ANVISA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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1. Anvisa’s Overview

2. Biological products - Current regulation

3. Comparability Development Pathway – Biosimilars

4. Interchangeability

5. Extrapolation of indications

6. Post-approval changes

7. Regulatory Guidelines

8. General Considerations
Areas of action

- Foods
- Cosmetics
- Sanitizer
- Tobacco
- Pesticides
- Health Service
- Medicines
- Medical devices
- Official Laboratories
- Pharmacovigilance
- Advertisement
- Ports, airports and borders
- International affairs
- SNVS coordination
Anvisa’s Overview
Organization chart

Board of directors

- Institutional management
- Regulation
- Articulation of the national surveillance system
- Authorization and registration
- Control and monitoring

General Office of Drugs and Biologicals

Office of Biologicals
Regulatory Acts Concerning Biological Products

- **Labeling**
  - RDC 47/2009
  - RDC 60/2012

- **Package insert**
  - RDC 71/2009
  - RDC 61/2012

- **Import**
  - RDC 81/2008

- **Quality control**
  - RDC 234/2005

- **Good manufacturing practices**
  - RDC 17/2010

- **Marketing Authorization**
  - RDC 55/2010

- **Post-approval changes**
  - RDC 49/2011

- **Blood products**
  - RDC 46/2000

- **Allergenics**
  - RDC 233/2005

- **Probiotics**
  - RDC 323/2003

- **Stability**
  - RDC 50/2011

- **Antivenom serums**
  - Ordinance 174/1996

- **Law 6.360/1976**
- **Decree 8.077/2013**
- **Marketing Authorization**
- **Post-approval changes**
I. Vaccines
II. Antivenom immunoglobulins
III. Blood products
IV. Biomedicines, obtained from:
   a) Biological fluids or animal tissues
   b) Biotechnological procedures
V. Monoclonal antibodies
VI. Medicines containing live, attenuated or dead microorganisms
VII. Probiotics
VIII. Allergens

- **Biological product**
  - medicine containing a molecule with a known biological activity, licensed in Brazil.

- **New Biological product**
  - medicine containing a molecule with a known biological activity, still not licensed in Brazil.

- **Comparator Biological Product**
  - registered based in a full dossier.

- **Full dossier**
  - quality, efficacy and safety.
Biological Products Current Regulation

RDC nº 55/2010

**Quality**
- Information about the API
- Production report
- Quality control
- Stability studies
- GMP

**Efficacy and safety**
- Non clinical studies
- Clinical studies (Phases I, II and III)
- Immunogenicity
- Pharmacovigilance and risk minimization plan
Biological Products
Current Regulation

- New Biological Product
  - Complete Dossier
    - Quality, Safety and Efficacy

- Biological Product
  - Stand Alone Pathway
    - Complete Dossier
  - Comparability Development Pathway
    - Comparability Exercise
      - Quality, Safety, Efficacy

STAND ALONE
BIOSIMILARS
Comparability Development Pathway – Biosimilar Approach

Comparability exercise: Quality, Efficacy and Safety.

<table>
<thead>
<tr>
<th>Comparator product</th>
<th>Biosimilar</th>
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<tr>
<td>Quality</td>
<td></td>
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<tr>
<td>Non-clinical</td>
<td></td>
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<tr>
<td>Clinical</td>
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- Physicochemical characterization
- Biological characterization
- Preclinical PK/PD
- Clinical

Confirmation of biosimilarity

Head-to-head comparison

Full registration dossier
Comparability Development Pathway

• Comparator Biological Product: is the biological product already licensed by Anvisa, based on submission of a full dossier and that has already been commercialized in Brazil.

• The same comparator must be used in all stages of the comparability exercise.
Comparability Exercise - Clinical evaluation

• Clinical comparability exercise
  - Stepwise procedure $\rightarrow$ PK and PD studies followed by pivotal clinical trials

• Clinical efficacy studies are required
  - The selection of a sensitive population and adequate endpoints is a critical consideration.
    - Immunogenicity comparative study is necessary.

• Design
  - Equivalence is preferable.
  - Non-inferiority, if justified.
The principles of Brazilian regulation for biological and biosimilar products are aligned with WHO recommendations;

Regardless of the regulatory pathway chosen to license a biological product in Brazil, RDC 55/2010 demands proof of quality, safety and efficacy of all products.
<table>
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<th>EMA (European Medicines Agency)</th>
<th>FDA (US Food and Drug Administration)</th>
<th>Health Canada</th>
<th>Anvisa (Agência Nacional de Vigilância Sanitária)</th>
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<tr>
<td>Individual countries in EU have adopted varying policies</td>
<td>US law allows FDA to designate a product as interchangeable. However, decisions about substitution by the pharmacy are governed by state laws</td>
<td>Health Canada doesn’t declare interchangeability for biosimilars</td>
<td>Interchangeability is under discussion. Currently, Anvisa only considers interchangeability after the review of the clinical data obtained for this purpose</td>
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Interchangeability – Brazil’s perspective

- The demonstration of interchangeability is not mandatory for the license of the biosimilar product;
- It is necessary to conduct specific clinical trials;
Extrapolation of therapeutic indications

- A sensitive test model has to be used, which has to be able to detect potential differences between the biosimilar and the comparator.

- The mechanism of action and/or involved receptor(s) must be the same.

- Safety and immunogenicity have to be sufficiently characterized.
Top 3 Challenges - Biosimilars

- Interchangeability

- Extrapolation of indications

- International non-proprietary name or INN
Post-approval changes

RDC 49/2011

Provides requirements for post-approval changes submissions of biological products and other provisions
Post-approval changes

RDC 49/2011

Post-approval changes classified by risk

- Level 1 change (minor change)
- Level 2 change (moderate change)
- Level 3 change (major change)
Level 1 Changes

Immediate implementation

Refer to changes that have no impact on product’s quality

Usually included in pharmacopoeia or do not imply the need for analysis of the molecular structure
### Level 2 Changes

- Require prior approval of ANVISA
- Refer to changes that may impact on product quality and to modifications of non-compendial methodologies
- May imply the need of molecular structure analysis
- Molecular analysis need to be robust to demonstrate that the change does not affect product quality
Level 3 Changes

- Require prior approval of ANVISA
- Refer to changes that have great chances to impact the molecular structure and/or that leads to the need of conducting clinical trials.
- Usually implies the need to perform a new molecular characterization.
- If analytical techniques indicate impact on the molecular structure or are insufficient to assess it: need for non-clinical and/or clinical trials.
Comparability Exercise Guideline
Guideline for elaboration of Clinical Study Reports – Biological Products

Guia para Elaboração de Relatórios de Estudos Clínicos para fins de Registro e/ou Alterações Pós-registro de Produtos Biológicos
Guideline for Non-clinical and clinical studies - Heparins
Developed by Comparability
Guideline for Non-clinical and clinical studies - Interferon Alpha
Developed by Comparability

Guia para realização de estudos não clínicos e clínicos para registro de alfainterferona como produto biológico pela via de desenvolvimento por comparabilidade
Guideline for transport qualification of biological products
Perspectives

- Review current guidelines
- Publish new guidelines
- Review current legal framework
- Strengthen international cooperation
THANK YOU