



Brazilian Health Regulatory Agency



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Medicinal Products Regulation in Brazil

Recent Regulatory Update and Regulatory Progress
for Promoting Cutting-edge technology

4th Brazil-Japan Seminar of Regulations
on Pharmaceuticals and Medical Devices



Medicinal Products Outline

- RDC 200/2017 – inclusion of some types of innovation
- RDC 204/2017 – Priority Pathway
- RDC 205/2017 – Special procedure for rare diseases
- Cases in clinical research and registration

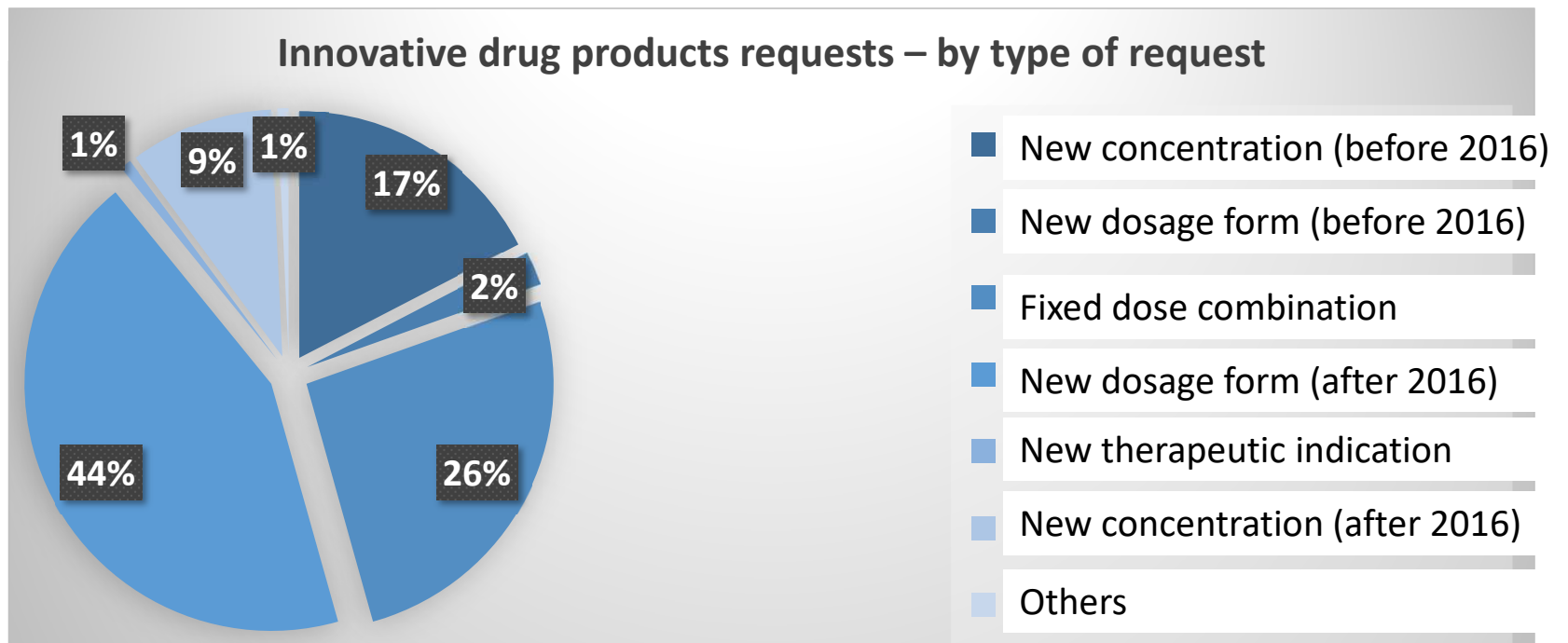


RDC 200/2017– innovative drug products

- Radical innovation (new molecule) – new drug
- Incremental innovation (improvements in a drug that already exists)
- Innovative drug product: drug with some improvements – may include new salts, esters, isomers, etc.
- Clear criteria and flexibility for registration of innovative drug products



RDC 200/2017 – innovative drug products



Almost 80% new concentration / new dosage form



RDC 204/2017 – Priority Review Pathway

Eligibility criteria

- Emergent or neglected disease – significant improvement in treatment
- Vaccine for National Immunization Programme
- New or innovative drug product, API manufactured in Brazil
- Public Health Emergencies and shortages
- First Generic

Timelines

- Registration: 120 calendar days (cd) Agency time/clock stops (vs. 365 days regular pathway)
- Variations / Post-approval changes: 60 cd Agency time/clock stop (vs. 180 days regular pathway)
- Clinical trial authorization: 45 cd first evaluation (vs. 90 or 180 days regular pathways)



RDC 204/2017 – Priority Pathway

Number of requests 2018

- Approximately 40 registrations (in process + finalized)
- e.g. new drugs to treat several cases of cancer, vaccine for influenza in elder patients, first generics
- 5 cases of misuse of the pathway for registration (request denied, did not fulfill eligibility criteria - should be regular pathway)

Response time

- Timelines were accomplished in all cases
- Generally 1 deficiency letter required (120 days for sponsor's response), totalizing 240 days from request to final response
- In some cases 2 deficiency letters were required, impacting in a longer final review time
- Approval before FDA and EMA in 2 cases (new therapeutic indication – daratumumab and pembrolizumab)
- Approval before EMA in 1 case (new therapeutic indication Yervoy + Opdivo combination)
- In general, it is possible to approve a few days or few months after FDA and EMA (depending on submission time by sponsor)



RDC 205/2017 – Special Procedure – rare diseases

Flexibility in technical requests

- On going stability studies
- Finished Phase II + on-going Phase III

Timelines

- GMP certification: 120 cd
- Registration: 60 cd first evaluation + 30 cd sponsor's response + 30 cd final decision
- Clinical trial authorization: 30 cd first evaluation + 30 cd sponsor's response + 45 cd final decision



RDC 205/2017 – Special Procedure – rare diseases

Submission format

- CTD format
- Encourages submission of the same dossier in different regions

Sponsor's responsibility

- Pre-submission meeting to be scheduled
- Submissions in Brazil part of the first wave



RDC 205/2017 – Special Procedure – rare diseases

Number of requests 2018

- Approximately 20 registrations (in process + finalized)
- e.g. new treatments for Spinal muscular atrophy (SMA), Sly Syndrom, some rare cancers, etc.
- Pre-submission meetings are mandatory to align concepts and avoid pathway misuse
- Sponsors informed that the number of requests will increase in 2019

Response time

- Lead time accomplished by sponsors and by the Agency
- In some cases, written post-approval commitments required



Cutting-edge technology and clinical research

Some clinical trials regarding Advanced Therapies already submitted in Brazil

Need for extensive training and information exchange with sponsor and other agencies

New clinical studies and registration submissions expected to 2019

Challenging points to analyze in research and in registrations (e.g. control strategy, manufacturing, study models, inclusion criteria)



Cutting-edge technology – Nanotechnology-based drugs

Internal Discussion Group created

Complex evidences required

Difficult to establish harmonized procedure

Nanotechnology product submitted (in evaluation)

Challenge: regulation of nanotechnology products



Cutting-edge technology in Quality / CMC

- Continuous manufacturing – 1 post-approval variation and 1 new registration approved with this technology
- Need to update concepts and regulation
- Resolutions particularly impacted: RDC 73/2016 (post-approval variations) and RDC 17/2010 (GMP)
- It also involves paradigm-shifting changes in analytical procedures and concept of quality control analysis



Brazilian regulatory system for advanced therapy medicinal products ATMPs

Office of Blood, Tissues, Organs and Cells– **GSTCO**
Directorate of Authorization and Registration- **Diare**
Brazilian Health Regulatory Agency - **Anvisa**

Brasília, nov. 2018





Project Brazilian Regulatory Framework for ATMP

ATMP: Substantially manipulated cells or tissues or innovation in original function (not intended to be used for the same essential function)

Advanced Cell Therapy

Gene Therapy *ex vivo*

Tissue engineered product

Cell Products

Somatic cell products

Cell products w/ recombinant nucleic acid

Cell engineered in tissues products

Biologic Products

Therapeutics recombinant gene products

Gene Therapy *in vivo*

Good Cell Practices
Resolution n°214, feb.2018



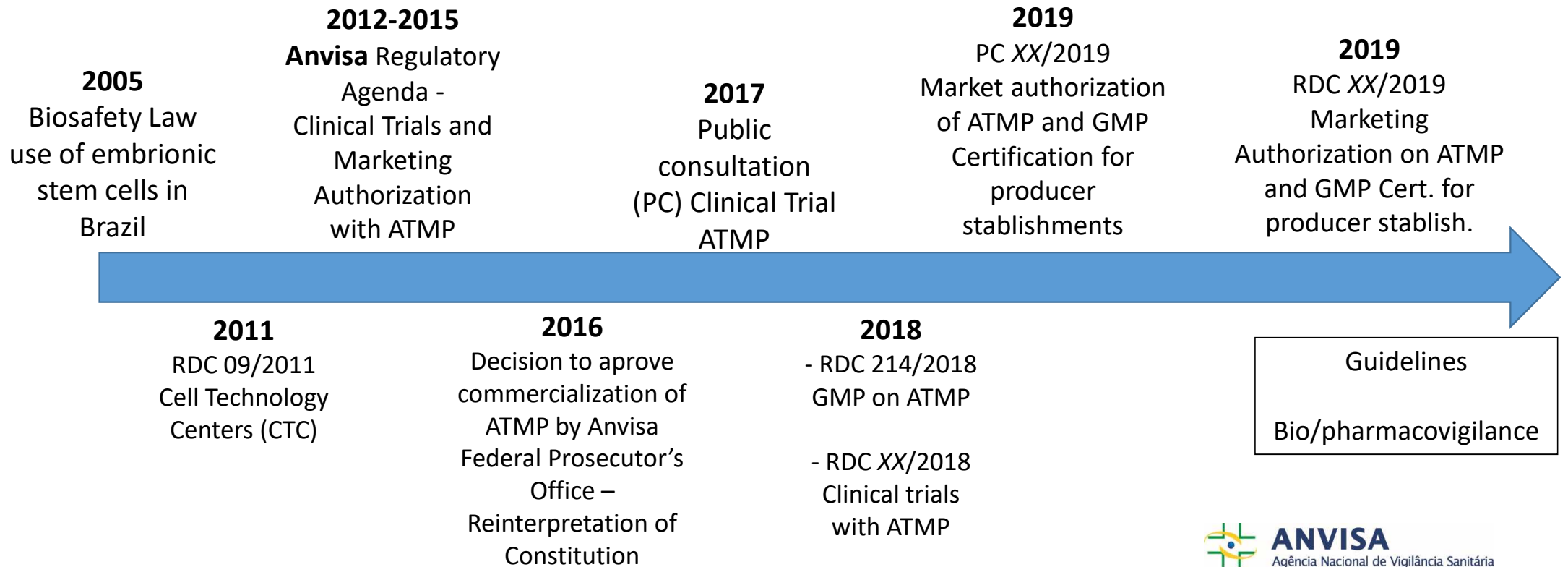
Brazilian Regulatory Framework for ATMP

Classification of ATMP (early development) – Anvisa supported by Brazilian CAT (Committee for Advanced Therapies)

| ATMP CLASS I Minimal manipulation with innovation in original function | ATMP CLASS II Substantial manipulation |
|---|---|
| <p>Clinical Trials application (Simplified)</p> <p>Main concerns - Safety and Efficacy</p> <p>Automatic start studies, based on submission application</p> <p>Approval by Ethics Committee (CONEP)</p> <p>Monitoring by risk-based inspection program</p> | <p>Clinical Trials application (Complete)</p> <p>Main concerns – Safety, Quality and Efficacy</p> <p>Approval of Anvisa to start studies</p> <p>Approval by Ethics Committee (CONEP) and Biosafety Commission (CTNBio)</p> <p>Monitoring by risk-based inspection program</p> |



Brazilian Regulatory Framework for ATMP UPDATES





Regulatory Progress for Promoting Cutting Edge Technology

❖ Rules to accelerate the approval process: **rare disease products**, **priority products** for the Public Health System and also for **special situations** in the absence of therapeutic alternatives.

❖ Providing a reflection on the traditional regulatory instruments for medicines and health products. For ex.:

- conditional marketing authorization
- simplification of process analysis
- approving clinical trials based on risk assessment

❖ Opportunities

- Develop Guidelines (Standards)
- Regulatory environment for ATMPs, worldwide, is dynamic and complex
- International harmonization of regulatory approaches
- Continual need to have current regulatory intelligence
- Early, frequent and appropriate interaction between regulatory agency and researchers/producers is highly recommended



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Medical Devices Regulation in Brazil

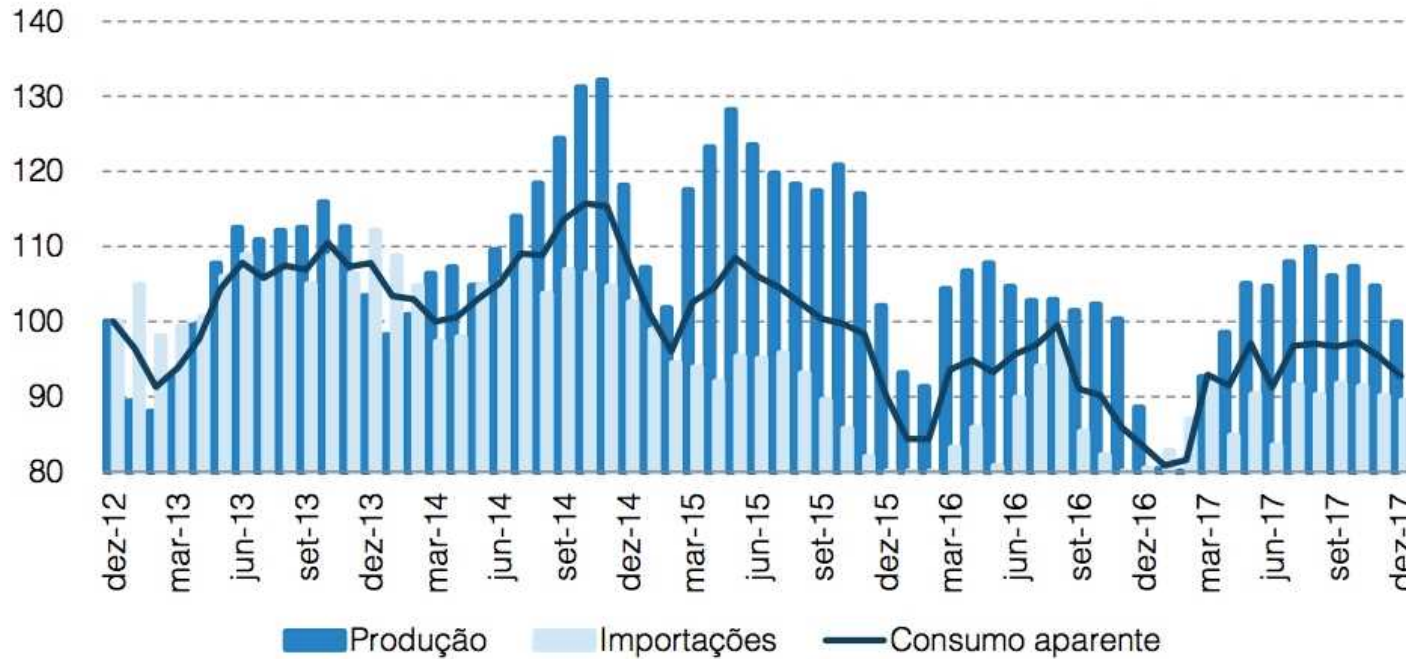
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LEANDRO RODRIGUES PEREIRA
GENERAL MANAGER
MEDICAL DEVICES OFFICE



MEDICAL DEVICES MARKET IN BRAZIL



MD market in Brazil in 2017

- USD 9.1 billion
- 134,400 jobs (industry + commerce)
- After two years of retraction, the medical device sector has grown again.



MEDICAL DEVICES REGULATION

Federal Law and Decrees

- **Act 6360/1976** – Legal provision for product registration
- **Act 6437/1977** – Sets violations of federal health legislation and establishes their respective sanctions
- **Act 8080/1990** – Defines the Unique Health System
- **Act 9782/1999** – Establishes Anvisa's roles and responsibilities, defines the National Health Surveillance System
- **Decree 8077/2013** – Replaces Decree 79094/1977 – Interpretation of Act 6360/1976





MEDICAL DEVICES REGULATION

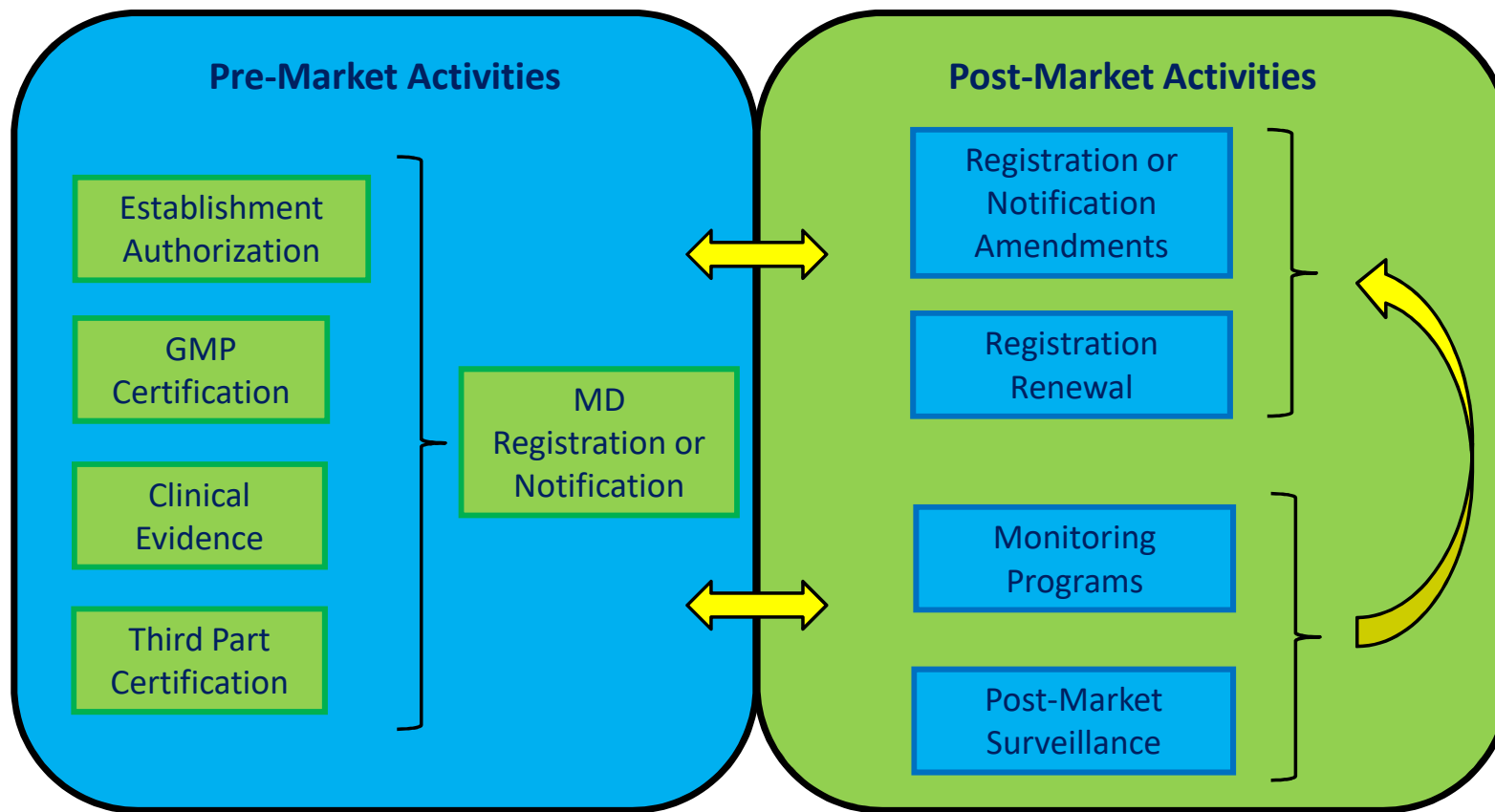
Main RDC's for MD

- **RDC 185/2001** – Premarket approval process for medical devices (non-IVDs)
- **RDC 36/2015** – Premarket approval process for IVDs
- **RDC 56/2001** – Essential Requirements of Safety and Effectiveness
- **RDC 16/2013** – Good Manufacturing Practices Requirements for MD
- **RDC 40/2015** – MD Notification (non-IVDs)
- There are also other RDCs which defines additional requirements for specific devices





OVERVIEW OF THE REGULATORY SCHEME





MEDICAL DEVICE PREMARKET REVIEW AND APPROVALS

RDC ANVISA 185/2001; 40/2015; 36/2015

- There are two types of premarket applications:
- **Cadastro** (classes I and II)
 - No renewal
 - Simplified technical dossier
 - GMP must be followed (no need for certification)
- **Registo** (classes III and IV)
 - Valid for 10 years (updated regulation in 2018)
 - Must be renewed
 - Full technical dossier must be submitted
 - GMP certification is required
- Submitted by domestic manufacturer or importer (this last, on behalf of the foreign manufacturer)
- GMP Certification shall be obtained before registration final decision
- For both cases an authorization number is issued

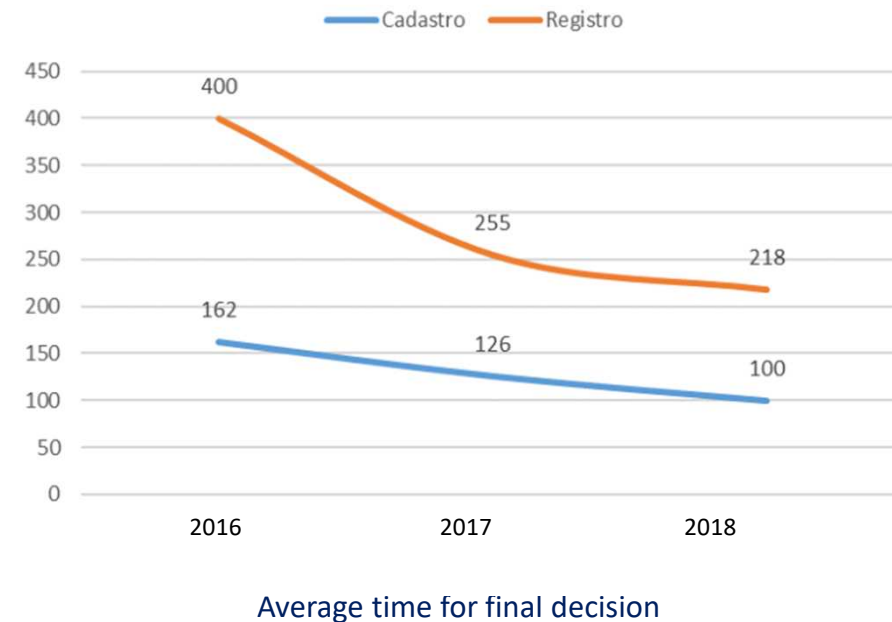




TIMEFRAMES AND FEES

RDC ANVISA 185/2001; 40/2015; 36/2015

- **Cadastro** (classes I and II)
 - Approximately 45 days for first assessment
 - Approximately 100 days on average from submission to final decision
 - Fee USD 50 - 500, depending on the revenue (size) of the applicant company
- **Registro** (classes III and IV)
 - Approximately 45 days for first assessment
 - Approximately 218 days on average from submission to final decision
 - Fee USD 300 - 6000, depending on the revenue (size) of the applicant company





LABELLING REQUIREMENTS

- Requirements for labelling of nIVD's are established on RDC 185/2001 and of IVD's on RDC 36/2015
- All labelling must be in Portuguese
- For imported devices it is allowed the importation without labels in Portuguese. However, all labels and companion documents must be translated into Portuguese before distribution
- E-labelling is allowed according to requirements of IN 4/2012, except for some types of devices (e.g. the ones indicated for domestic use and/or operation by lay user)



GOOD MANUFACTURING PRACTICES REQUIREMENTS

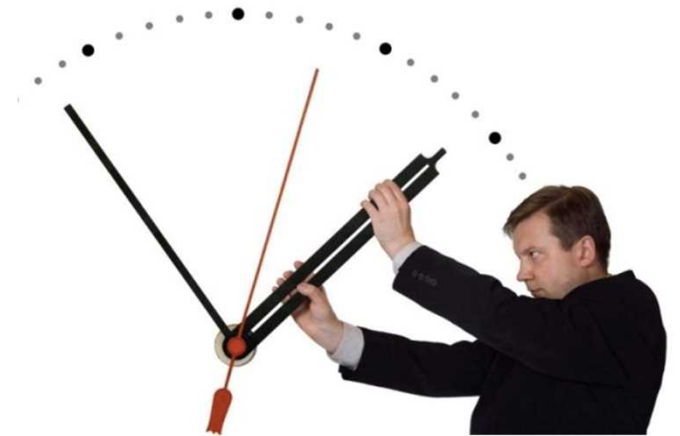
- **GMP certificate** is required for registration of class III and class IV medical devices
- GMP rules are provided on **RDC 16/2013** – Mercosur harmonization
- Using a **MDSAP audit report** the Anvisa GMP certificate can be issued around 3 months after submission
- Fee USD 19,500 for international manufacturers
- Fee USD 375 - 7000 for national manufacturers (depends on the company's revenue)
- GMP audit reports from other Regulatory Authorities (agreements) or from recognized Auditing Organizations may be used to issue Anvisa GMP certificate – **RDC 183/2017**





EXTENSION OF REGISTRATION VALIDITY

- Products subject to **registration** (classes III and IV)
- Before January 2018 – registration valid for 5 years
- Publication of **RDC 211/2018**
- Extension of all registered medical devices by 5 years
- New registered products – **Registration valid for 10 years**
- **Same requirements for renewal, including fees**





CUSTOM MADE MEDICAL DEVICES

- Public Consultation n° 546/2018- Closed

Elements of the new regulatory for custom-made and patient-specific devices include:

- Manufacturers of Class III and IV devices must have valid Brazilian Good Manufacturing Practice (BGMP) certifications;
- Manufacturers or importers of custom-made devices must provide annual reports to ANVISA detailing all products imported and/or manufactured for sale in Brazil;
- All ANVISA medical device vigilance and safety requirements are applicable to custom-made devices;
- Companies must provide traceability labels as part of regulatory compliance.



NATIONAL IMPLANT REGISTRY (RNI)



- ANVISA has launched the National Implant Registry (RNI) on may/2018.
- The online system will initially collect voluntary registration information on surgical procedures for hip and knee prostheses, and coronary stents.
- Resolution RDC n° 232/2018- Mandatory bar code (UDI standard) into patient cards of cardiovascular stents, hip and knee prostheses.



OTHER ONGOING INITIATIVES



- Public consultation [CP 528/2018](#) – Change low risk medical devices (class I) regulation
- Adoption of ISO 15197:2013 requirements for Glucosemeters assessments – [IN 24/2018](#)
- Update of medical devices classification rules – Proposal to Mercosur under discussion - Almost identical to the European classification (GHTF basis)
- Development of regulation for Software as Medical Device
- Development of an electronic submission platform (web based) for medical devices registration- Preparation for Regulated Product Submission (RPS - IMDRF)



THANK YOU!

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