FUKUMA
ADVOGADOS & CONSULTORES

Drug & Device Development & Approval Process

September 25th, 2018.

Fukuma Presentation

- ❑ Founded in 2002.

- ❑ Focused on:
- ✓ Sanitarian regulatory (ANVISA, local health agency – VISAs and MAPA);
- ✓ Biotechnology (CTNBio).

- ❑ Market segments:
- ✓ Drugs;
- ✓ Medical devices;
- ✓ Food;
- ✓ Cosmetics.

Fukuma Presentation

MAIN OBJECTIVE - support, not only on administrative and/or legal proceedings, but especially on preventive measures, by assisting companies on:

- Applicable rules;

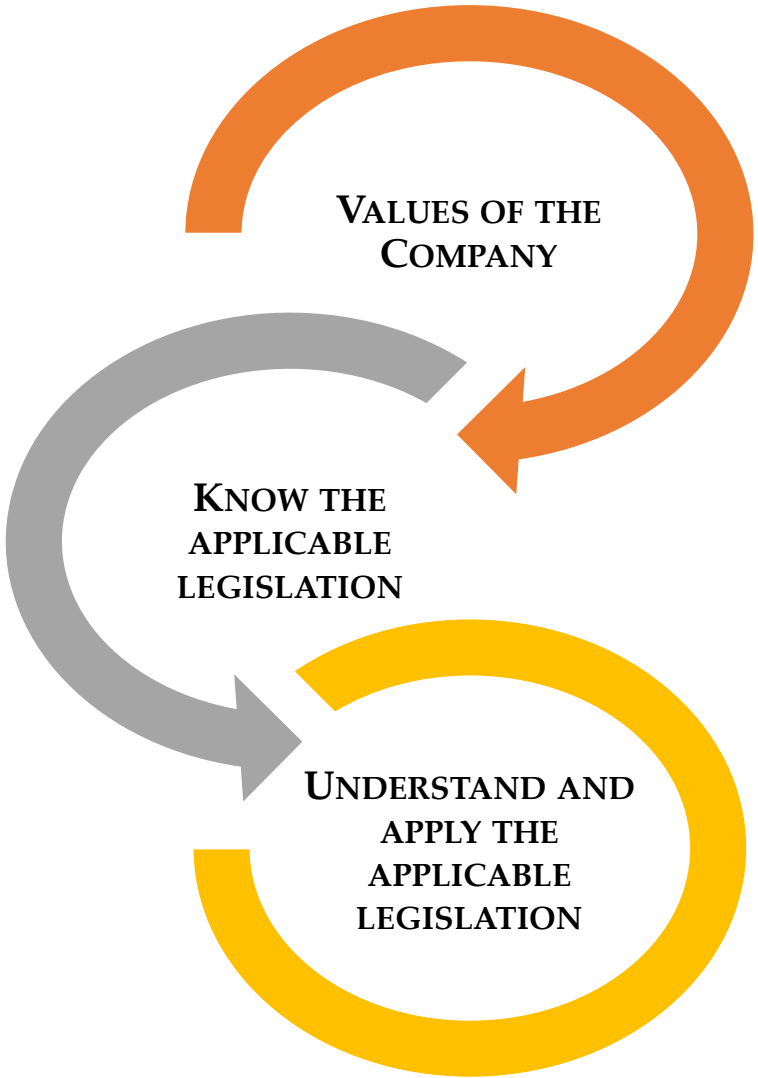
- Sanitary due diligence;

- Procedures to regularize products and companies from a sanitary perspective;

- Requirements issued by ANVISA, VISAs, MAPA and INMETRO;

- Elaboration of legal memorandums;

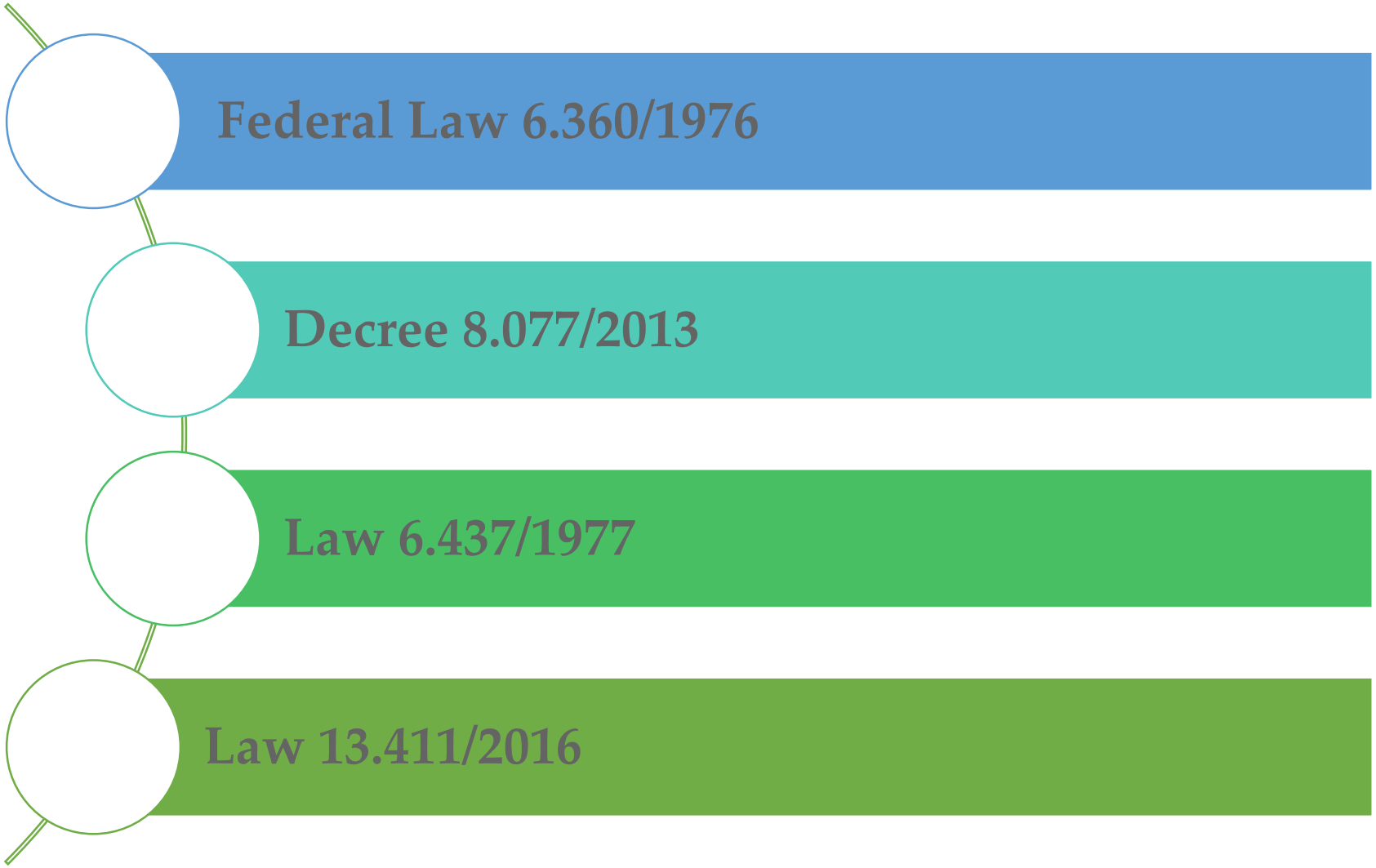
COMPLIANCE



ALIGNMENT OF THESE POINTS = COMPLIANCE

We strongly believe that being in compliance is a value, a commitment of the company, showing responsibility to and with the consumers. Building a strong image is less costly than solving problems for not being in compliance.

Main Laws for Drugs and Medical Devices in Brazil



Main Laws for Drugs and Medical Devices in Brazil

Federal Law 6.360/1976

- Pharmaceutical products, APIs, medical devices, hygiene and cosmetics and sanitizing products;
- Sets forth rules for production, commercialization, advertising, labelling, inspection, quality control, penalties, importation and marketing authorizations.

Decree 8.077/2013

- Decree: regulates the above mentioned law.

Main Laws for Drugs and Medical Devices in Brazil

Law 6.437/1977

- Sets out the penalties applicable upon the violation of the sanitary laws and regulations, including criminal sanctions.

Law 13.411/2016

- Changes some articles of Law 6.360/1976, establishing new rules for medicine registration renewals and timings for ANVISA's evaluation, among others.

ANVISA – Brazilian Health Regulatory Agency

ANVISA
AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

- ANVISA was created by Law 9.782/99;
- Governmental regulatory agency with its administrative independence, financial autonomy and the stability of its directors;
- Connected to the Ministry of Health;
- Ruled by a Collegiate Board of Directors composed of 5 members;
- Holds police power;

ANVISA – Brazilian Health Regulatory Agency

ANVISA
AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA

- Primary goal: to protect and promote public health, by exercising health surveillance over products and services, including processes, ingredients and technologies that pose any health risks;

- Responsible for health control in ports, airports and borders and for establishing relations with foreign organisms and institutions that deal with international affairs comprising health surveillance.

Sanitary Licensing

- **Sanitary License:** private act under the competence of the States, Federal District and of the Municipalities, containing the permission for the premises to operate and to perform activities subject to the sanitary surveillance set forth in Law 6.360/1976, upon evidencing the compliance with certain specific technical and administrative requirements;

- **Federal Authorization**: private act under the competence of ANVISA (obliged for the sanitary surveillance of the products that are provided for in the legislation), containing the permission for the companies to perform activities subject to the sanitary surveillance set forth in Law 6.360/1976, upon evidencing the compliance with certain specific technical and administrative requirements (AFE/AE);

- **Sanitary Inspection:** technical proceeding conducted by the sanitary authority at the premise or on equipment, which are subject to sanitary surveillance. It is aimed to monitor and intervene in activities that may result in health risk. It can be performed by the sanitary authority or requested by the interest third party. Term to be conducted depend on the local sanitary authority.

SANITARY LICENSING

- **Company's Enrollment** – inclusion of company's data, legal responsible and technical responsible within the ANVISA's system;
- **AFE – Federal Authorization**: for all products, except for food;
- **AE – Special Authorization**: controlled medicine/raw material;
- **Company's Size** – classification of the company with the aim to obtain discounts in the applicable fees: Big (I and II); Average (III and IV); EPP and Micro. Initially, it is an assumed classification. Annually, the adequation is based on the income tax declaration and in the corporate document/certificate;
- **Risks**: classification by activity:
  - High Complexity – manufacturing;
  - Low Complexity – food retail.
- **GMP (biannual)** – National or international manufacturer (medicine and medical devices);

SANITARY LICENSING

❑ **COMPANY MUST HAVE:**

✓ **Corporate Purpose** within the Articles of Organization - activities subject to sanitary surveillance (with aligned CNAES - activity economic codes);

✓ Appointed **technical responsible – TR** (pharmacist is mandatory for the drug segment);

✓ Register the company and the TR before the **Professional Council**; and

✓ Obtain a **positive inspection report** from VISA evidencing that the company has technical and operational capacity to develop activities subject to sanitary surveillance (medicines or medical devices);

SANITARY LICENSING

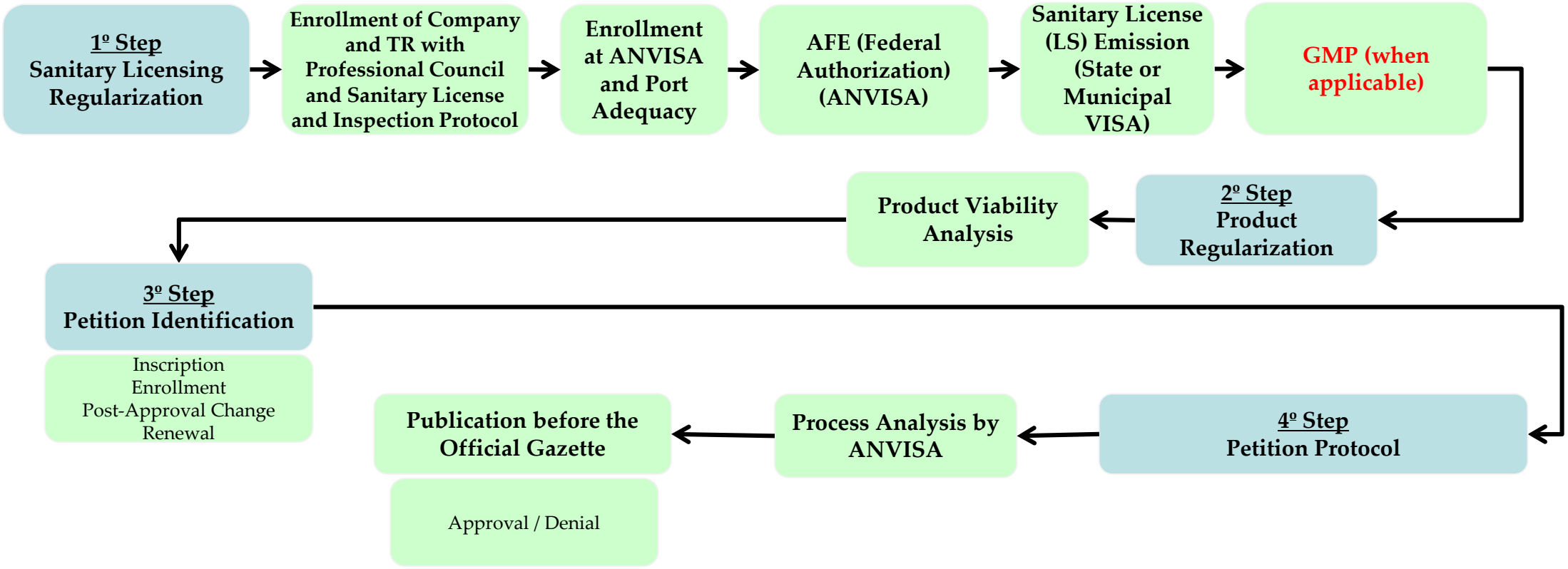
✓ **With the report from local authorities at hand, request AFE and AE before ANVISA:**

- Non–controlled medicines/inputs: AFE is granted for the head office and its branches, if any. Each branch will need its own LS;
- Controlled medicines/inputs, it is necessary an AE for each establishment that has activity with this kind of product;
- Medical devices, AFE is granted for each establishment with sanitary activity.

✓ **After having the published AFE, the local sanitary authority will grant the local sanitary license.**

SANITARY LICENSING

Sanitary Licensing Regularization Flow (Manufacturer / Importer)



COMPANY REQUIREMENTS TO HOLD A MARKETING AUTHORIZATION (REGISTRATION)

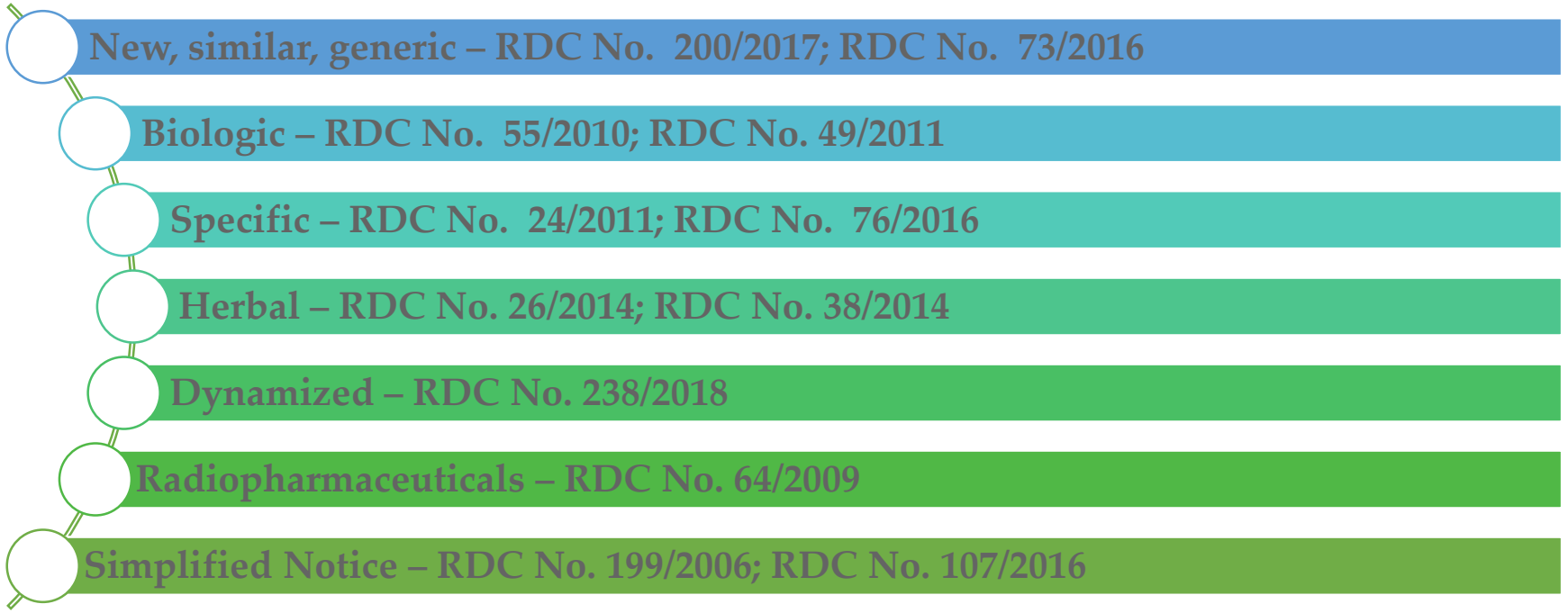
- ✓ Only importers and manufacturers companies can hold a marketing authorization (MA);

- ✓ In the past, there were special requirements to companies that import medicines – to own a warehouse and quality control laboratory. After the Resolution RDC No. 234/2018, companies that will import medicines can outsource the storage and the quality control tests;

- ✓ Other State and Municipality rules must also be observed and complied with (e.g. some cities require the LTA (Architectonic Project) prior approval for the issuance of the sanitary license).

Pharmaceutical Products Regularization

- Pharmaceutical Products requirements for regularization are determined through Resolutions according to the product category;
- Main Categories:



Medical Devices Regularization

- ✓ Medical devices (materials, implants, equipment and software for medical purpose), except products for in vitro diagnostics (IVD), are regulated by Resolution RDC No. 185/2001, as amended by Resolutions RDC No. 207/2006 and RDC No. 40/2015;

- ✓ IVD products must fulfill the requirements of Resolution RDC No. 36/2015;

- ✓ Each medical/diagnostic device is assigned to one of four regulatory classes (Class I, II, III or IV) based on the increasing scale of risk the device poses to the patient and/or user. Class I includes devices with the lowest risk and Class IV includes those with the greatest risk;

- ✓ Class I and II devices are not subject to registration, but as provided by ANVISA Resolution No. 40/2015, a "cadastro" (Inscription - simplified route) must be submitted.

NOTE: According to the Public Consultation No. 528/18, after the publication of the Resolution, the products Class I will be under "Notification". The intention is simplify the regularization of products Class I since they represent the most of the petitions submitted at ANVISA. The "Notification" of products Class I will be applied directly in the ANVISA´s web system and will not be published in the Official Gazette. The approval/release will be identified only the ANVISA´s web system.

The contributions for the Public Consultation No. 528/18 are in revision and ANVISA intends to publish the related Resolution by the end of 2018.

Medical Devices Regularization

- ✓ Class III and IV devices are subjected to registration and must have GMP certification for the manufacturing sites;

- ✓ In addition, all medical devices, regardless of the class must comply with principles of safety and effectiveness, as provided by Resolution RDC No. 56/2001;

- ✓ Certain devices, particularly electro-medical ones, require certification following INMETRO (National Institute of Metrology, Quality and Technology)'s and ABNT (Brazilian Association of Norms Techniques)'s standards;

- ✓ Products created to generate diagnostics are considered by ANVISA as medical devices and must comply with the regulations, seeking approval. Conversely, ANVISA has issued a brief statement that mobile applications with leisure and sporting purposes are not subject to regulation;

Clinical Trials

- ✓ Clinical trials are regulated by the National Health Council (CNS), linked to the Ministry of Health, through Resolution No. 466/2012, which sets out the main guidelines for clinical research, particularly concerning the ethical aspects of research involving humans;

- ✓ Resolution RDC No. 9/2015 rules the technical requirements for clinical trials with medicines;

- ✓ Resolution RDC No. 10/2015 rules the technical requirements for clinical trials with medical devices;

- ✓ These resolutions are aligned to international guidelines encouraging the development of clinical trials in Brazil, besides promoting Brazilian participation in clinical trials carried out simultaneously in different countries;

Registration Approval timelines

- ✓ Until March 2017, the whole process for regularization of medicines generally took from two years to five years, depending on the category of the medicine and on possible office actions that may be issued during ANVISA's analysis;

- ✓ For medical devices and IVD products it has taken between 3 and 6 months;

- ✓ However, Law No. 13.411/2016, that became in force in March 2017, amended Laws No. 6.360/76 and 9,782/99, creating categories and imposing specific deadlines to be followed by ANVISA while assessing marketing approval/post approval requests. Thus, for medical devices and in most cases, the first manifestation of ANVISA about the registration/inscription submitted is happening within the period of 90 days established in the legislation.

- ✓ The approvals are published in the Official Gazette.

NOTE: According the news published by ANVISA in September 03rd, the Agency will adopt a new format of the publication for medical devices. As of September 17th, the publications in the Official Gazette will only contain the essential information for the identification of the petition before ANVISA. The detailed information about the product and registration will be available in the ANVISA´s web system.

Marketing Authorization Renewal

- ✓ The registration renewal must be requested in the first semester of the fifth year of the registration validity;
- ✓ The renewal is considered automatically granted if contrary decision is not issued until the end of registration validity;
- ✓ The registration is declared obsolete/null if the renewal is not requested in the legal period;
- ✓ For IVD and medical devices products:

I - Registration is valid for 10 years;

II - Inscription (cadastro - simplified route) does not need to be renewed (according to RDC No. 40/2015).

- ✓ As per Law nº 13.411/2016 the registration will not be renewed:

I – for the product not classified as medicine that have no been produced in the period of validity of the expired registration;

II – for the medicine that have not been marketed during at least the time correspondent to the last two thirds of the validity. period of the expired registration (last 40 months).

PRICE APPROVAL - CMED

- ✓ The prices of new medicinal products and new presentations of medicines are strictly regulated in Brazil;

- ✓ Prices are set by the Pharmaceutical Market Regulation Council (CMED), after the marketing authorization is issued by ANVISA;

- ✓ CMED was created by Law No. 10.742/2003, and is responsible for monitoring and regulating the pharmaceutical market and establishing parameters and criteria for setting and adjusting the prices of medicines in Brazil, to stimulate competition in the market;

- ✓ Prices are reviewed annually in March and this review considers many factors, such as level of inflation, productivity and sector competition.

SIMPLIFICATION

- ✓ Clone registration (RDC No. 31/2014) – Simplification of registration, post-registration and renewal of medicines linked to the technical and clinical report of a matrix petition;

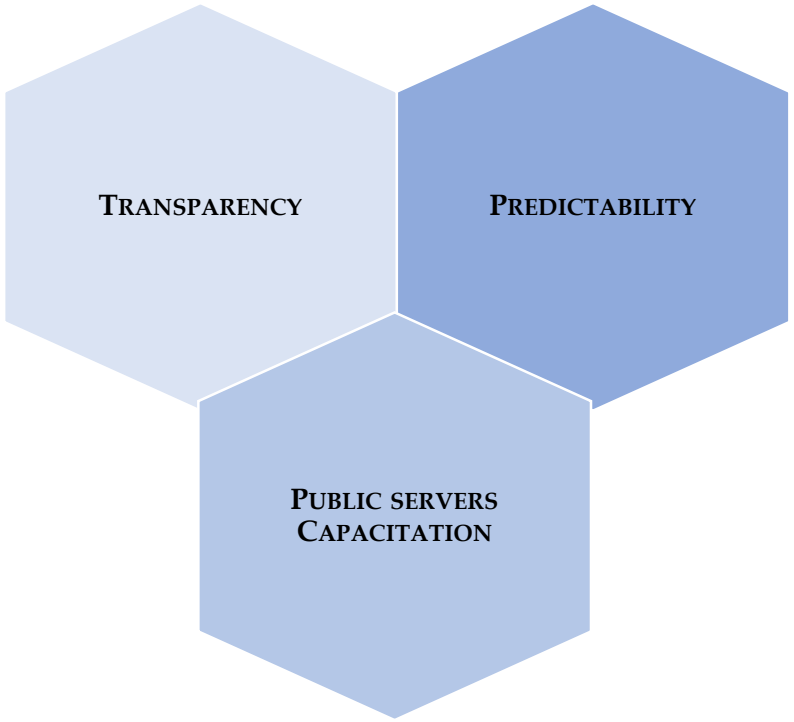
- ✓ Marketing Authorization Transfer (RDC No. 102/2016, amended by RDC No. 233/2018) – Transfer of marketing authorization upon the implementation of corporate restructurings and of commercial operation;

- ✓ Rare Diseases (RDC No. 205/2017) – Create a special proceeding for (i) clinic trials approvals for the evaluation of rare disease drugs; (ii) GMP applicable for the rare disease drugs premises; (iii) sanitary registration for new rare disease drugs;

- ✓ Outsourcing (RDC No. 234/2018) – Outsourcing of production steps, quality control analysis, transportation and storage of drugs and biologic products;

ANVISA Goals

- ✓ Being more efficient, ANVISA is reducing space for corruption, encouraging companies to begin or to increase their activities in Brazil and creating opportunities.



Sanitary Infraction – Applicable Penalties

- Upon incurring in a sanitary infraction, the following penalties may be applied (individually or jointly):

Sanitary Infraction definition and respective penalties:

- **Sanitary Infraction:**
  - Warning;
  - Penalty;
  - Product seizure;
  - Product destruction;
  - Product interdiction;
  - Sales suspension and/or product manufacturing;
  - Product registration cancelation;
  - Total or partial premise interdiction;
  - Publicity prohibition;
  - Company's federal authorization cancelation;
  - Company's sanitary license cancelation;
  - Intervention within the premise that receives public investment of any sphere;
  - Imposition of a rectifying message;
  - Publicity suspension.

- **Pecuniary Penalty:**
  - Minor infractions, from R$ 2,000.00 to R$ 75,000.00;
  - Severe infractions, from R$ 75,000.00 to R$ 200,000.00;
  - Serious infractions, from R$ 200,000.00 to R$ 1,500,000.00;
  - Applied in double in case of reoccurrence.

Sanitary Infraction – Applicable Penalties

- ✓ Companies can also be obliged to perform a recall of the product;
- ✓ Law 9.782/1999 sets forth in its Article 41-B, that if it is evidenced the commercialization of products subject to the sanitary surveillance, improper for consumption, the responsible company is obliged to publicize an alert to the population, within the term and the conditions provided for by the sanitary authority and being subject to the payment of a corresponding fee presented by ANVISA;
- ✓ Resolution RDC No. 55/2005, on its turn, sets forth the minimum requirements of the drug recall;
- ✓ Consumer Defense Code is also applicable for this case (art. 10) and the Ordinance No. 487/2012.

Negative consequences resulting from sanitary infractions

- ✓ Image of the company before the authorities and consumers may be damaged;
- ✓ Depending on the infraction and its severity, it can be considered a crime in Brazil (e.g. having a product in the market with a different formulation from the one submitted to ANVISA without due regularization – post registration);
- ✓ High recall costs and costs involved on rebuilding the company's image and consumers trust on the company.

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Thank you!

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