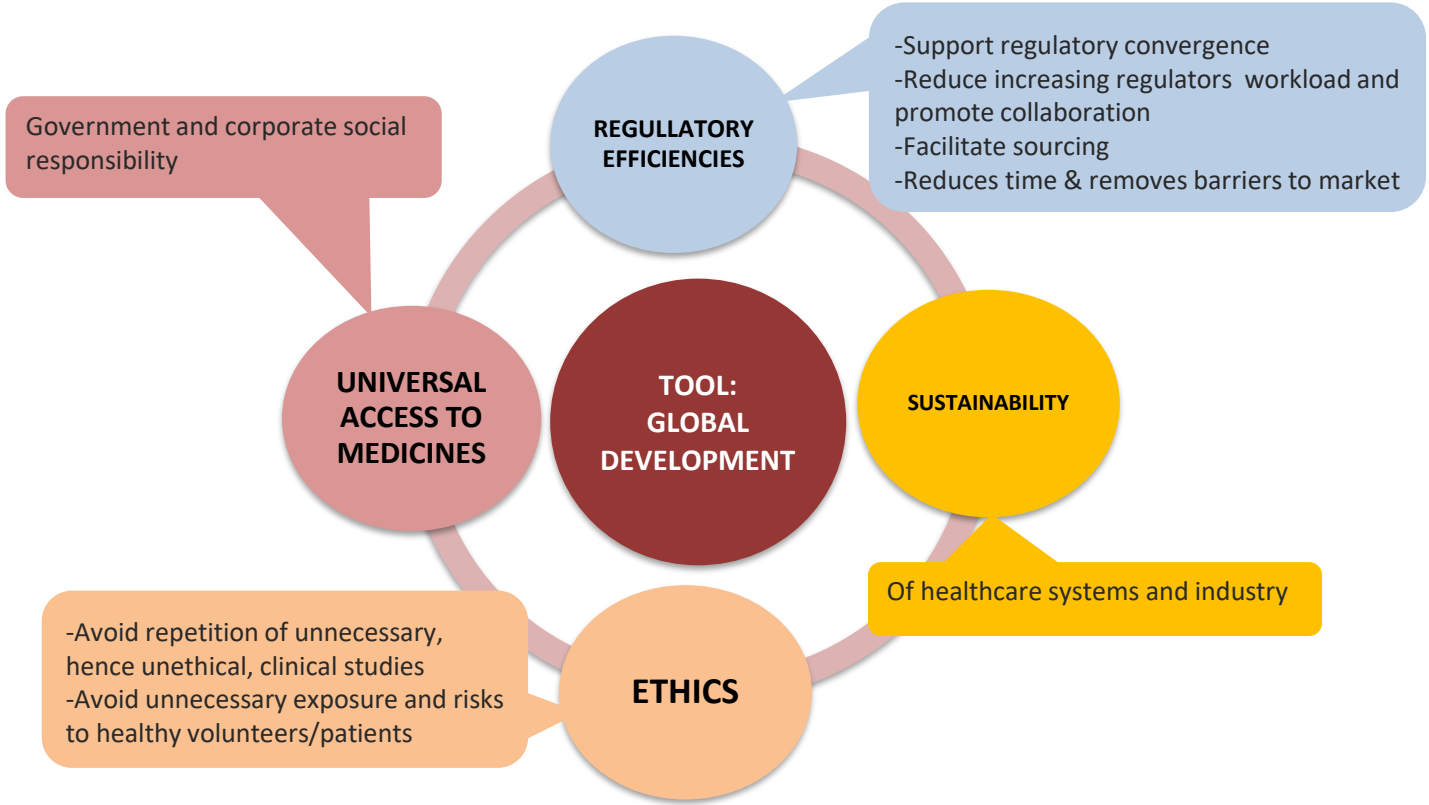
True Global Development frameworks needed for off-patent medicines



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FDA supports multinational development programmes

- *« FDA is involved with several international efforts for biosimilars to **help support global development** of these products and promote scientific alignment to streamline development. FDA is especially focused on strengthening partnerships with regulatory authorities in Europe, Japan, and Canada. These partnerships can facilitate global economies of scale in biosimilar development programs »*
  - Dr. Leah Christl/FDA, 12 April 2018 live chat Q&A
- "*Creating efficient economies of scale for biosimilars requires a global market. This means harmonizing requirements for their development, and sharing regulatory experience across national boundaries. And so, we're especially focused on strengthening partnerships with regulatory authorities in Europe"*
  - Commissioner Gottlieb speech: "Capturing the Benefits of Competition for Patients" @ America's Health Insurance Plans' (AHIP) National Health Policy Conference; 7 March 2018
- FDA Biosimilars Action Plan/Hearing questions
  - «What additional steps can FDA take to faciliate **multinational development programs** that may include non-US-Licensed comparators, to help support development of biosimilar products?»

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Foreign Comparator Product accepted

- For the comparability exercise, Reference Product (RP) must be authorised in the EEA
- **A non EEA-authorised version of the reference product (comparator RP)** may be used for certain clinical and in vivo non-clinical studies if it has been authorised based on similar scientific and regulatory standards as in the EU
- Aim is to **support global development**
  - 2014: Guideline on similar biological medicinal products page 5 : choice of Reference Product http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
- Comparator product must be representative of the RP in the EEA to stay in line with the legal framework
- Similar approach taken by FDA

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Bridging studies required for a submission as a biosimilar product in selected countries[1] in addition to a complete comparability exercise conducted against the EU RP

complete comparability exercise against EU-authorized reference product	+ US [3]	+ JP [3]	+ CH [3]	+ AU [3]	+ SK [3]	+ TW [3]
Clinical: 2-way efficacy & safety study, EU vs biosimilar	Clinical: add. obligations (transition study for chronic indications; switching for nterchangeability	Clinical package includes either 1) sub-group analysis with JP subjects				
PK/PD: 2-way study: EU vs. Biosimilar (potentially 3-way required if bridging to US-licensed product in efficacy and safety study is requested)	PK/PD: 3-way: EU vs.US vs. Biosimilar	2) PK studies with JP subjects vs. JP reference product 3) PK studies with JP subjects vs authorized foreign reference product				
In-vivo[2]: 2-way: EU vs. biosimilar Includes: PK/PD, Toxicity, Efficacy, local tolerance, tissue cross reactivity						
In vitro: 2-way: EU vs. biosimilar Includes: approximately 10 functional assays, i.e. binding (e.g. target binding, receptor binding), mode-of-action (e.g. ADCC, CDC, apoptosis)	3-way: EU vs. US vs. Biosimilar	customized package including additional comparability against the local JP reference product	EU package plus comparability against CH reference product	EU package plus comparability against AU reference product	EU package plus comparability against SK reference product	EU package plus comparability against TW reference product
Physico-chemical: 2-way: EU vs. biosimilar Includes: 30-60 quality attributes like primary structure, higher order structure, size variants, charge heterogeneity (e.g. C- and N-terminal), post-translational modifications (e.g. glycosylation, glycation, oxidation, deamination), comparative stability, forced degradation studies	3-way: EU vs. US vs. Biosimilar	customized package including additional comparability studies against the local JP reference product	EU package plus comparability against CH reference product	EU package plus comparability against AU reference prod	EU package plus comparability against SK reference product	EU package plus comparability against TW reference product

[1] = *Jurisdictions selected on the basis of their Agency's requirement of a comprehensive comparability exercise.*
[2] = *in vivo animal studies are becoming significantly less relevant for biosimilars and are expected to be considered unethical in the near future*
[3] = *sizes of the boxes represent the relative additional work needed to bridge to the requirements of thespecific region EU: European Union; US: United States; JP: Japan; CA: Canada; CH: Switzerland; AU, Australia; SK: South Korea; TW: Taiwan*

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A ‘Global Reference’ Comparator for Biosimilar Development

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A ‘Global Reference’ Comparator for Biosimilar Development

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Open Access | Current Opinion
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Open Access at : https://link.springer.com/article/10.1007/s40259-017-0227-4

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Same Pivotal Clinical Data Supporting the Approvals of Biologics in Multiple Jurisdictions

Biologic	Trade Name	Sponsor	Countries in which First Approvals Were Based on the Same Studies*	Studies Submitted for First Approvals in More Than One Country	Indications Studied
Infliximab	Remicade	Janssen	US, EU, Canada, Australia	T16, T21	Crohn's disease
Etanercept	Enbrel	Amgen	US, EU, Canada, Australia	16.009, 16.014	Rheumatoid arthritis
Adalimumab	Humira	AbbVie	US, EU, Canada, Australia	DE009, DE011, DE019, DE031	Rheumatoid arthritis
Pegfilgrastim	Neulasta	Amgen	US, EU, Canada, Australia	980226, 990749	Febrile neutropenia in treatment of non-myeloid cancers
Bevacizumab	Avastin	Genentech/Roche	US, EU, Canada, Australia	AVF2107g, AVF0780g	Metastatic colon cancer
Ranibizumab	Lucentis	Genentech	US, EU, Canada, Australia	FVF2598g, FVF2587g, FVF3192g	Age-related macular degeneration

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A 'Global Reference' comparator for biosimilar development, Christopher J. Webster – Gillian R- Woollett

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There is effectively only a single comparator approved globally
Clinical properties remain unchanged after manufacturing changes

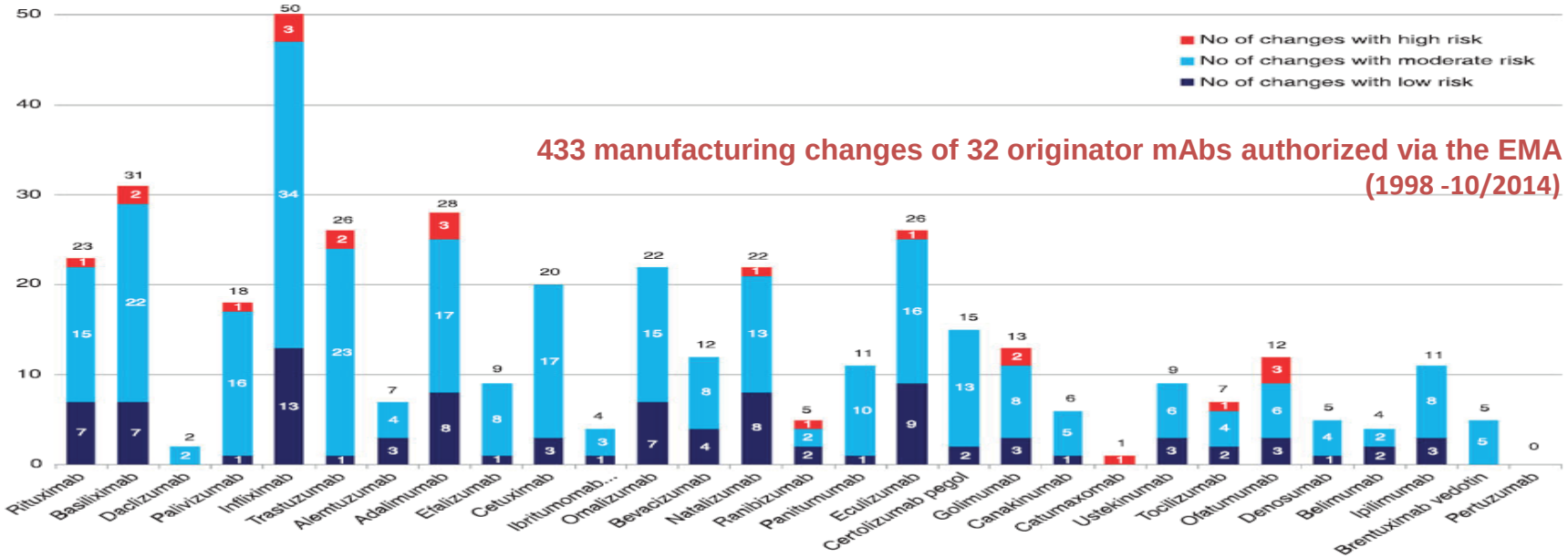

Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

Vezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016 May;32(5):829-34

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Time has to come for introducing concept of Global Comparator Product

- True global development framework needed to reduce complexity, duration and costs
- 12-plus years of regulatory and clinical experience with biosimilars
  - Lessons learned: time to move to the next level
- Multiplication of bridging studies by each sponsor/unnessary, hence unethical clinical studies
- Need to increase regulatory efficiency
- Significant costs (millions of EUR) providing no patient benefit or scientific value
- Joint regulatory efforts to overcome scientific challenges and increase collaboration
- Implementation of ISO IDMP standards
- Accessibility of Reference Products /Refusal to sell samples of products for biosimilar testing
- WHO Prequalification pilot procedure for rituximab and trastuzumab/ Access to biologics
- **Faster and broader access for patients**
- **Establish criteria for a framework without bridging studies requirements, using the global comparator product approach**

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Consensus needed on terminology and definitions

- **Reference medicinal product (RP)**
  - Serves as legal reference for the generic/hybrid/biosimilar application
- **Comparator product**
  - Is the local or foreign RP used as comparator during the development to support application and approval
  - Comparator, if foreign product, must be representative for the local reference product
  - Comparator Product must have been approved by a SRA/WHO-Listed Authority (WLA-ML 4), in order to be recognized by another jurisdiction.
- **Tentative definition of global comparator product**
  - A **Global Comparator Product** is any originator product, authorised by any SRA/WHO-Listed Authority (WLA ML4) **and** qualified as Reference Product .
  - It can be used for follow-on product development to support its application and approval in any jurisdiction around the world.

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Circumstances where bridging studies between local and foreign reference can be waived

- Foreign Reference
  - meets the criteria to qualify for comparator product (CP);
  - contains a version of the same active pharmaceutical ingredient (API), and has the same pharmaceutical form and same route of administration as the local reference;
  - has the same composition of excipients as the locally-approved reference product (local reference), or, if the qualitative compositions of excipients are different, the sponsor provides a justification showing the excipients have been assessed and are not expected o impact clinical efficacy and safety;
  - was approved in the respective jurisdiction based on essentially the same original data package as the locally-approved reference product (local reference) as demonstrated via evidence in the public domain;
  - subsequent manufacturing changes were regulated according to ICH Q5E principles to ensure that the clinical properties remain unchanged.

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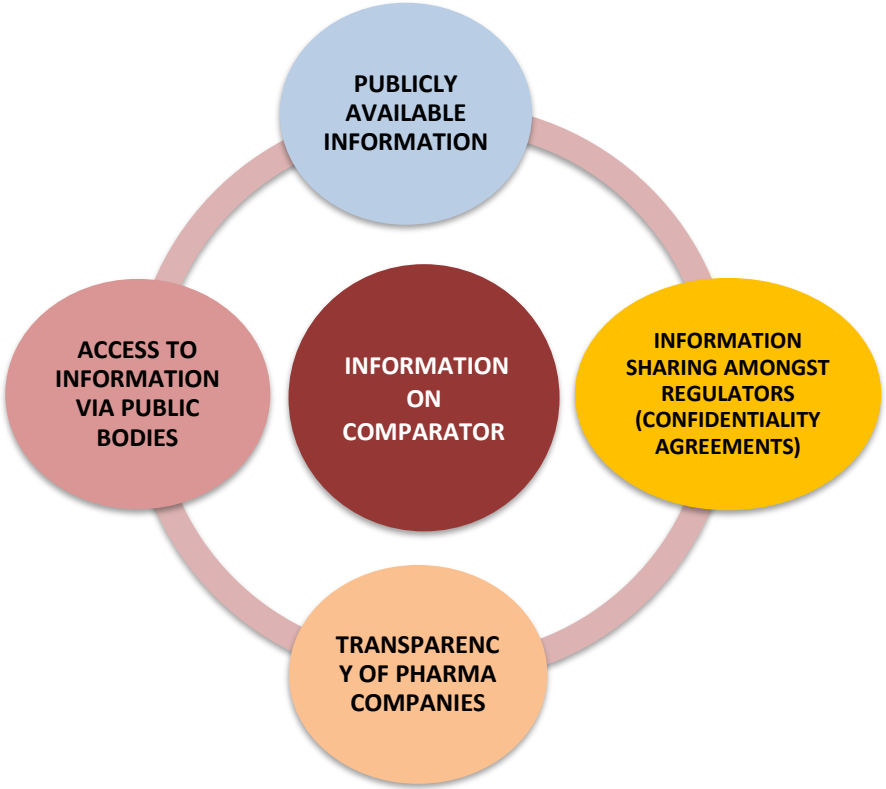
Information sources on Global/Foreign Comparator Product



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Burden of proof regarding “sameness” of reference and comparator product to be shared with regulators

- Consensus needed regarding information needed
  - Product, assessment report, decision report
- Established or achievable prerequisites for sharing of information amongst Regulators
  - Similar scientific and regulatory standards
  - Trust based on collaboration experience
  - Confidentiality/secrecy arrangements
  - New future tool: Implementation of ISO IDMP STANDARDS linked to business and regulators needs
    - ISO IDMP have been specifically developed during many years to allow consistent and reliable sharing of information on medicines between regulatory agencies

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Positive example: Health Canada's clarification with IGBA

- A version of the reference product, not sourced in Canada, can be used as the comparator product
- Canada does NOT require 3-way bridging studies involving either the U.S. or the EU version, the Canadian version and the biosimilar as part of the quality information to support a marketing application for a biosimilar
- As long as the comparator product is authorised by a stringent regulatory authority, a suitable paper link to the Canadian reference product is acceptable.
- If studies provided to HC BGTD use multiple reference products, then bridging studies will be required

Confirmed by Anthony Ridgeway/Health Canada - March 2019

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WHO Prequalification Procedure

- Rituximab and Trastuzumab added to the WHO Essential Medicines List
- Great interest from manufacturers
- Pilot prequalification procedure ongoing
- Should lead de facto to a WHO global comparator product list
- Global comparator approach and waiving of bridging studies, where appropriate, should be promoted by WHO and be reflected in the Q&A related to the WHO SBP guideline

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Priority Topic for International Regulators Fora

- International Pharmaceutical Regulators Programme (IPRP): Biosimilar Working Group: largest forum where biosimilars are discussed
- ACSS (Australia, Canada, Switzerland and Singapore) Consortium
- TGA/Australia is consulting on the use of foreign comparator products and wants to introduce the reforms in order to:
    - reduce regulatory barriers for applicants seeking to register generics, while maintaining existing safety, quality and efficacy standards
    - make the application process easier by making regulatory requirements clearer and more transparent
    - **support international work sharing opportunities**
    - provide incentives for specific generics applications, where these would support a more robust supply of medicines.

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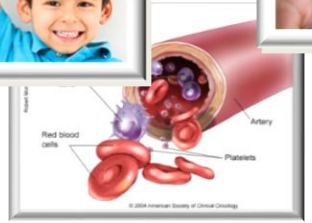
Keep up the momentum

Patients are waiting

Cancer

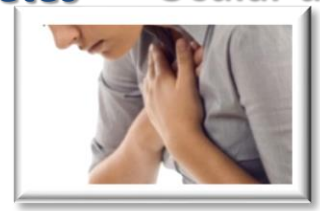
Rheumatic disorders, Psoriasis



Growth & Hematopoietic disorders

Diabetes

Ocular diseases



Asthma

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THANK-YOU!

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www.igbamedicines.com

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About IGBA

- Founded in March 1997 as the International Generic Pharmaceutical Alliance
- Renamed **International Generic and Biosimilar medicines Association (IGBA)** in September 2015
- Legally incorporated in Geneva, Switzerland I 2015
- Admitted as Assembly Member of ICH in June 2016
- Maintains constant dialogue with the WHO, WTO, WIPO, ICH and other national, regional and international bodies

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Members

- IGBA is committed to promoting generic and biosimilar medicines worldwide, and consists of the following associations:

  - Association for Accessible Medicines (AAM-United States)
  - Canadian Generic Pharmaceutical Association (CGPA-Canada)
  - Generic and Biosimilar Medicines Southern Africa (South Africa)
  - Indian Pharmaceutical Alliance (IPA-India)
  - Japan Generic Medicines Association (JGA-Japan)
  - Jordanian Association of Pharmaceutical Manufacturers (JAPM-Jordan)
  - Medicines for Europe (Europe)
  - Taiwan Generic Pharmaceutical Association (TGPA-Taiwan)

  The generic and biosimilar medicines associations of Australia, Brazil, Malaysia, Mexico and Saudi-Arabia are Associate Members.

- In addition, IGBA includes:
  - Biosimilars Canada
  - Biosimilars Council (AAM Division)
  - Biosimilar Medicines Group (Medicines for Europe Sector Group)

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