Global Pharmaceutical Regulation 2017

April 14-15, 2017 Florida State University, Tallahassee

Disputes over Biosimilar Regulations

- Approval of Biosimilars and Changes Impacting Already Approved Products-

Xavier Seuba
Senior Lecturer and Researcher
Academic Coordinator and Judicial Training Manager
Centre for International Intellectual Property Studies (CEIPI)
University of Strasbourg

Relevance of Biologics...

Public health

- NCDs amount to 70% of deaths
- The most sophisticates MABs are used to treat
  - Cancer
  - Autoimmune diseases
  - Alzheimer
- Biologics also for the treatment of
  - Chronic diseases such as diabetes (insulin)
  - Infectious diseases (recombinant vaccines)

Market

- In 2020
  - world market for biotech drugs will amount to USD 250 billions
  - 55% top 100 drugs will be biologic
  - Expiry of US patents of 14 biotech: sales worth up to 67 billions in 2014
- But competition is desperately needed
  - trastuzumab price should reduce from 70% to 95% to be accessible in Latin America

... importance of biosimilars and their market authorisation

I. Abridged regulatory path for the approval of biosimilars? Would it be a trade barrier?

Differences in size and structure of some macromolecules make difficult full characterization and exact copies may be impossible

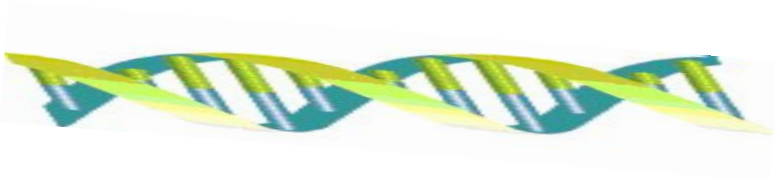
The challenge is demonstrating that differences between the biosimilar and the reference medicinal product do not have a significant impact on clinical efficacy and/or safety

The economic and social function of fostering competition and access is the same for “biosimilars” and “generics”. From that standpoint, they can be called “biogenerics” :

- Fulfil the same medical function
- Promote competition
- Use the same INN (although...)

Abridged approval of biosimilars

- Two commonly accepted principles that rule the marketing approval process for biosimilars:
  - Extended characterization exercise: demonstrate that the physicochemical and functional characteristics are very similar to those of the medicine or standard of reference.
  - Specific tests to assess the identity, purity, potency and immunogenicity of biocompetitors



- Colombian decree on MA of biotechnological medicines includes an "abridged" comparability path for biosimilars
- It proposes that, in some cases, information available in relevant countries and authorities will be used to accelerate entrance and save unnecessary tests
- Negative reaction of industries producing biotechnologicals, and their home countries

Route	Type of product
Complete	New biologic
Comparability	Known biologic
Abridged comparability	Known biologic

Information requested in the three routes

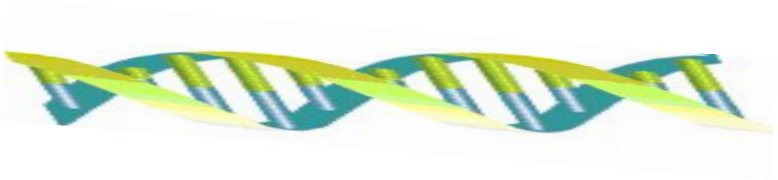
- Description of the process and place of production
- Expression system
- Biological identity tests
- Potency evaluation
- Physicochemical characteristics
- Evaluation of the biologic activity
- Evaluation of purity
- RM plan
- Immunogenicity studies

... continues what others also do

- "**In specific circumstances, a confirmatory clinical trial may not be necessary.** This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern."

  CHMP/ 437/04 Rev 1 (into effect, April 2015)

- Colombian "third" path has not been yet tested. There is a similar regulatory process in Brazil, but products are not considered biosimilars
- The idea is that **scientific advances and increased knowledge on proteins allow going beyond the paradigm of clinical comparability**
- The ultimate goal is promoting generic competition of assured quality



Reaction on two fronts: trade and health

Trade

- Colombia notified draft decree to the **WTO TBT Committee**. US, EU, US stakeholders, and a Colombian patient groups submitted comments expressing concern
- The EU has been addressing this issue in the context of the WTO TBT Committee and the implementation of the EU-Colombia and Peru FTA
- The **EU** claims that the decree may damage health, be detrimental of the interests of EU companies, and **create barriers to trade**
- The **US** also addressed this issue in the context of **trade barriers** regulation (National Trade Estimate Report on Foreign Trade Barriers)

Health

- US Vice President **Biden** said that it was believed by WHO and US experts' "that the biologic[al]s decree could put health and **safety at risk**"
- The Colombia regulation would **violate** the 2009 WHO guidelines and the "**spirit**" of the 2014 WHO guidelines
- "The view of the **industry** is that regulatory approval path should be on a stand-alone basis, as under the '**complete file path'** route."
- **Similar** concerns expressed over **Indian guidelines:** "potential exists for reduced non-clinical and clinical testing programs if there is proof of strong quality comparability and manufacturing process consistency" (Mysler *et al* 2016)

Is the WTO TBT Agreement relevant at all?

- National **regulations cannot** become unnecessary **barriers to trade**
  - "necessity test": permitted to restrict trade where a legitimate goal is pursued, i.e. Including the protection of public health and it matches with international standards
- **BIO** (et al**) allege** that Colombian third path is different from WHO standards (which would be the standard of reference), and hence the **TBT Agreement** enters into play
- In this case, **however**, the legal framework adopted does **not run against, but in favour, TBT objectives**
  - It creates a more competitive framework
  - Benefits national and foreign companies –highly possible, foreign
- Relation with **international standardisation and institutional and power** dynamics behind it: ICH growing preponderance

II. What to do with “old” market authorisations when the regulation or product changes?
(and *biomimics*)

Topics of discussion

- Disputes over validity of already granted MA when the normative framework changes
  - Broader discussion on procedures and data requirements for changes to approved products & regulation
  - Relevance of international standardisation
  - Use of (unlearned) courts to alter competition
  - Debate around 'intended copies' or 'biomimics'
- Innovative biotech producers demand the immediate disposal from the channels of commerce:
  - "old" products do not fulfil new conditions, in particular with respect PhV requirements and RM plans
  - They argue that the right to health entitles them to demand cancellation of old MA and intervene in the MA process of 3rd parties

- Originators argue that products introduced in the market prior to the implementation of regulatory pathways for the approval of biosimilars are just “intended copies” or “biomimics”
  - Their efficacy, safety and clinical performance are put globally into question

- 23 intended copies would exist in Mexico, + 25 in India (Pfizer)

Table 3 Countries in which intended copies of listed biologics for rheumatic conditions are approved and/or marketed without biosimilar regulations [14, 17, 91, 92]

Year of market introduction	Rituximab	Etanercept
2007	India (Reditux™)	–
2008	Peru (Reditux™)	Colombia (Etanar™)
2010	Chile, Bolivia (Reditux™) Mexico (Kikuzubam®)[a]	–
2011	Jamaica, Ecuador (Reditux™)	China (Yisaipu)
2012	Paraguay (Reditux™)	Mexico (Etart™; Infitam™)
2013	–	India (Etacept™)

[a] Withdrawn in 2014

Source: (Mysler *et al* 2016)

From general principle to implementation

- Principle: fulfilment of the most updated versions of regulatory requirements. This is the case of comparative pharma-biotech legislations.
- Controversy, however, concerning specific actions with respect already existing products and the timing of those actions
- Some court in emerging economies are requesting immediate removal of "old" products from the market... But WHO 2016 would seem to take a more nuanced approach
  - WHO Expert Committee on Biological Standardization *Guidelines on procedures and data requirements for changes to approved biotherapeutic products* (draft Nov 2016)

Guidelines on procedures and data requirements for changes to approved biotherapeutic products

- Inform and support national authorities and producers about changes on already approved products to ensure both QSE and access
- Key aspects
  - Changes refer both to the product and norms
  - Changes (and guidelines) impact both innovators and biosimilars
  - Standards must be changed adopting a risk-management approach that impacts both on competitors and innovators.
- Principles
  - The most updated standards must be demanded in the processes for the renewal of marketing authorizations.
  - Active programs for verification of standards must be put in place by checking products in the market
  - Implementation of new regulations should not impact on provision and access to products

WHO: action will change depending on the area and impact

- WHO guidelines basic scheme, distinguishes...
  1. Assessment
  2. Identify area of concern (Q, S&E, labeling or adtve information) plus relevance of the impact (major, moderate, minor, no impact)
  3. Action
     - Suspend
     - Ad-hoc procedure to supplement the information
     - Wait for the renewal of the marketing authorization to supplement the information
- *vs.* immediate removal requested by originators

Strategic Areas & Combined factors

- **Social**: sophisticated legal and technical field, attention and understanding of broader public
- **Judicial**: courts as "scientific gatekeepers" (*Daubert v. Merrell Dow Pharmaceuticals*)
- **Legal**: IP exclusivities strengthened by means of regulatory exclusivities
- **Governance**: global governance of pharma standards
  - Internation guidelines prone to be influenced by objectives going beyond health
  - Transition from national to global via non-open forums