DCVMN Annual General Meeting

# Vaccine Regulatory Framework and Agency Modernization

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**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

Law 6.360/1976
Decree 8.077/2013

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

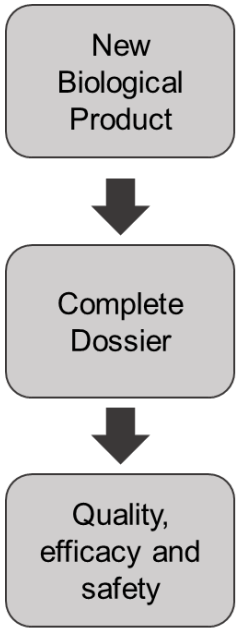
New Biological Product: biological product containing a drug substance with a known biologic activity not yet licensed in Brazil → innovator product → reference product

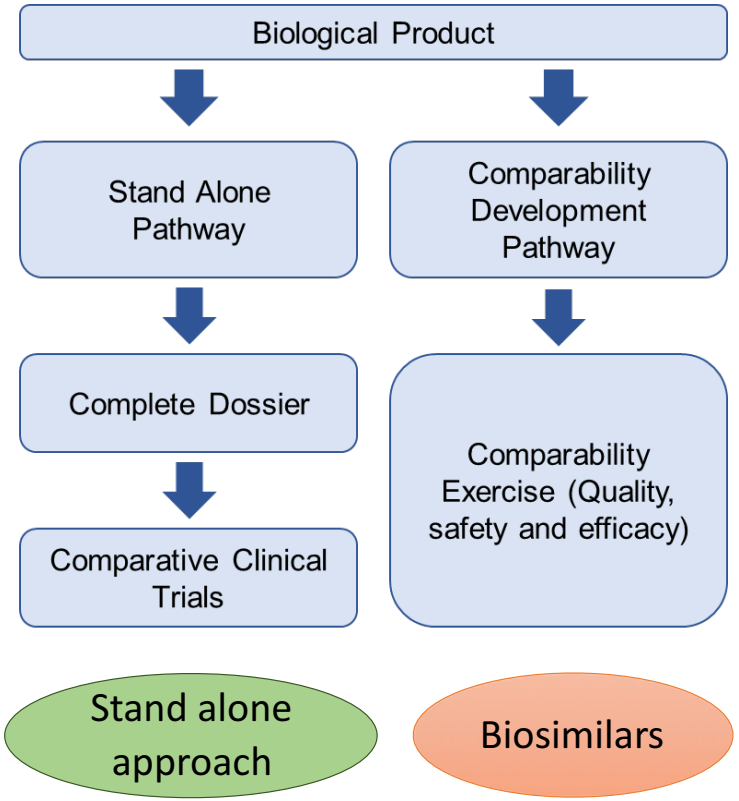
(Non new) Biological Product: biological product containing a drug substance with a known biologic activity already licensed in Brazil.

# Regulatory framework

- Resolution RDC 55/2010

Marketing authorization of Biological Products in Brazil



# ines – 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

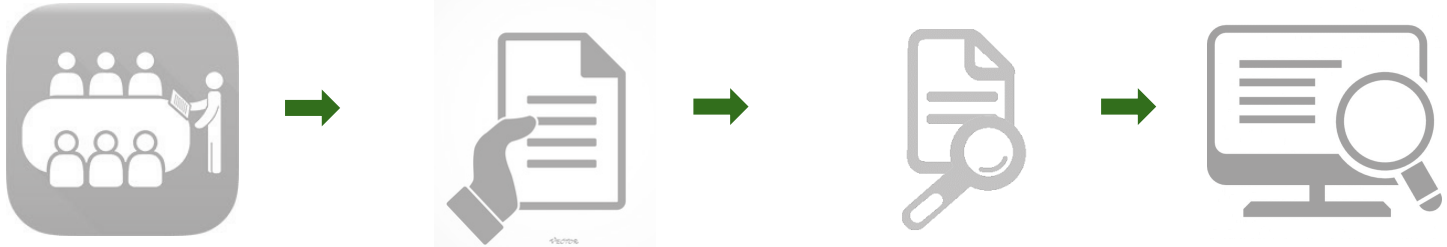
# ines – CMC Report

- 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, analythical 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

# ines – Specific Requirements

- Strains – origin, identification, atenuation 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 inativation process.

# Review process for market authorization



Pre-submission Meeting

Electronic or manual submission

Individual review

External expert

List of questions

Applicant's response

ACCEPT REJECT

Final opinion and decision letter

# 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;
- Guidance Document Post-Notice of Compliance (NOC) Changes: Quality Document - Appendix 3: Quality Post-NOC Changes (Biologics), Health Canada 2016;
- Guidance Document Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document, Health Canada 2018.

# 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).

# Prioritization

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.

# Prioritization

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.

# Prioritization

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)

# Drugs for Rare Diseases

Resolution RDC nº 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

Clinical Trial Consent
Anvisa: 30 days for first analysis
Company: 30 days for reply
Anvisa: 30 days for analysis of response

Certificate of Good Manufacturing Pratices

Anvisa: 120 days for publishing the decision

Registration
Anvisa: 60 days for first analysis
Company: 30 days for reply
Anvisa: 45 days for analysis of response

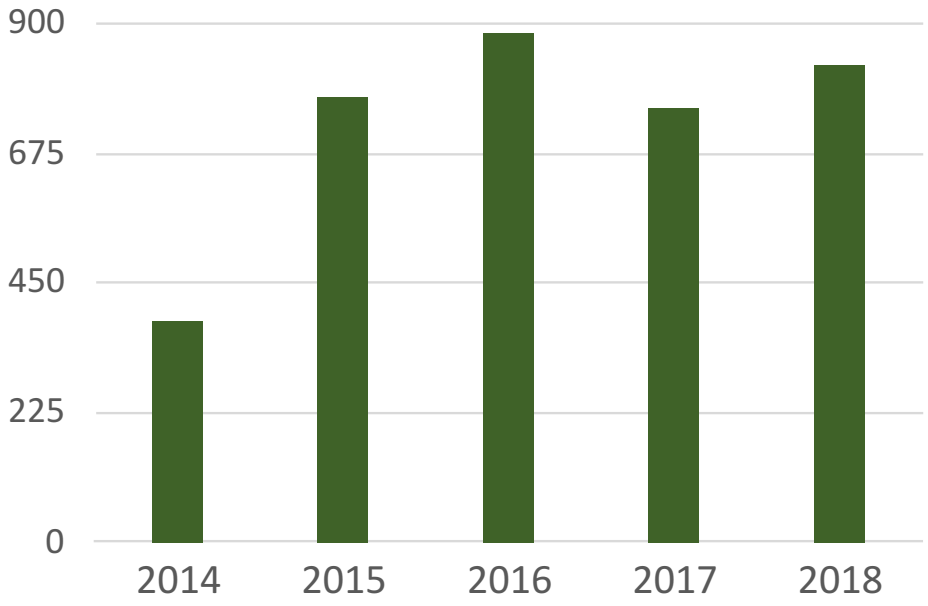
Pricing

Company: protocol concomitant with the registration request

Commercialization

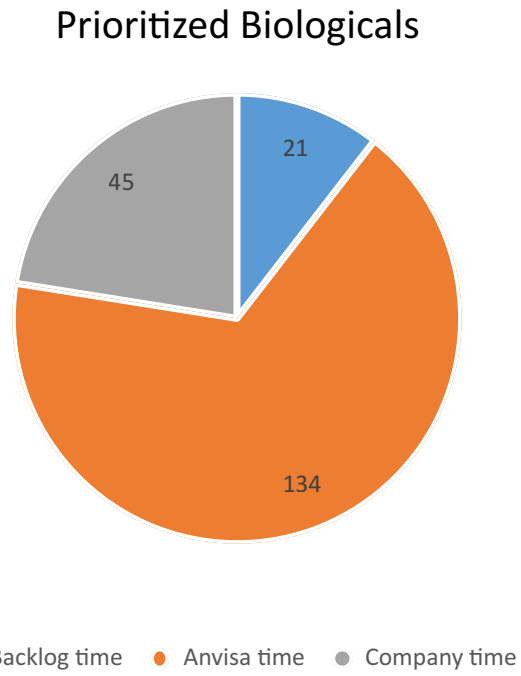
Company: 365 days after publication of the registration

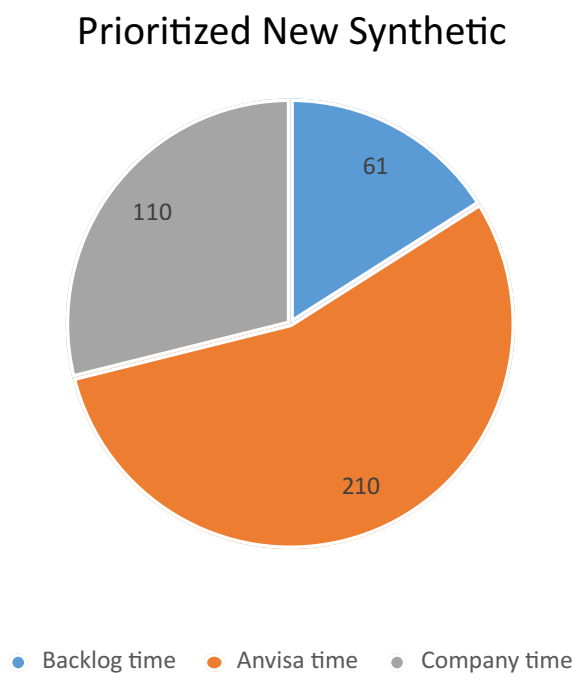
# Registrations granted




- 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



# Refinement initiatives

# Reliance Projects

OS Nº 45, February 2018 (Service Orientation)

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

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

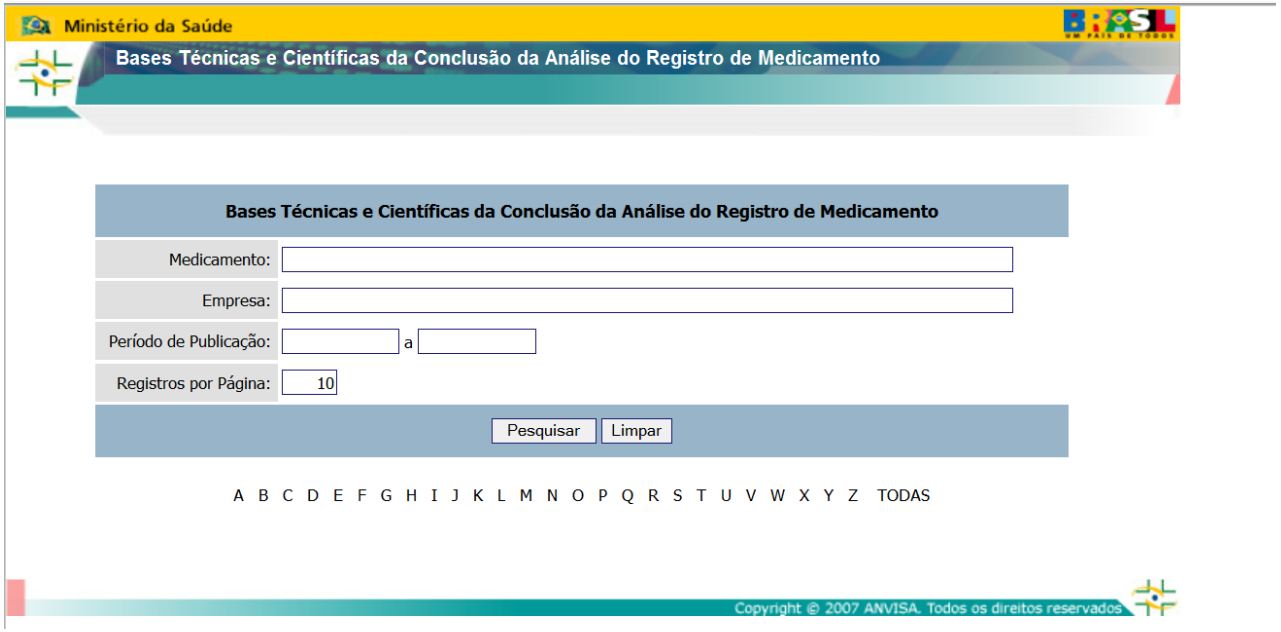
- Approval Reports should be provided

# Transparency

- Drug Approval and Refusal Letters

✓ Make drug letters available on Anvisa's website.

✓ Anvisa's reasons to approve or refuse a product.



# Transparency

## Search for the information available on Anvisa's website

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

Clinical trials authorized
http://www7.anvisa.gov.br/Datavisa/Consulta_Comunicados/Consulta_CE_Autorizados.asp

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

Anvisa's legislation
http://portal.anvisa.gov.br/legislacao#/

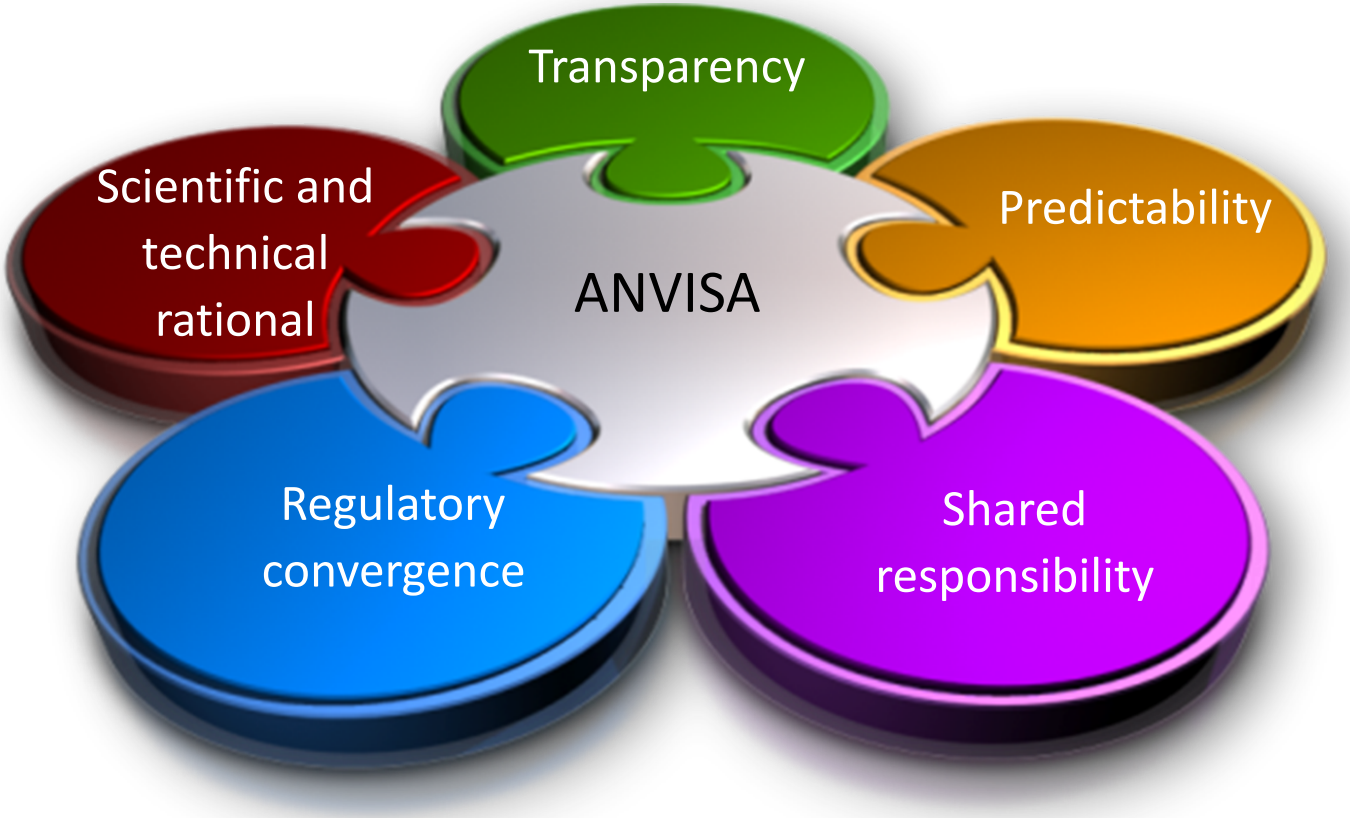
Product's prescribing information
http://portal.anvisa.gov.br/bulario-eletronico1

Regulatory agenda 2017-2020 http://portal.anvisa.gov.br/2017-2020

# Perspectives

- 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;

# Goals


Transparency
Scientific and technical rational
ANVISA
Predictability
Regulatory convergence
Shared responsibility

# Thank you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