Vaccine Regulatory Framework and Agency Modernization

Bernardo Luiz Moraes Moreira
Second Board – Assessor
ANVISA
Rio de Janeiro, 2019
Biological Products

➢ Vaccines;
➢ Hyperimmune sera;
➢ Blood products;
➢ Biomedicines classified as:
   a) medicines obtained from biological fluids or animal-originated tissue;
   b) medicines obtained through biotechnological procedures.
➢ Medicines containing live, attenuated or dead microorganisms;
➢ Probiotics;
➢ Allergens.
Regulatory framework

- RDC 47/2009 Package insert
- RDC 71/2009 Labelling
- RDC 234/2005 Quality control
- RDC 301/2019 GMP
- RDC 55/2010 Marketing Authorization
- RDC 49/2011 Post-approval changes
- RDC 50/2011 Stability
- RDC 46/2000 Blood products
- RDC 194/2017 Allergenics
- RDC 323/2003 Probiotics
- RDC 187/2017 Hyperimmune Sera
Regulatory framework

RDC n° 55/2010

New Biological Product: biological product containing a drug substance with a known biologic activity not yet licensed in Brazil → innovator product → reference product

(Non new) Biological Product: biological product containing a drug substance with a known biologic activity already licensed in Brazil.
Resolution RDC 55/2010

Marketing authorization of Biological Products in Brazil

- New Biological Product
  - Complete Dossier
  - Quality, efficacy and safety

- Biological Product
  - Stand Alone Pathway
  - Comparability Development Pathway
    - Complete Dossier
    - Comparative Clinical Trials
    - Comparability Exercise (Quality, safety and efficacy)

- Stand alone approach
- Biosimilars
Vaccines – General Requirements

➢ Immunobiological medicines containing one or more antigens, when innoculated are able to induce active and specific immunity in order to protect, reduce the severity or fight the diseases caused by the microorganism.

➢ GMP for all manufacturers issued by Anvisa.

➢ CMC Report

➢ Clinical Data Report

➢ Pharmacovigilance Report

➢ Package insert and label draft
Vaccines – CMC Report

➢ Description of manufacturers (cell bank, drug substance, intermediates, drug product)

➢ History of product development

➢ Manufacturing (manufacturing summary, IPC, equipments, critical steps, batch size, validation report for critical steps)

➢ Quality Control (tests and specifications DS – DP, analytical method validation, reference standards)

➢ Transport validation

➢ Excipients (QC tests and specifications, preservative efficacy, physical-chemical interaction with API)

➢ Stability protocol and report

➢ Impurities characterization and specification; adventitious agents evaluation for starting materials
Vaccines – Specific Requirements

➢ Strains – origin, identification, attenuation process, certificate of analysis.

➢ Master and working seed lot – origin, identification, characterization, stability, adventitious agents.

➢ Master and working cell banks – beside MSL and WSL requirements, passage number definition.

➢ Embryonated eggs – origin, identification and certificate of analysis.

➢ Maximum in vitro age determination.

➢ Manufacturing process and Quality control of carrier protein.

➢ Description of conjugation and inactivation process.
Pre-submission Meeting → Electronic or manual submission → Individual review → External expert

Final opinion and decision letter

ACCEPT

REJECT

Applicant’s response

List of questions
Post-approval changes and stability

- Resolution RDC 49/2011
  Stablishes requirements and procedures for post-approval changes of Biological Products

- Resolution RDC 50/2011
  Stablishes requirements and procedures for stability studies of Biological Products

Under review
Resolution on Stability (RDC 50/2011)

✓ Objectives:

- Update the procedures and conditions for conducting stability studies of biological products;
- Alignment with Q5C principles and other complementary guidelines.
Resolution on Stability (RDC 50/2011)

✓ References:

- ICH - Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products - Q5C
  - ICH - Stability testing of new drug substances and products - Q1A(R2);
  - ICH - Stability testing: photostability testing of new drug substances and products – Q1B;
  - ICH - Bracketing and matrixing designs for stability testing of new drug substances and products - Q1D;
  - ICH - Specifications: test procedures and acceptance criteria for biotechnological/biological products - Q6B;
  - ICH - Validation of analytical procedures: text and methodology - Q2(R1);
  - CPMP - Note for guidance on in-use stability testing of human medicinal products.
Resolution on Stability (RDC 50/2011)

✓ Main topics

- Stability protocol;
- Long term stability (conditions);
- Accelerated/stress stability (conditions);
- Photostability (conditions);
- Cycling studies (conditions);
- In use stability;
- Stability requirements for marketing authorization application (DS, intermediates, diluents, adjuvants, reference standards, DP).

* Stability for post-approval
Resolution on Post-approval changes

✓ Objectives:

• Update procedures, data requirements and categorization for post-approval changes of biological products of RDC 49/2011;

• Alignment with WHO guideline for changes to approved biotherapeutic products and other complementary guidelines.
Resolution on Post-approval changes

✓ Main references:

- Guidelines on procedures and data requirements for changes to approved biotherapeutic products – WHO 2017;
- Guidelines on procedures and data requirements for changes to approved vaccines - Annex 4 WHO Technical Report Series No. 993, 2015;
Resolution on Post-approval changes

Main topics

- Quality changes: refer to CMC changes (manufacturing process, quality control testing, equipment, facility, product composition, stability)

  - Drug Substance (manufacture, control, reference standards, container closure system, stability)

  - Drug Product (description and composition, diluent, adjuvant, manufacture, control, reference standards, container closure system, stability)
Resolution on Post-approval changes

Main topics
- Safety and Efficacy and Labelling changes:

Refer to changes that have an impact on the clinical use of the biological product (e.g., addition or expansion of a safety or efficacy claim, including expansion of the population; change in the route of administration; change in the recommended dose/dosing range; co-administration with other biotherapeutic products or medicines; changes that have the potential to improve the risk management measures (e.g., new adverse events, instructions on dosing, deletion or reduction of contraindications).
Resolution RDC nº 204, December 27th, 2017

• Focus on prioritizing drug registrations relevant to public health

• Highlights:
  • Pediatric population;
  • Neglected diseases;
  • Emerging or reemerging diseases;
  • Public Health Emergencies;
  • Serious debilitating conditions;
  • Vaccines to be incorporated in the National Immunization Program;
  • First 3 new generics for a given drug.
Resolution RDC nº 204, December 27th, 2017

• Focus on prioritizing post-approval changes for:
  • Rare diseases;
  • Pediatric population;
  • Neglected diseases;
  • Emerging or reemerging diseases;
  • Public Health Emergencies;
  • Serious debilitating conditions;
  • Vaccines to be incorporated in the National Immunization Program.
Resolution RDC nº 204, December 27th, 2017

- Timelines for the final decision:
  
  - 120 days - registration (365 days for ordinary category);
  
  - 60 days - post-approval changes (180 days for ordinary category);
  
  - 45 days - clinical trial submissions (90 days for ordinary category)
Resolution RDC n° 205, December 28th, 2017

✓ Establishes special procedures for clinical trials, GMP certification and registration of new drugs.

✓ Applies to medicines for rare diseases used in serious debilitating conditions and proposed to change in a clinically significant way the evolution of the disease or make possible the remission of the disease.
Drugs for Rare Diseases

Resolution RDC nº 205, December 28th, 2017

✓ Faster procedures;

✓ Differentiated criteria compared to conventional procedures, but not compromising safety, efficacy and quality (eg. CTD format, suppression of quality control in Brazil, ongoing stability studies, ongoing phase III clinical trials);

✓ Stimulate the conduction of clinical trials and the license of medicines for rare diseases.
## Drugs for Rare Diseases

RDC nº 205/2017 - timelines

<table>
<thead>
<tr>
<th>Category</th>
<th>Anvisa</th>
<th>Company</th>
<th>Anvisa</th>
<th>Analysis of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial Consent</td>
<td>30 days for first analysis</td>
<td>30 days for reply</td>
<td>30 days for analysis of</td>
<td>45 days</td>
</tr>
<tr>
<td></td>
<td>Anvisa</td>
<td>Company</td>
<td>response</td>
<td></td>
</tr>
<tr>
<td>Certificate of Good Manufacturing Practices</td>
<td>120 days for publishing the</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>decision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>60 days for first analysis</td>
<td>30 days for reply</td>
<td>45 days for analysis of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anvisa</td>
<td>Company</td>
<td>response</td>
<td></td>
</tr>
<tr>
<td>Pricing</td>
<td>Company: protocol concomitant with the registration request</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercialization</td>
<td>Company: 365 days after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>publication of the registration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In 2018, Anvisa had authorized 827 drug registrations.

173 priorizations were granted.

10 new medicines for rare diseases.
Timelines for registration of prioritized drugs in 2018

Prioritized Biologicals

- Backlog time: 45
- Anvisa time: 21
- Company time: 134

Prioritized New Synthetic

- Backlog time: 110
- Anvisa time: 61
- Company time: 210
Refinement initiatives
OS Nº 45, February 2018 (Service Orientation)

➢ Establishes a Optimized Review Pathway for Biological Products (registration and variations/post approval changes);

➢ Eligibility criteria: Registered in the USFDA and EMA; same indications; dosage; adverse reactions; precautions.

➢ Approval Reports should be provided
Transparency

- Drug Approval and Refusal Letters
  - Make drug letters available on Anvisa’s website.
  - Anvisa’s reasons to approve or refuse a product.
Search for the information available on Anvisa's website

- Authorized drugs
  http://portal.anvisa.gov.br/medicamentos/consultas

- Public assessment reports
  http://www.anvisa.gov.br/datavisa/Fila_de_analise/index.asp

- Product’s prescribing information
  http://portal.anvisa.gov.br/bulario-eletronico1

- Clinical trials authorized

- Anvisa’s legislation
  http://portal.anvisa.gov.br/legislacao/

- Regulatory agenda 2017-2020
  http://portal.anvisa.gov.br/2017-2020
• License of less complexity biological products;

• Review of resolutions for stability studies and post-approval changes of biological products;

• Timelines for license renew;

• Stability studies for synthetics;

• Implementation of the common technical document (CTD) for medicines registration.

• Implementation of Quality System for Biological Products in accordance with Good Revision Practices;
ANVISA

Goals

- Transparency
- Predictability
- Shared responsibility
- Regulatory convergence
- Scientific and technical rational
Thank you

diretoria2@anvisa.gov.br

http://portal.anvisa.gov.br/english