Biological Drug Products in Brazil

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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 Biological Products
Regulatory Acts Concerning Biological Products

- Labelling: 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
- Law 6.360/1976
- Decree 8.077/2013
- Marketing Authorization: RDC 55/2010
- Post-approval changes: RDC 49/2011
- Stability studies: RDC 50/2011
- Allergens: RDC 233/2005
- Probiotics: RDC 323/2003
- Pre-meeting submission: Ordinance 219/2015
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 Products
Current Regulation

**RDC 55/2010** – Marketing authorization of biological products.

- **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.
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 plan and risk minimization plan
Biological Products
Current Regulation

New Biological Product

Complete Dossier

Quality, Safety and Efficacy

Biological product

Stand Alone Pathway

Full registration dossier

Comparative Phase III clinical trials

Comparability Development Pathway

Comparability exercise
Quality, Safety, Efficacy

NON-INNOVATIVE BIOLOGICAL PRODUCTS

BIOSIMILARS
Comparability Development Pathway – Biosimilar Approach

Head-to-head comparison

- **Quality**
- **Non-clinical**
- **Clinical**

Comparability exercise: Quality, Efficacy and Safety.

- Physicochemical characterization
- Biological characterization
- Preclinical PK/PD
- Clinical

Confirmation of biosimilarity

Full registration dossier

Comparability Development Pathway

Current Regulation
## Regulatory requirements for the license of biological products in Brazil

<table>
<thead>
<tr>
<th></th>
<th>New Biological Products</th>
<th>Biological Products (not new)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Comparability</td>
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<tr>
<td><strong>CMC</strong></td>
<td>Needed</td>
<td>Comparative</td>
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<tr>
<td><strong>Pre-clinical</strong></td>
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<td><strong>Clinical 1 and 2</strong></td>
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<td><strong>Clinical 3</strong></td>
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<td>Comparative</td>
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<tr>
<td><strong>Immunogenicity</strong></td>
<td>Needed</td>
<td>Comparative</td>
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<tr>
<td><strong>Same comparator</strong></td>
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<td>Yes</td>
</tr>
<tr>
<td><strong>Risk management plan</strong></td>
<td>Needed</td>
<td>Needed</td>
</tr>
<tr>
<td><strong>Extrapolation</strong></td>
<td>Not applicable</td>
<td>Possible</td>
</tr>
</tbody>
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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 → 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.
Brazilian regulation for biological and biosimilar products is 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.
Individual countries in EU have adopted varying policies. US law allows FDA to designate a product as interchangeable. However, decisions about substitution by the pharmacy are governed by state laws. Health Canada doesn’t declare interchangeability for biosimilars. Interchangeability is under discussion. Currently, Anvisa only considers interchangeability after the review of the clinical data obtained for this purpose.
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

- Interchangeability

- Extrapolation of indications

- International non-proprietary name or INN (BQ – under discussion)
Biological Products
Current Regulation
RDC 49/2011

Provides requirements for post-approval changes submissions of biological products and other provisions
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 from 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 has to be sufficient to demonstrate that the change does not affect product quality
Level 3 Changes

Require prior approval from ANVISA

Refer to changes that have great chances to impact the molecular structure and/or that leads to the need of conducting clinical trials: major complexity

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
Guideline for Non-clinical and clinical studies - Heparin Development by Comparability
Guideline for Non-clinical and clinical studies - Interferon Alpha Development 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
Agência Nacional de Vigilância Sanitária – ANVISA
Gerência Geral de Medicamentos e Produtos Biológicos – GGMED
Gerência de Avaliação de Produtos Biológicos – GPBIO
Coordenação de Bula, Rotulagem e Medicamentos Clones – CBREM

NOTA DE ESCLARECIMENTO Nº 002/2016/GPBIO/CBREM/GGMED/ANVISA

OBJETO: Textos de bula de produtos biológicos desenvolvidos pela via de comparabilidade (biosimilares).

1. De acordo com a RDC 55/2010, os produtos biológicos (não novos) podem ser registrados pela via de desenvolvimento individual ou pela via de desenvolvimento por comparabilidade. Em ambos os casos, devem ser apresentados, nos dossiês de registro, os modelos de bula e embalagens primária e secundária, de acordo com a legislação vigente. Dessa forma, os textos de bula dos
Transparency

• Drug Approval and Refusal Letters

✓ Make drug letters available on Anvisa’s website.

✓ Anvisa’s reasons to approve or refuse a product.
Perspectives

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

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