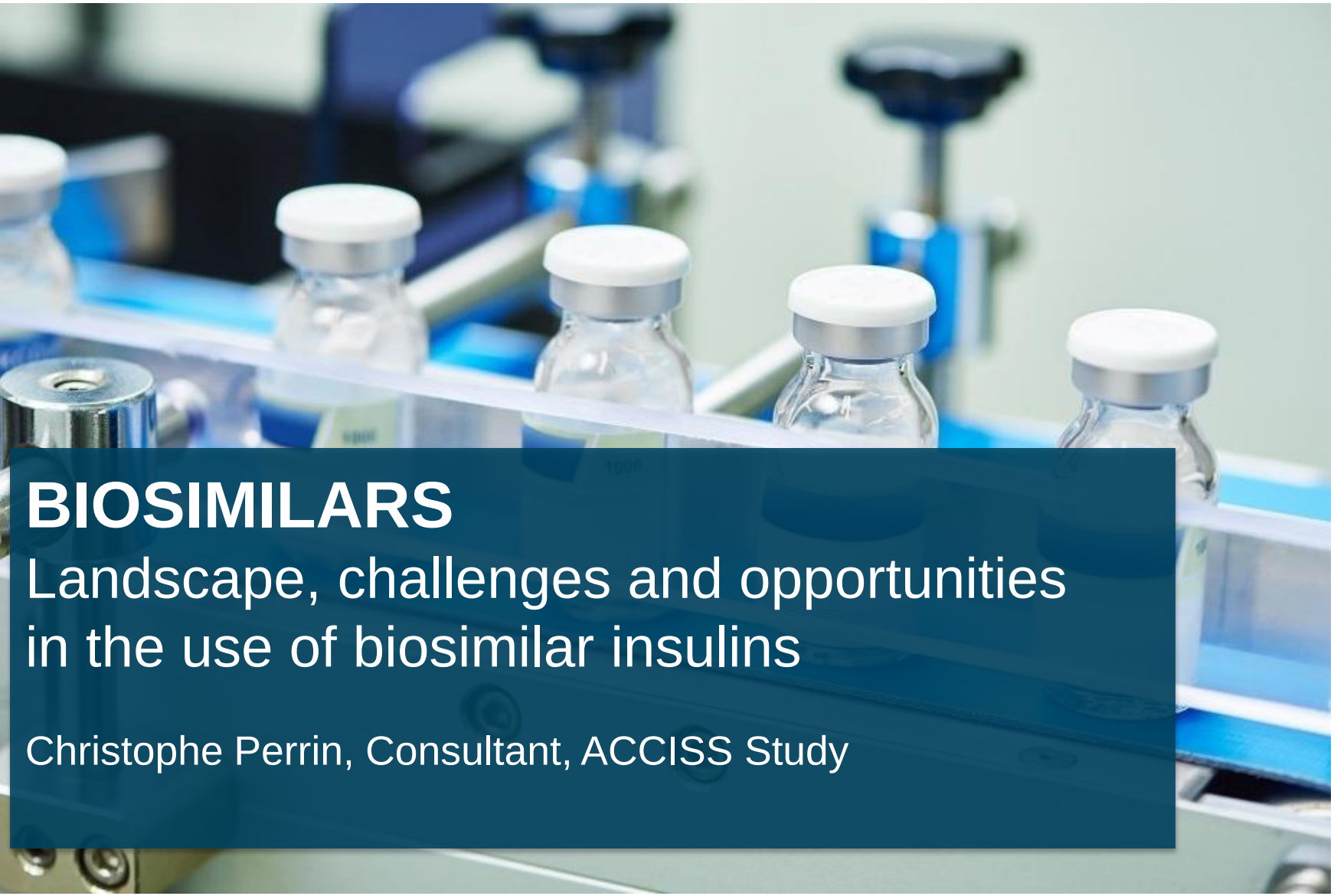

BIOSIMILARS

Landscape, challenges and opportunities in the use of biosimilar insulins

Christophe Perrin, Consultant, ACCISS Study

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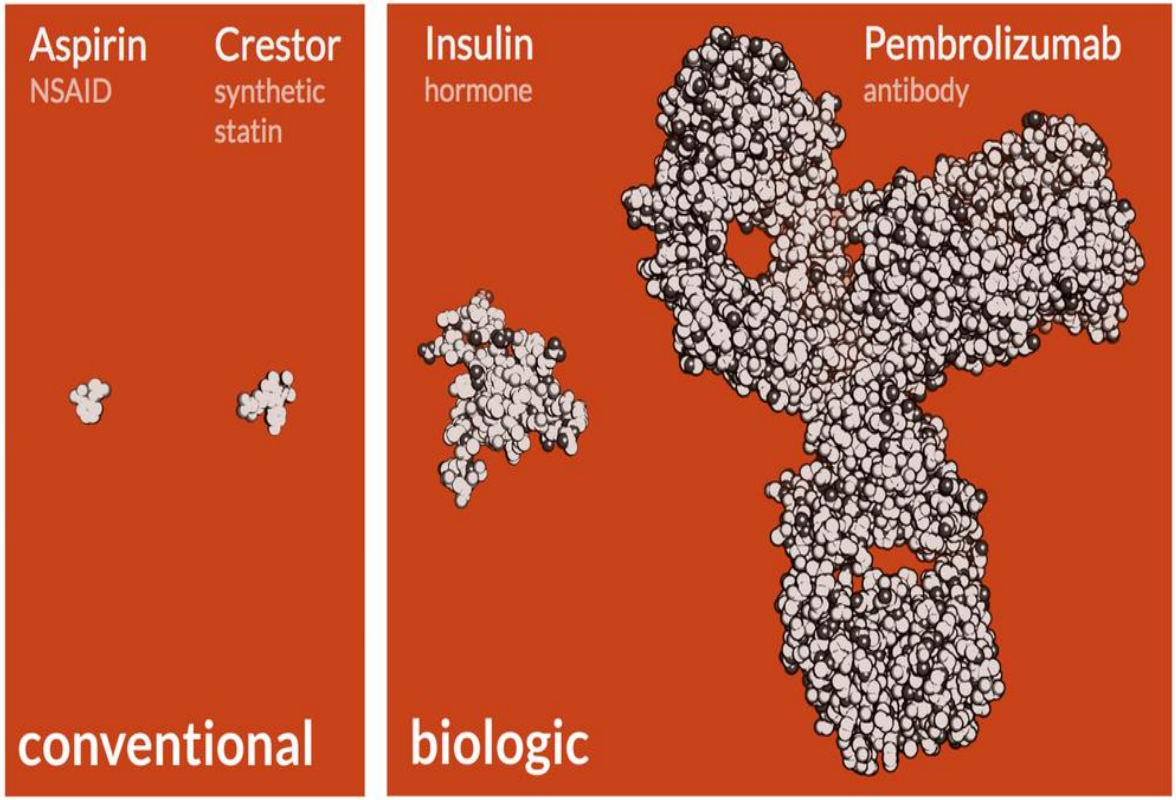
Biologic medicines

- Proteins derived from cell culture / fermentation processes with bacteria or yeast, therefore produced in living organisms
- Examples: recombinant human & analogue insulins, cytokines, monoclonal antibodies, human growth hormone, erythropoietin
- Larger & more complex compared to conventional synthetic active ingredients; more variability due to the manufacturing characteristics



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Definitions of Biosimilars

- **US Food & Drug Administration Follow-on Biologic or Biosimilar**

  "A biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".

- **European Medicine Agency Biosimilar**

  "A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established".

- **WHO Similar Biotherapeutic Product**

  "A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product"

- **Japanese PMDA Follow-on Biologic or Biosimilar, Health Canada Subsequent Entry Biologic,…**

Biosimilar medicines

- Produced in living organisms (mammal cells, bacteria, yeast)
- More challenges than for conventional synthetic active ingredients
- Sources of heterogeneity
  - ✓ Inherent property of natural isoforms
  - ✓ Variations in cell culture conditions
  - ✓ Downstream processing
- Regulatory challenges in terms of equivalence to reference products: interchangeability

Biosimilar insulins

- A biosimilar insulin is similar to an existing insulin (reference) but cannot be considered identical because of the different manufacturing processes (different cell lines, protein sources, extraction and purification techniques)

- Published studies that have compared biosimilar and reference insulins

Source: https://doi.org/10.1371/journal.pone.0195012

→ suggest that the biosimilars have comparable safety and clinical efficacy as the reference product

  - all PK and / or PD studies showed comparable parameters within pre-specified equivalence margins
  - clinical studies showed similar clinical efficacy and immunogenicity
  - adverse events were similar between groups across studies

Regulatory frameworks

- Two main benchmarks for the regulation of biosimilars:
- European Medicines Agency (EMA)
- WHO guidelines

→ Technical debate remains on the precise requirements that biosimilars should fulfil in order to be properly considered similar or therapeutically equivalent to reference products (interchangeability)

Regulatory frameworks

- 2006: first biosimilar registered in the European Union (EU)
- September 2014: EMA granted 1st market authorisation valid throughout the EU for a biosimilar insulin, and the latest at the end of May 2017
- EMA was the first regulatory authority to develop insulin-specific guidelines; have been adopted by many countries for the assessment of biosimilar insulins

Approval requirements through the biosimilar pathway for insulins appear to be simpler than those for a number of other recombinant proteins:

if the quality attributes of the biosimilar insulin are highly comparable to the reference product, the non-clinical and clinical data can be limited to pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity studies

=>no interchangeability challenges

Biosimilar regulatory guidelines

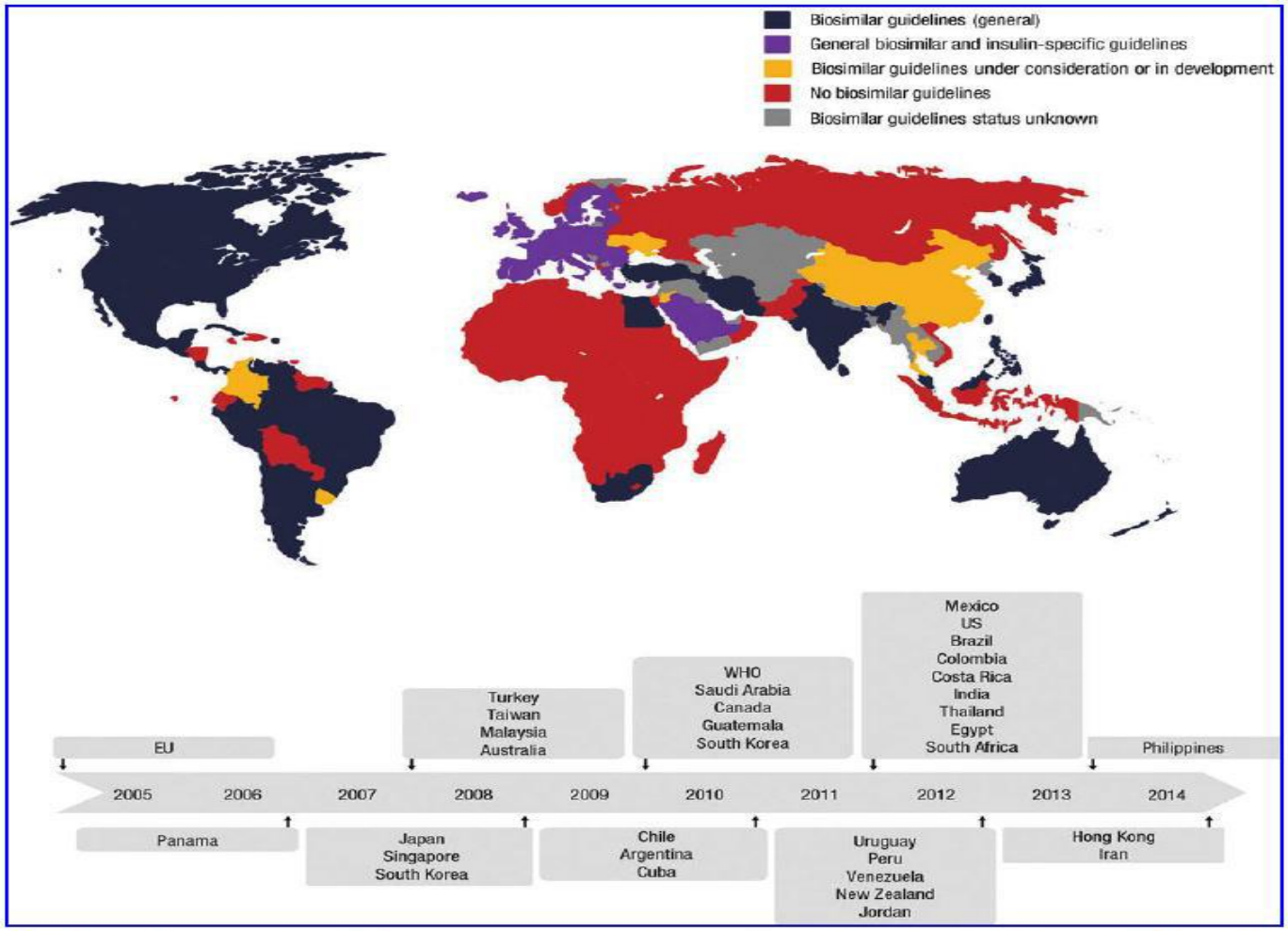

FIG. 1. Global overview of availability of general and insulin-specific biosimilar guidelines. EU, European Union; WHO, World Health Organization. After Scheinberg and Kay.[9]

Biosimilar regulatory guidelines, EAEU

- January 2015: creation of the EurAsian Economic Union (EAEU)
- Armenia, Belarus, Kazakhstan, Kyrgyzstan and the Russian Federation
- agreement to establish a common pharmaceutical market, which aims to harmonise key regulatory aspects across the 5 Member States

- Working Group (WG) on biological / biosimilar products within the EAEU
- follows EMA biosimilar guidelines which have been translated directly to Russian without changes
- work of this WG is backed up by an EAEU technical department based in Moscow
- technical advice accessible from this WG for Russian-speaking countries

Categories of insulin manufacturers

Current market landscape (indicative list): at least 10 independent biosimilar manufacturers worldwide

A. Insulin manufacturers controlling full manufacturing process	
Originator insulin manufacturers	**Denmark (Novo Nordisk), France (Sanofi), USA (Eli Lilly)**
Biosimilar insulin manufacturers with in-house insulins (crystal & finished product) on the market	**India, China, UAE, Poland, Russian Federation, Ukraine, USA**
B. Manufacturers of finished product(s) only	
With crystals from Novo Nordisk, Lilly and Sanofi (unknown type of partnership)	**Belarus, India**
With crystals from biosimilar insulin manufacturers	**Bangladesh, Brazil, China, India, Mexico, Morocco, Poland**

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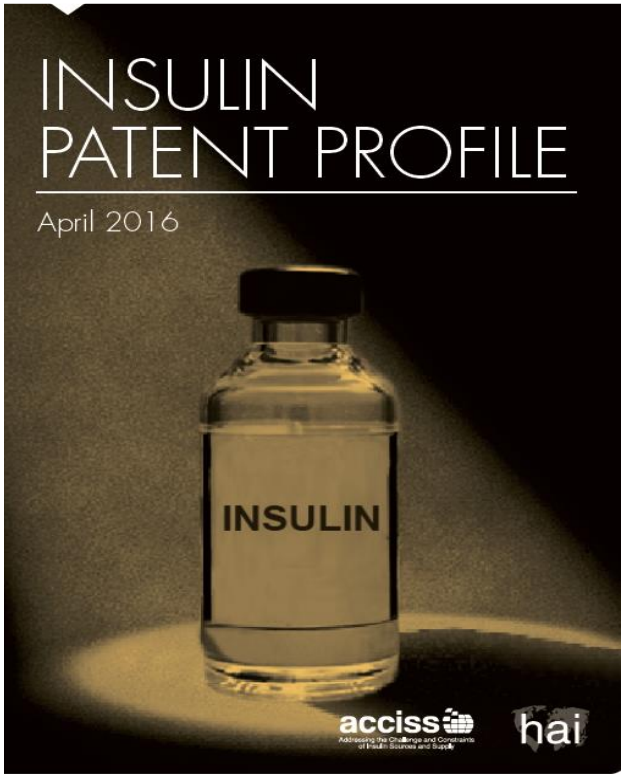
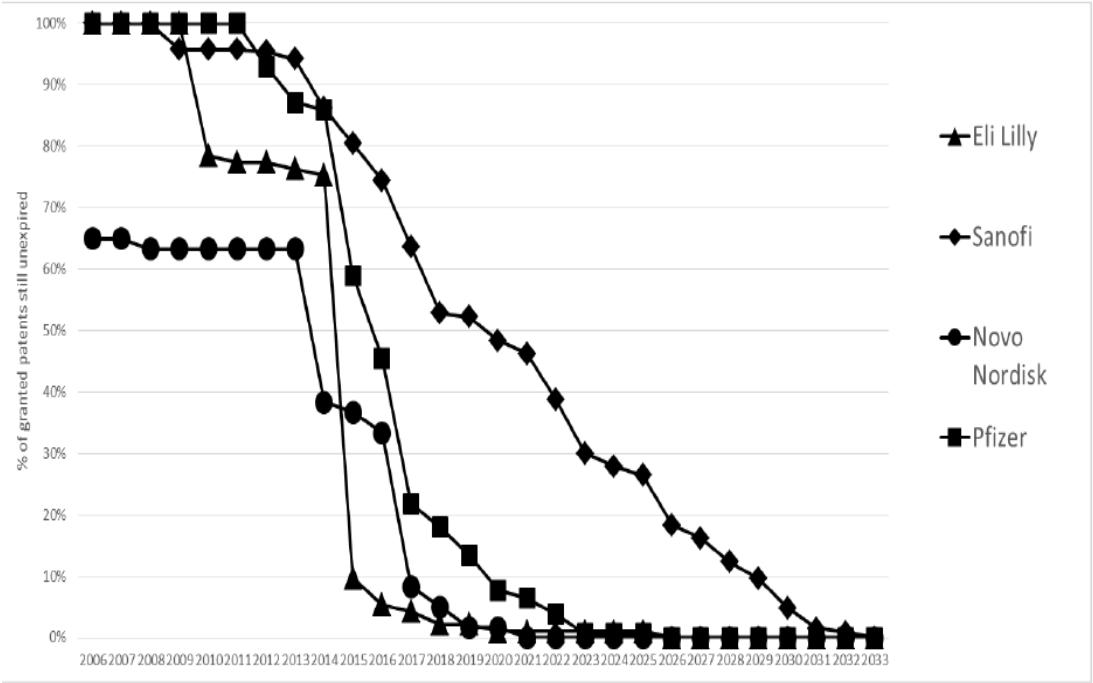
Biosimilar insulins & patents

- Biosimilar market significantly increasing with many biological products coming off patent

→ patent protection for several insulin analogues expired in June 2014





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Biosimilar insulins & prices

- Cost reductions at market launch for biosimilars (20-30%) more modest compared to those offered to small molecule generic medicines

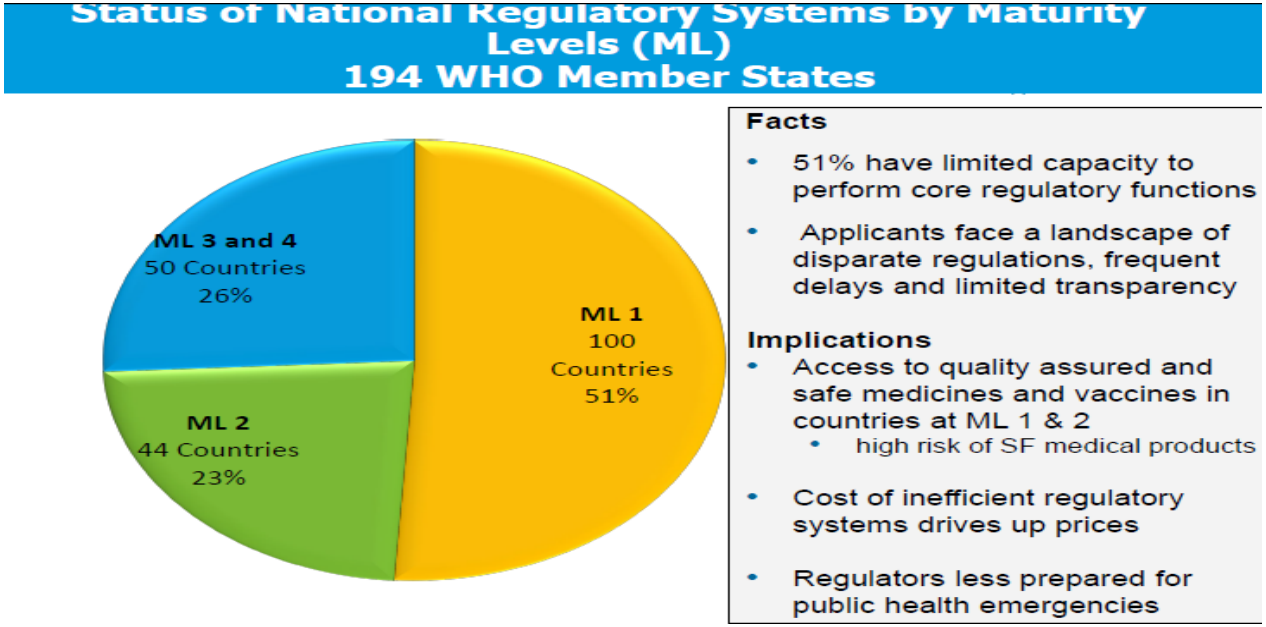
- In the USA and EU, originator brands have decreased in price by 12-51% once a biosimilar is introduced (Source: ACCISS report, Insulin price report, 2016)

- Opportunities of price reduction for **analogue** insulins:
- 2015: Lilly received marketing authorization from the EMA & US FDA to market its biosimilar glargine Basaglar®. In the UK, the list price is 15% lower than the price of the originator Sanofi's Lantus® (Source: ACCISS report, Insulin price report, 2016 – UK Medicine information)

- Opportunities of price reduction for **human** insulins:
- September 2019: Biocon Biologics offers human insulin at US$ 0.10 per day (40 units) to low- and middle-income countries i.e. US$ 2.50 for a 10ml vial

Biosimilar insulins & challenges

- Limited expertise in most National Medicines Regulatory Authorities to:
- assess manufacturing sites and product dossiers of biologic medicines, including biosimilars
- monitor safety and efficacy when made available on their markets



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Biosimilar insulins & opportunities

- Biosimilar analogue insulins are now registered in a number of countries including the EU, Australia, Japan, USA

- WHO Prequalification programme:

- 2017: pilot project initiated to assess biotherapeutic medicines
  → 2 cancer monoclonal antibodies (reference products & biosimilars)
- 2020: plans to expand the list of biotherapeutics to human insulins, including biosimilars

- Initial work at WHO to update the 2013 Guidelines on the evaluation of similar biotherapeutic products (SBPs)

- On-going WHO regulatory strengthening on the assessment of biotherapeutic medicines

→ on-going discussions to expand this work to Regional Regulatory Harmonisation initiatives (EAEU, East African Community, West African Medicines Regulatory Harmonisation, etc)

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